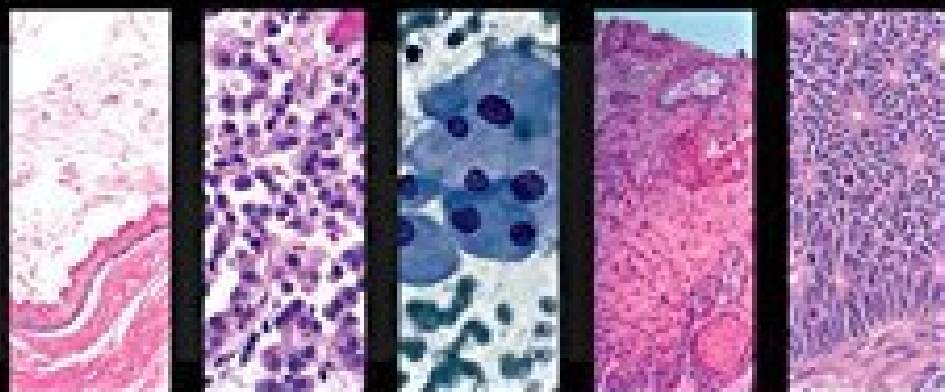


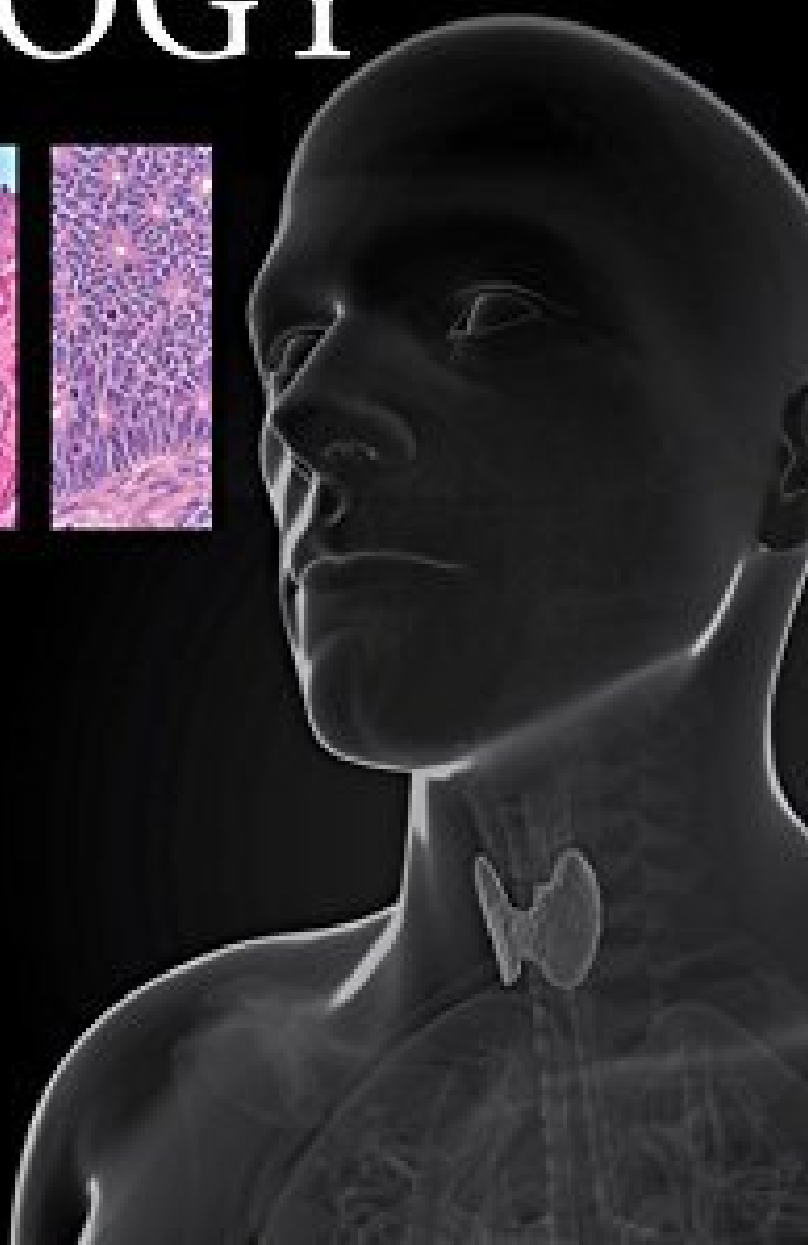
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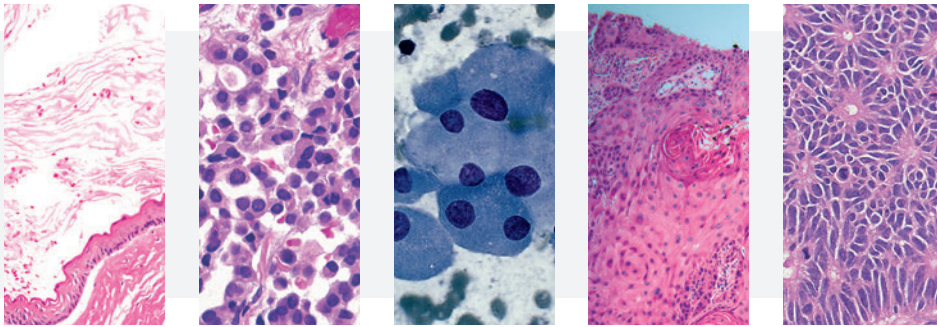
Bruce M. Wenig

THIRD EDITION

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Atlas of HEAD AND NECK PATHOLOGY



THIRD EDITION

Bruce M. Wenig, MD

Chairman

Department of Diagnostic Pathology and Laboratory Medicine
Mt. Sinai Beth Israel, Mt. Sinai St. Luke's and Mt. Sinai Roosevelt

Vice Chairman for Anatomic Pathology

Department of Pathology

Mt. Sinai Health System

Professor of Pathology

Icahn School of Medicine at Mount Sinai
New York, New York

ELSEVIER

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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Content Development Specialist: Katie DeFrancesco

Publishing Services Manager: Jeff Patterson

Project Manager: Carol O'Connell

Design Direction: Maggie Reid

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*To my love, my wife Ana Maria
and our children Sarah, Eli, and Jake
for their unwavering love and support.*

In Memoriam



To my father, Louis Wenig (1926-2014), devoted son, husband, father, grandfather, and great-grandfather, athlete, World War II veteran, good guy, and pillar of his community who so ably provided for his family and set a standard for all of us to follow. I love you Dad and miss you.



To my mother-in-law, Ursula Karin Klostermann Urrutia (1928-2014), loving mother, grandmother, and great-grandmother whose strong will and opinions are sorely missed by everyone who knew her.



To my uncle-in-law, Juan José Urrutia, MD (1932-2014), the standard-bearer of his family who lived an exemplary life; his quiet and confident demeanor served as example for all of his family.

Preface to the Third Edition

It has been a daunting task to undertake revising this atlas not so much for the dedicated time and effort committed to completing it but for keeping apprised of all the new information that appears in the literature on a near daily basis. Molecular diagnostics has reached the “prime time” in assisting physicians in managing their patients, specifically (but not solely) in the advances achieved in targeted therapy offering better outcomes and, more importantly, hope to patients and their families in treating diseases that previously were considered to be untreatable/incurable. For pathologists, advances in molecular biology have provided a better understanding of the diseases we diagnose. However, relative to compiling a book such as this one, the advances in molecular biology are akin to a moving target with near weekly publications that provide new information and/or information that renders previous knowledge relative to a given disease essentially moot. I have to the best of my ability tried to provide the most current information relative to the diseases included in this atlas. I sincerely hope I have succeeded in this endeavor or to at least have made this atlas a valuable resource to a wide spectrum of individuals with interest in diseases of the head and neck.

The third edition of the *Atlas of Head and Neck Pathology* updates and revises the information detailed in the second edition. I have attempted to correct any/all mistakes that were present in the previous edition. As in the second edition, this third edition is an attempt to be as complete as possible relative to diseases of the head and neck within the context of the atlas format. The format of the atlas remains similar to that of the previous editions, with information provided in accessible bulleted statements rather than in a narrative style. The changes in this edition include separate sections on the pharynx and the neck previously subsumed within the section on the oral cavity in the second edition. Various sections have been expanded to include more disease-specific entities including but not limited to odontogenic lesions/neoplasms in the Oral Cavity Section. Molecular diagnostics has become integral to diagnostic surgical pathology, and I have tried to include as much relevant molecular diagnostic information as it applies to the identification of new diseases/neoplasms, the understanding of disease/neoplastic pathogenesis, and the advances in treatment and prognosis. The illustrations are a key component of any atlas. To this end,

there are 3338 images in the third edition, including approximately 1570 new images.

Over the past nearly 30 years, I have been fortunate to have worked in three superb medical facilities. I began my pathology career in the Department of Otorhinolaryngic and Endocrine Pathology at the Armed Forces Institute of Pathology (AFIP) in Washington, DC, in 1986, mentored by Drs. Vincent Hyams and Dennis Heffner in the Division of Otorhinolaryngic Pathology, and Clara Heffess, MD, in the Division of Endocrine Pathology. Subsequent to my joining the staff at AFIP, our department added Drs. Carol Adair and Lester Thompson, creating one of the strongest diagnostic divisions in all of the AFIP. Close collaboration with the Oral and Maxillofacial Pathology Division at AFIP allowed me to learn and collaborate with their many outstanding oral pathologists. I am forever grateful for having been given the opportunity to work at the AFIP and honored to have served on active duty in the United States Navy.

In 1998 I joined the Department of Pathology at the Albert Einstein College of Medicine, Bronx, New York. Under the leadership of Michael Prystowsky, MD, PhD, I was fortunate to work in an environment that fostered and valued diagnostics, research, and education. In 2001, I moved to the Department of Diagnostic Pathology and Laboratory Medicine at Continuum Health Partners in New York City that included Beth Israel Medical Center, St. Luke's Hospital, and Roosevelt Hospital thanks to the support of the Chairman, Neville Colman, MD, PhD, whose unfortunate death in 2003 was a blow to the entire Health System. Over the past 14 years spent at Continuum Health Partners, I have worked with an outstanding group of diagnostic surgical pathologists and have appreciated their support of me, of the Department, and of the Health System. These past 14 years also brought together a unique core of high-level and accomplished physicians focused on providing care to patients with diseases of the head and neck. This multidisciplinary team of clinicians has included Drs. Louis Harrison, Roy Sessions, Mark Persky, Mark Urken, Ken Hu, Roy Holiday, Bruce Culliney, and Jean-Marc Cohen, creating one of the strongest groups of physicians focused on diseases of head and neck within New York and the United States. Change is inevitable, and in 2013, Continuum Health Partners merged with the Mount Sinai Hospital to

create the Mount Sinai Health System. The Department of Pathology under the leadership of Carlos Cordon-Cardo, MD, PhD, is among the largest in the United States. Once again I am fortunate to be in a department led by an individual who provides an environment that fosters academics, diagnostics, and education.

I would like to acknowledge my brother Barry L. Wenig, MD, my sister Hally Frist, and my uncle Siegfried Mayer, MD, as well as the entire extended Wenig and Urrutia families for their steadfast support and love.

I am indebted to the individuals at Elsevier, including William Schmitt, Kathryn DeFrancesco, Carol

O'Connell, and the entire Elsevier staff for their patience and understanding in awaiting completion of this atlas and for assistance in facilitating the publication of this edition. Thank you.

To Matt Townsend, my "drill sergeant," for the grueling early morning workouts he put me through that allowed me to maintain my physical well-being as well as my sanity in the unique environment of living and working in New York City.

Bruce M. Wenig, MD

Embryology, Anatomy, and Histology of the Sinonasal Tract

NASAL CAVITY

Embryology

- Facial prominences (frontonasal, maxillary, and mandibular) appear around the fourth week of gestation and give rise to the boundaries and structures of the face.
 - Nasal placodes, representing bilateral thickening of the surface ectoderm along the frontonasal prominence, form the nasal pits, which, by growth of the surrounding mesenchyme, become progressively depressed along their length and give rise to the primitive nasal sacs, the forerunners of the nasal cavities.
 - Anterior portion of the nasal cavity is the vestibule, the epithelium of which is ectodermally derived and represents the internal extension of the integument of the external nose.
 - The epithelium lining the nasal cavities proper (Schneiderian membrane) is of ectoderm origin.
 - Nasal septum develops from the merged medial nasal prominences.
 - Regions of continuity between the nasal and oral cavities following rupture of the oronasal membrane develop into the choanae.
 - Conchae (turbinates) develop as elevations along the lateral wall of each nasal cavity.
 - Olfactory epithelia develop in the superior posterior portion of each nasal cavity and differentiate from cells in the ectodermally derived nasal cavity epithelium.
- Frontal and nasal bones form the anterior sloping part.
 - Cribriform plate of the ethmoid bone forms the horizontal part and separates the nasal cavity from the anterior cranial fossa (medial part of floor); this area represents the deepest part of the cavity.
 - Body of the sphenoid bone forms the posterior sloping part.
 - Inferior (floor): majority (75%) is formed by the palatine processes of the maxillary bone, thereby intervening between the oral and nasal cavities; the remainder is formed by the horizontal process of the palatine bone.
 - Lateral: formed in the most part by the nasal surface of the maxilla below and in front, posteriorly by the perpendicular plate of the palatine bone, and above by the nasal surface of the ethmoidal labyrinth separating the nasal cavity from the orbit
 - Along the lateral wall of each nasal cavity are identified three horizontal bony projections: the superior, middle, and inferior conchae; occasionally a small fourth concha is identified above the superior concha and is called the supreme concha.
 - Air spaces or meatuses (superior, middle, and inferior) lie beneath and lateral to the conchae and are named according to the concha immediately above it.
 - Medial: formed by the bony nasal septum entirely formed by the vomer and the perpendicular plate of the ethmoid; the anterior portion of the nasal septum represents the septal cartilage.

Anatomic Borders (Figs. 1-1 and 1-2)

- Nasal cavity is divided into right and left halves by the septum; each half opens on the face via the nares or nostrils and communicates behind with the nasopharynx through the posterior nasal apertures or the choanae.
- Each half of the nasal cavity has the following borders (walls):
 - Superior (roof): slopes downward in front and back and is horizontal in its middle:

Innervation

- Innervation of the mucous membranes of the nose is supplied by the ophthalmic and maxillary branches of fifth (trigeminal) nerve via the pterygopalatine (sphenopalatine) ganglion.
- Olfactory mucous membrane contains the cells of origin of the olfactory nerve fibers, which collect into bundles traversing the cribriform plate and end in the olfactory bulb.

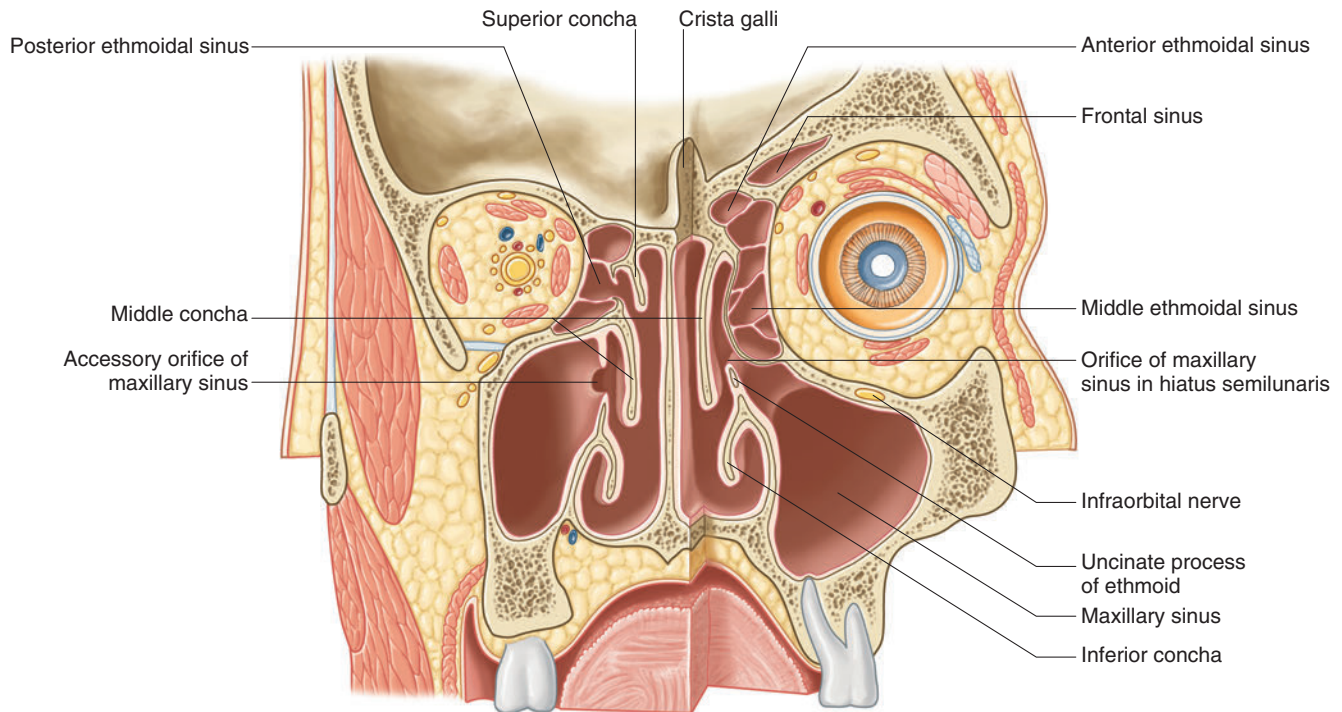
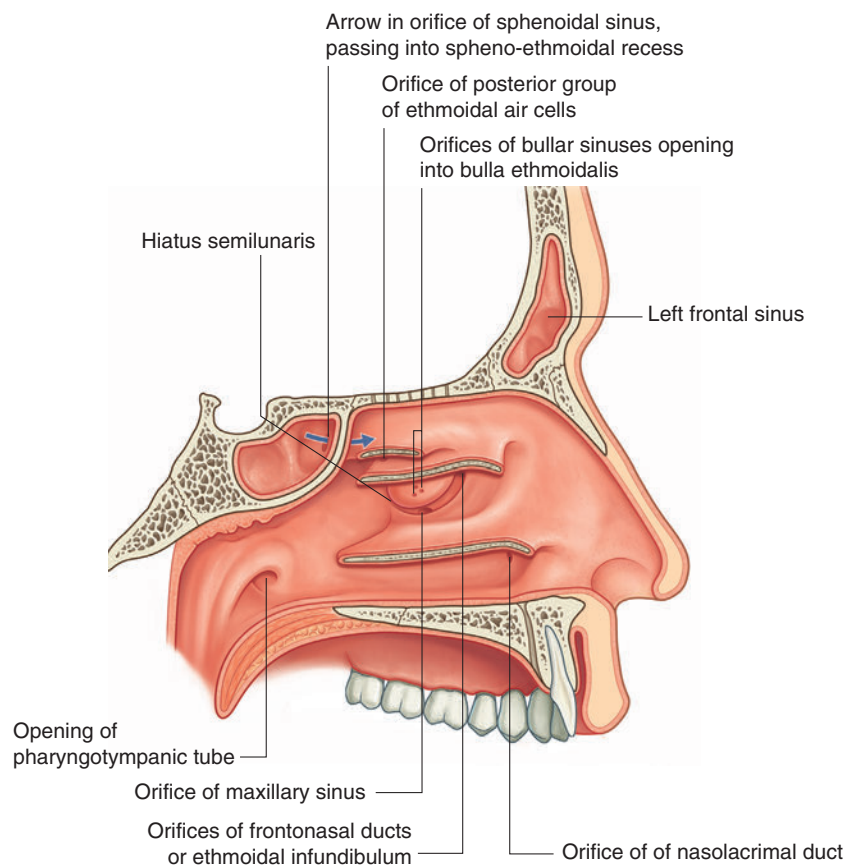


Fig. 1-1. A coronal section through the nasal cavity, viewed from the posterior aspect.

The plane of the section on the right side is more anterior. The normal orifice of the maxillary sinus is shown on the right side and an accessory orifice on the left side. (By permission from Berkovitz BKB, Moxham BJ: *Head and neck anatomy*, London, 2002, Martin Dunitz, Fig. 32-10.)

Fig. 1-2. Lateral wall of the nasal cavity.

The conchae have been removed to show the positions of the ostia of the paranasal sinuses and the nasolacrimal duct. (From Drake RL, Vogl AW, Mitchell AWM: *Gray's anatomy for students*, ed. 3, Philadelphia, 2014, Elsevier.)



Vascular Supply and Lymphatic Drainage

- Arteries and veins:
 - Arterial supply to the nasal cavity comes from several sources including the sphenopalatine branch of the internal maxillary artery (a branch of the external carotid artery), the anterior and posterior ethmoidal artery branches of the ophthalmic artery (a branch of the internal carotid artery), and the facial artery (a branch of the external carotid artery).
 - Veins of the nose parallel the arteries with drainage via the sphenopalatine foramen into the pterygoid plexus and then into the internal jugular vein, via the ophthalmic veins into the cavernous sinus and then into the dural venous sinuses, and via the facial vein into either the internal or external jugular vein.
- Lymphatics:
 - Anterior portion of nose drains to the lymphatics, draining the skin covering the external nose, and pass to the submandibular nodes.
 - Majority of the lymphatics of the nasal cavity drain via the retropharyngeal lymph nodes to the deep cervical lymph nodes.

Histology (Figs. 1-3 and 1-4)

- Nasal vestibule is a cutaneous structure composed of keratinizing squamous epithelium and underlying subcutaneous tissue with cutaneous adnexal structures (hair follicles, sebaceous glands, and sweat glands).
- Mucocutaneous junction (limen nasi) is approximately 1 to 2 cm posterior from the nares and represents the point at which the epithelial surface changes from keratinizing squamous epithelium to a ciliated pseudostratified columnar (respiratory) epithelium including identifiable mucocytes (goblet cells); the respiratory epithelium lines the entire nasal cavity and, as previously detailed, is ectodermally derived.
- Submucosa underlying the epithelium is thin, is noteworthy for the presence of seromucous (minor salivary) glands arranged in distinct lobules, normally contains a mixed inflammatory cell infiltrate, including mature lymphocytes and scattered plasma cells but no lymphoid follicles/aggregates, and has a distinct vascular component consisting of large, thick-walled blood vessels:
 - Vascular structures are particularly prominent along the inferior and middle turbinates and may be mistaken for a hemangioma.
- Nasal septum separates the nasal cavities and includes elastic cartilage and lamellar bone:

- Overlying nasal mucosa is closely apposed to these structures, with the periosteum and perichondrium attached so closely as to constitute a single membrane referred to as mucoperiosteum.
- Along the anterior part of the nasal septum the submucosa is rich in thin-walled blood vessels.
 - Referred to as Little's or Kiesselbach's area
 - Represents a frequent site of nosebleeds
- Nasal cartilage is of the hyaline type and has a bluish, translucent, homogeneous appearance.
- Olfactory epithelium consists of: (see Fig. 1-3)
 - Bipolar, spindle-shaped olfactory neural (receptor) cells composed of myelinated axons penetrating the basal lamina to protrude from the mucosal surface and nonmyelinated proximal processes, which traverse the cribriform plate
 - Columnar sustentacular or supporting cells
 - Rounded basal cells lie on basal lamina
 - Olfactory or Bowman glands in the lamina propria representing purely serous type glands

PARANASAL SINUSES

Embryology

- Paranasal sinuses (maxillary, ethmoid, sphenoid, and frontal) develop as outgrowths of the walls of the nasal cavities and become air-filled extensions of the nasal cavities.
- Maxillary and portions of the ethmoidal sinuses develop during late fetal life, whereas the frontal and sphenoid sinuses, which are not present at birth, develop during the early years of life.

Anatomic Borders (see Fig. 1-1)

- Maxillary sinuses: largest of the paranasal sinuses and located in the body of the maxilla; from above, the maxillary sinus has a triangular shape with the base formed by the lateral wall of the nasal cavity and the apex projecting into the zygomatic arch; borders include:
 - Superior (roof): orbital surface of the maxilla (floor of the orbit)
 - Inferior (floor): alveolar and palatine process of the maxilla
 - Anterolateral: facial surface of the maxilla
 - Posterior: infratemporal surface of the maxilla
 - Medial: lateral wall of the nasal cavity
 - Maxillary ostium (hiatus semilunaris) is on the highest part of the medial wall of the sinus and does not open directly into the nasal cavity but into the posterior ethmoid infundibulum (uncinate groove), which opens into the middle meatus of the nasal cavity.

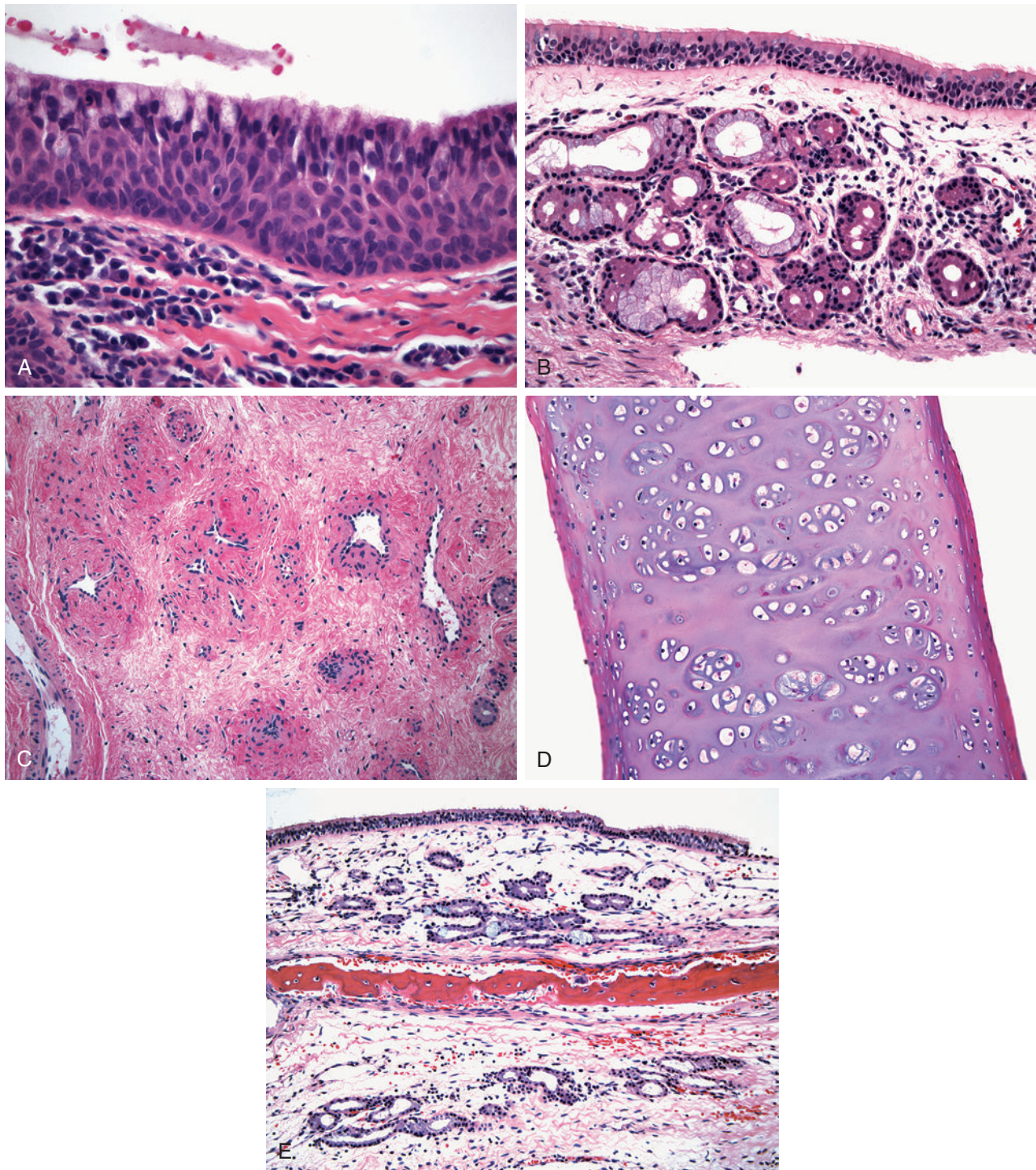


Fig. 1-3. Sinonasal mucosa.

A, Transitional area from cutaneous portion of nasal vestibule (not shown) to mucosal portion shows the presence of intraepithelial mucocytes and absence of cutaneous adnexal structures; the presence of mucocytes identified the epithelium as being of mucosal (Schneiderian) and not cutaneous origin. **B**, Surface of the entire sinonasal tract is lined by ciliated respiratory epithelium separated from the submucosa by a basement membrane; submucosal seromucous glands are present throughout the sinonasal tract. **C**, Thick-walled vascular structures are normal structures found in the nasal turbinates. **D**, Normal (hyaline) cartilage of the nasal septum. **E**, Mucoperiosteum showing the presence of sinonasal mucosa lying in close apposition to subjacent lamellar bone.

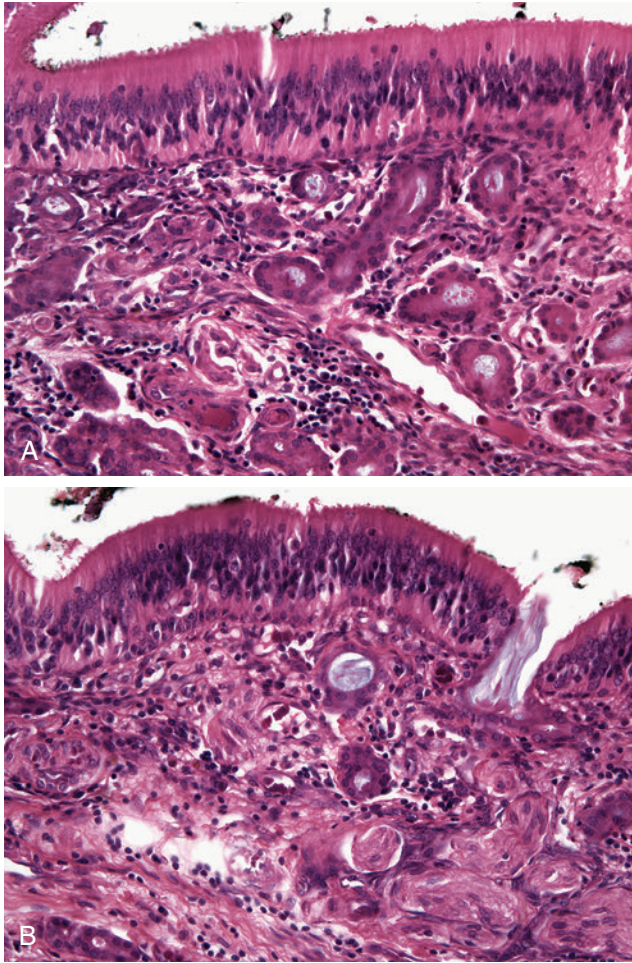


Fig. 1-4. Olfactory mucosa.

A, Spindle-shaped olfactory (neural) cells with microvilli; basal cells lie on the basal lamina; olfactory or Bowman glands in the lamina propria are serous-type glands.

B, Small nerve fibers lie immediately below the olfactory epithelium.

Osteomeatal Complex or Unit

- Not a discrete anatomic structure but refers to a functional unit of structures that include the maxillary sinus ostium, ethmoid infundibulum, hiatus semilunaris, and frontal recess
- Common final pathway for drainage of secretions from the maxillary, frontal, anterior, and middle ethmoid sinuses into the middle meatus
- Obstruction of osteomeatal complex plays pivotal role in development and persistence of sinusitis.
- Coronal high-resolution computed tomography (HRCT) is the preferred imaging modality, providing exquisite detail of these structures.

Ethmoid Sinuses

- Consist of thin-walled cavities in the ethmoidal labyrinth completed by the frontal, maxillary, lacrimal, sphenoidal, and palatine bones varying in size and number, usually consisting of two to eight anterior and middle ethmoid cells and two to eight posterior ethmoid cells.
- Based on the relation to the ethmoid infundibulum the ethmoid cells are grouped into:
 - Anterior group: ostia open directly in relation to the ethmoid infundibulum
 - Middle or bullous group: ostia open on or above the ethmoid infundibulum
 - Posterior group: ostia open into the superior meatus

Frontal Sinuses

- Roughly pyramidal and located in the vertical part of the frontal bone; these sinuses are frequently asymmetric in size and often contain septa subdividing the cavity:
 - Ostia of the frontal sinus opens into the anterior part of the middle meatus.
 - Important anatomic relation includes proximity to the anterior cranial fossa and orbit separated only by a thin plate of bone from these structures.

Sphenoid Sinuses

- Contained within the sphenoid bone situated posterior to the upper part of the nasal cavity:
 - Related above to the optic chiasm and the hypophysis cerebri
 - Related on each side to the internal carotid artery and cavernous sinus
 - Opens into the sphenoethmoidal recess lying above and behind the superior nasal concha

Innervation

- Maxillary sinuses
 - Innervation supplied by the maxillary branches of fifth (trigeminal) nerve, including the anterior, middle, and posterior superior alveolar nerves and the infraorbital nerve
- Ethmoid sinuses
 - Innervation supplied by the ophthalmic and maxillary branches of fifth (trigeminal) nerve, including the nasociliary, anterior ethmoid, and posterior ethmoid nerves and the orbital branches of the pterygopalatine (sphenopalatine) ganglion
- Frontal sinuses
 - Innervation supplied by the supraorbital and supratrochlear branches of the frontal nerve, a

derivative of the ophthalmic branch of fifth (trigeminal) nerve

- Sphenoid sinuses
 - Innervation supplied by the ophthalmic and maxillary branches of fifth (trigeminal) nerve, including the posterior ethmoid nerve and the orbital branches of the pterygopalatine (sphenopalatine) ganglion

Vascular Supply and Lymphatic Drainage

Arteries and Veins

- Maxillary sinuses
 - Major blood supply comes from branches of the maxillary artery (infraorbital, greater palatine, postero- and anterosuperior alveolar arteries and sphenopalatine artery) with smaller contribution from the facial artery; the maxillary and facial arteries are branches of the external carotid artery.
 - Venous drainage occurs anteriorly via the anterior facial vein to the jugular vein and posteriorly via the maxillary vein to the jugular system by way of the retromandibular vein; in addition, in the region of the infratemporal fossa, the maxillary vein communicates with the pterygoid venous plexus, which anastomoses with the dural sinuses through the base of the skull.
- Ethmoid sinuses
 - Receives its blood supply from the internal and external carotid arteries via branches of the ophthalmic (anterior and posterior ethmoidal arteries) and maxillary (nasal branch of sphenopalatine artery) arteries, respectively
 - Venous drainage occurs by two routes:
 - Into the nose via the nasal veins, which flow to the maxillary vein and then retromandibular vein and ultimately into the external jugular vein
 - Via the ethmoidal veins to the ophthalmic veins to the cavernous sinus
- Frontal sinuses
 - Receives its blood supply from branches of the ophthalmic artery (supraorbital and supratrochlear arteries), a branch of the internal carotid artery
 - Venous drainage is to the cavernous sinus by way of the superior ophthalmic vein.
- Sphenoid sinuses
 - Receives its blood supply from the internal and external carotid arteries via branches of the oph-

thalmic (posterior ethmoidal artery) and maxillary (sphenopalatine artery) arteries, respectively

- Venous drainage occurs to the maxillary vein, which flows to the external jugular vein by way of the retropharyngeal vein and to the pterygoid plexus, which flows to the facial vein, which empties into the internal jugular vein.

Lymphatics

- Maxillary sinuses
 - Lymphatic drainage is to the submandibular lymph nodes.
- Ethmoid sinuses
 - Lymphatic drainage occurs to the submandibular (from the anterior and middle ethmoid groups) and the retropharyngeal (from posterior ethmoid group) lymph nodes.
- Frontal sinuses
 - Lymphatic drainage occurs to the submandibular lymph nodes.
- Sphenoid sinuses
 - Lymphatic drainage occurs to the retropharyngeal lymph nodes.

Histology (see Fig. 1-1)

- All of the sinuses are lined by ciliated pseudostratified, columnar epithelium including identifiable mucocytes (goblet cells) and together with the nasal cavity are referred to as the Schneiderian membrane:
 - Schneiderian epithelium is ectodermally derived in contrast with the similar appearing epithelium lining the nasopharynx, which is of endodermal derivation.
- Although the epithelia of the paranasal sinuses is the same as that of the nasal cavity, the mucous membranes of the paranasal sinuses are thinner and less vascular than those of the nasal cavity and have a fibrous layer adjacent to the periosteum.
- Seromucous glands are scattered throughout the paranasal sinus submucosa, particularly seen in the ostial areas.

FURTHER READING

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Non-Neoplastic Lesions of the Sinonasal Tract

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE SINONASAL TRACT (Box 2-1)

BOX 2-1 Classification of Non-Neoplastic Lesions of the Sinonasal Tract

- Rhinosinusitis
- Sinonasal polyps:
 - Nasal (inflammatory) polyps
 - Antrochoanal polyp
- Paranasal sinus mucocele
- Heterotopic central nervous system tissue and encephalocele
- Nasal dermoid sinus and cyst
- Hamartomas:
 - Respiratory Epithelial Adenomatoid Hamartoma (REAH)
 - Chondro-osseous and respiratory epithelial (CORE) hamartoma
 - Nasal chondromesenchymal hamartoma
- Infectious diseases:
 - Fungal (fungal sinusitis, others)
 - Bacterial (rhinoscleroma, others)
 - Protozoal (leishmaniasis, others)
 - Viruses
- Sarcoidosis
- Myospherulosis
- Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
- Vasculitides (e.g., granulomatosis with polyangiitis; Churg-Strauss disease)
- Necrotizing sialometaplasia
- Eosinophilic angiocentric fibroma
- IgG4-related diseases
- Others

RHINOSINUSITIS (Figs. 2-1 through 2-6)

Definition: Nonspecific or specific inflammation of the sinonasal tract that may be isolated to the nasal cavity (rhinitis), isolated to the paranasal sinuses (sinusitis), or involve nasal cavity and paranasal sinuses (rhinosinusitis).

Clinical

- Causes of rhinosinusitis are numerous (Box 2-2) and include:
 - Allergic (most common)

BOX 2-2 Causes of Rhinosinusitis

- Allergic (most common)
 - Infectious
 - Aspirin intolerance
 - Nonallergic rhinosinusitis with eosinophilia (NARES)
 - Idiopathic
 - Occupational or environmental exposure
 - Systemic diseases
 - Structural or mechanical causes
 - Medication-induced
 - Pregnancy
-
- Infectious
 - Aspirin intolerance
 - Nonallergic rhinosinusitis with eosinophilia (NARES)
 - Idiopathic
 - Occupational or environmental exposure
 - Systemic diseases
 - Structural or mechanical causes:
 - Deviated nasal septum
 - Neoplasms
 - Immotile cilia syndrome
 - Medication-induced:
 - Referred to as rhinosinusitis medicamentosa
 - May be caused by topical or systemic medications, such as:
 - Propranolol, oral contraceptives, reserpine, others
 - Nasal sprays
 - Pregnancy:
 - Thought to result from the combined effects on the nasal mucosa by pregnancy-related hormones, increased blood volume, and airway resistance
-
- Often the diagnosis of rhinosinusitis is straightforward by clinical evaluation and does not require radiographic imaging or tissue sampling; however, there are exceptions in which radiographic imaging and biopsies are required to establish a diagnosis of rhinosinusitis and to exclude other possible diseases that cause and/or are associated with rhinosinusitis.

Allergic Rhinosinusitis

- In adults, allergies are the most common cause of rhinosinusitis.

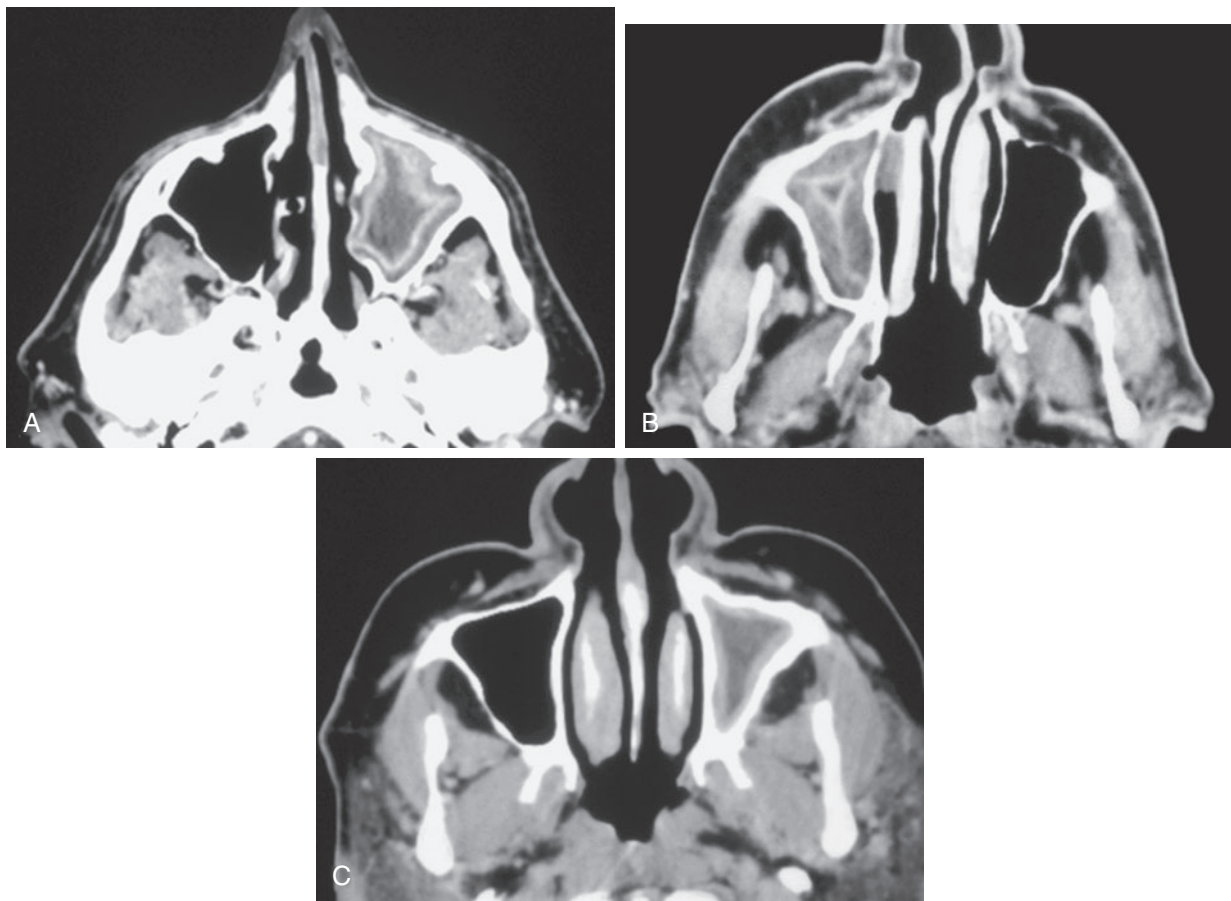


Fig. 2-1. Acute bacterial sinusitis.

Axial contrast-enhanced CT scans of three different patients. **A**, Enhancement of the inflamed mucosa within the left maxillary sinus. There is a zone of water attenuation separating this mucosa from the bony wall of the sinus. This zone is submucosal edema. There are also water attenuation secretions within the sinus cavity that represent increased surface secretions from the inflamed mucosa. This is the typical picture of sinus inflammation. **B**, Inflammation within the right maxillary sinus. In this case, there is more submucosal edema and a smaller amount of secretions than in **A**.

C, Inflammation within the left maxillary sinus. In this case, there is little submucosal edema and a large amount of surface secretions. These three cases illustrate the variations in reactions to inflammation. They do not predict outcome.

(From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, 2011, p 168, Fig. 3-2.)

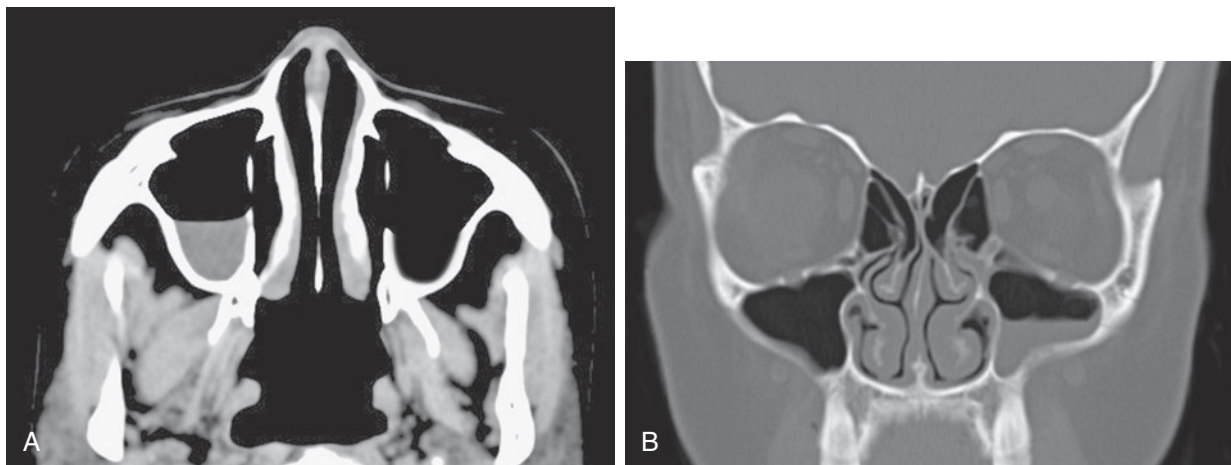


Fig. 2-2. Acute bacterial sinusitis.

Axial CT scan (**A**) shows an air-fluid level in the right antrum. The attenuation of this fluid is less than that of muscle and typically is watery sinus secretions. This could represent an acutely obstructed sinus, a sinus with poor drainage in a chronically supine (unconscious) patient, or a patient who had a recent antral washing for sinusitis. Coronal CT scan (**B**) shows a typical air-fluid level in the left antrum with minimal mucosal thickening and obstruction of the ostiomeatal unit. Some mucosal disease is also present in the left ethmoid and right maxillary sinuses. Clinically, this patient had acute sinusitis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, 2011, p 174, Fig. 3-10.)

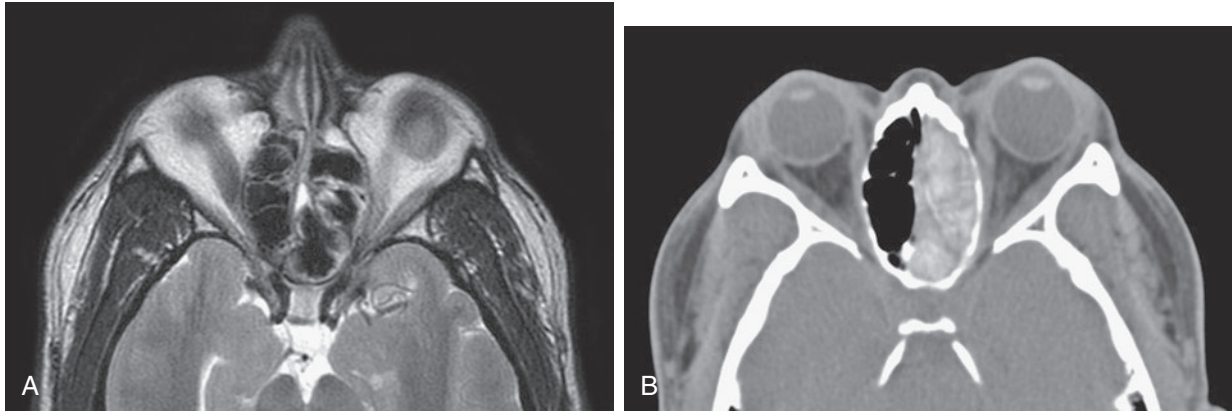


Fig. 2-3. Chronic bacterial sinusitis.

Axial T2-weighted MR image (**A**) shows apparent right-sided minimal, scattered mucosal thickening in the ethmoid and sphenoid sinuses. Axial CT scan (**B**) on the same patient as in **A** and performed on the same day shows opacification of the left ethmoid and sphenoid sinuses. Centrally within most sinuses is higher attenuation material representing either desiccated secretions or fungal mycetomas. This patient had chronic bacterial sinusitis. These images illustrate how MR may underestimate the amount of disease in some cases. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 179, Fig. 3-18.)

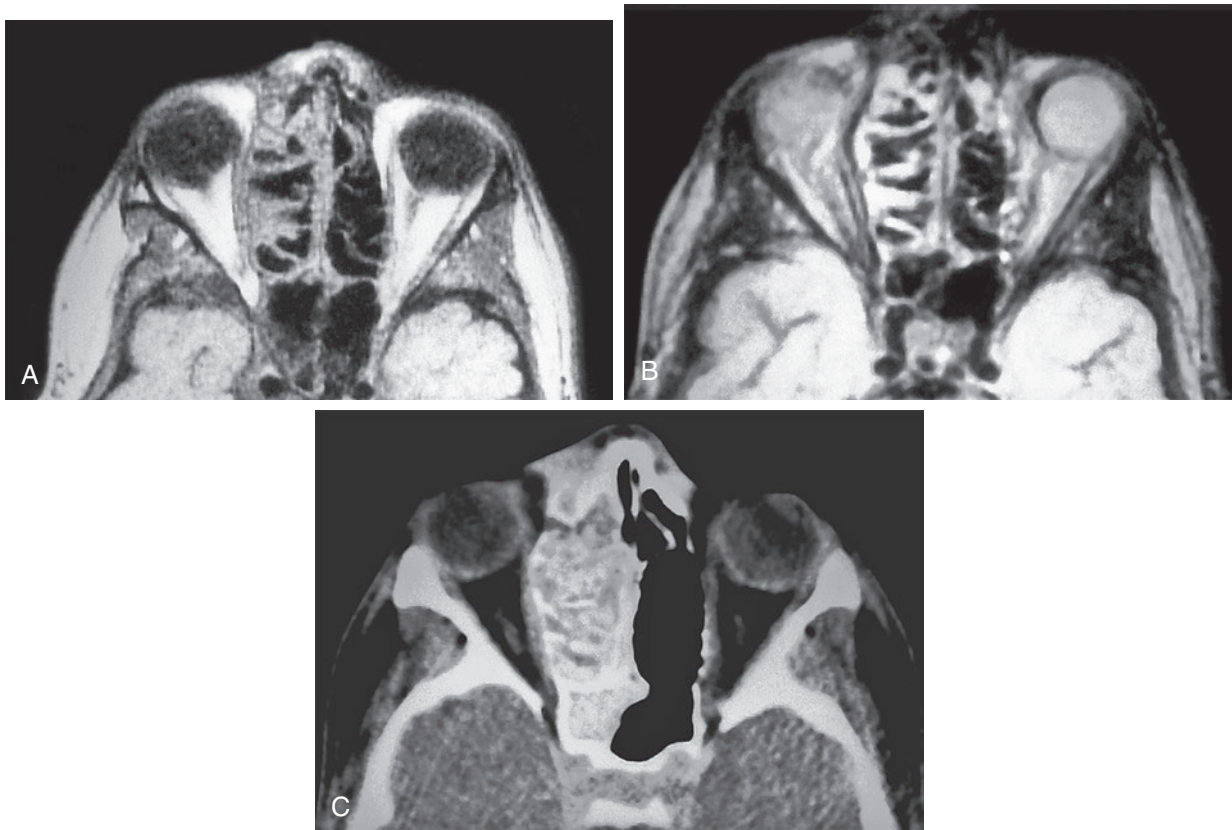


Fig. 2-4. Chronic sinusitis.

Axial T1-weighted (**A**) and T2-weighted (**B**) MR images show what appears to be moderate ethmoid sinusitis with residual aeration in scattered right ethmoid cells and in the right sphenoid sinus. In a CT scan (**C**), these sinuses are completely opacified, with desiccated secretions that are separated from the sinus walls by a thin zone of mucoïd attenuation. This patient had chronic sinusitis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 200, Fig. 3-19.)

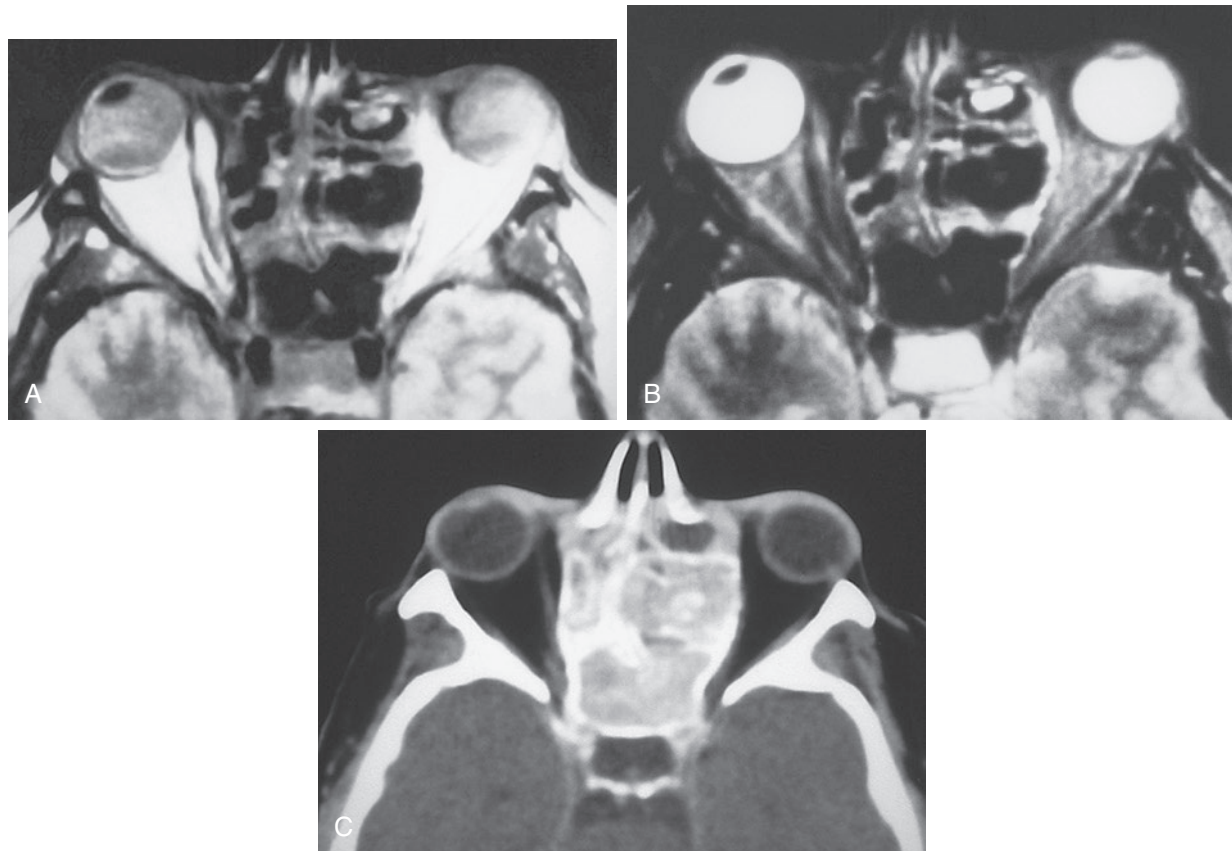


Fig. 2-5. Chronic sinusitis.

Axial T1-weighted (**A**) and T2-weighted (**B**) MR images show expansion of the ethmoid complexes, with apparently moderate mucosal thickening in the ethmoid sinuses. The sphenoid sinuses appear aerated. However, a CT scan (**C**) shows that the expanded ethmoid and sphenoid sinuses are totally opacified, with desiccated secretions. This patient had chronic sinusitis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 201, Fig. 3-20.)

- In children, allergies represent the second most common cause of rhinosinusitis second to viral upper respiratory infection.
- No gender predilection; occurs over a wide age range
- Caused by exposure to allergen in sensitized patient and mediated via type I IgE immune reaction:
 - Among the more common allergens are pollens, animal dander, dust mites, mold.
- May predispose patients to recurrent or chronic sinusitis
- May be familial
- In a sensitized patient, exposure results in allergic reaction that produces nasal congestion with rhinorrhea, sneezing, and itching:
 - In noninfected patients, the nasal secretions appear clear.
 - In infected patients, the nasal secretions appear purulent.
 - The reaction begins within minutes of exposure, peaking about 15 minutes later.
- The endoscopic appearance of the sinonasal mucosa is pale to bluish; inflammatory polyps may or may not be identified.
- Generally, the standard for allergy testing is considered to be skin testing:
 - Represents a reaction between antigen and sensitized mast cells in the skin, causing a wheal and flare skin response
 - Occasionally may be negative in allergic rhinosinusitis patients because of local (nasal) synthesis of IgE with the local (nasal) tissue being more sensitive than the distant (cutaneous) site
- Histopathologic findings include submucosal edema with a mixed inflammatory cell reaction dominated by the presence of eosinophils:
 - Squamous metaplasia of the surface epithelium may be present.
 - Neutrophils can be identified, especially in the presence of secondary bacterial infection.
- Treatment includes antihistamines, nasal cromolyn preparations (stabilizes mast cells against

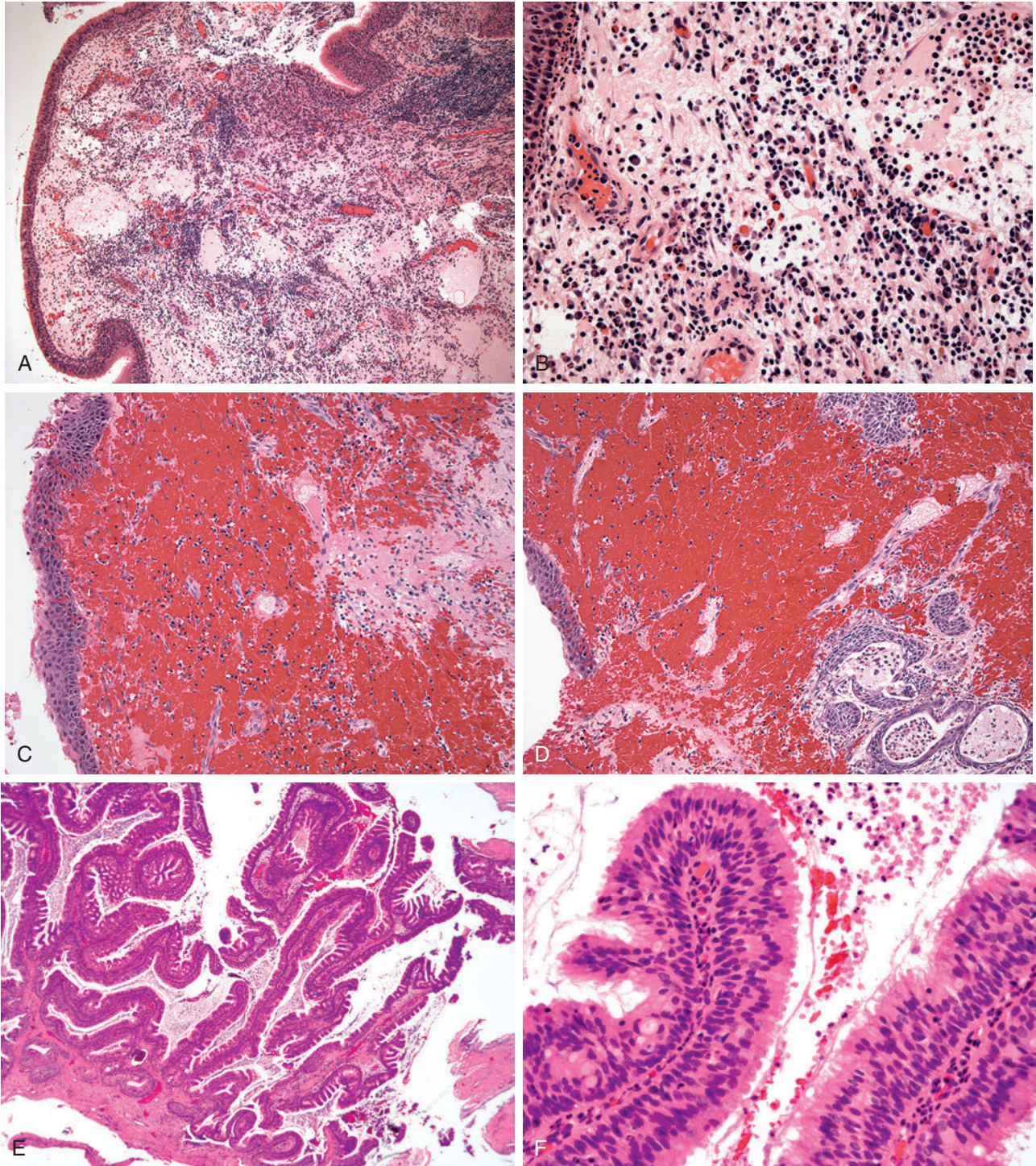


Fig. 2-6. Nonspecific chronic sinusitis.

A and B, The histopathologic changes include submucosal mixed inflammation, including mature lymphocytes with a variable admixture of plasma cells, eosinophils, histiocytes and neutrophils, and edema. **C and D,** Squamous metaplasia of the surface epithelium (normally a ciliated respiratory epithelium) is often present that may also include sialometaplasia (squamous metaplasia of seromucous glands; lower right in **D**). **E and F,** Secondary alterations that may occur in long-standing cases of chronic sinusitis include prominent papillary architecture composed of ciliated pseudostratified columnar epithelial cells with intermixed goblet cells. This appearance is clinically referred to hyperplastic papillary sinusitis.

degranulation and release of inflammatory mediators), topical corticosteroids, immunotherapy for documented IgE-mediated allergies.

Infectious Rhinosinusitis

- Caused by a variety of microorganisms, the most common of which are viruses and bacteria
- No gender predilection; occurs over a wide age range
- Viral rhinosinusitis results in the “common cold”:
 - Symptoms include nasal congestion and a watery nasal discharge.
 - Among the more common viruses implicated in causing disease are rhinoviruses, influenza and parainfluenza viruses, adenoviruses, and respiratory syncytial virus.
 - May be secondarily infected by bacteria manifested by a mucopurulent discharge
 - Usually self-limiting disease course
- Bacterial sinusitis:
 - Among the more common bacteria implicated in causing disease include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and α -hemolytic streptococci.
 - Associated with pain localized over infected site; headaches are uncommon.
 - May be acute, subacute, or chronic:
 - Acute:
 - Persistent and worsening symptoms longer than 7 days but less than 3 weeks
 - Subacute:
 - Symptoms lasting 3 weeks to 3 months
 - Chronic:
 - Symptoms last more than 3 months
 - Patients with resistant or refractory chronic sinusitis have increased incidence of *Staphylococcus aureus*, anaerobic bacteria, gram-negative organisms.
 - *Pseudomonas aeruginosa* is a commonly cultured organism in patients who have received multiple courses of antibiotics over extended periods of time.
 - The culturing of *Pseudomonas* sp. suggests an immune deficiency condition.
 - Appropriate antibiotic therapy is curative.

Atrophic Rhinosinusitis

- Also referred to as “ozena” (stench) and occasionally “rhinitis sicca”
- More common in women; begins in childhood often in the second decade of life at the onset of puberty
- Characterized by atrophy of the nasal mucosa, crust formation, and foul-smelling odor from the nasal cavity
- Caused by a variety of factors, including:
 - Chronic bacterial infection
 - Nutritional (e.g., vitamin A, iron) deficiencies

- Chronic exposure to irritants
- Prior radiation or surgery
- End stage of chronic infections
- Hypoestrogenemia
- Autoimmune disease
- Symptoms include nasal obstruction, headaches, nasal crusting, anosmia, epistaxis, halitosis, and foul-smelling nasal odor.
- Histologically, biopsies show various degrees of squamous metaplasia of the mucosal surface epithelium, submucosal edema with nonspecific chronic inflammation, fibrosis, and atrophic and decreased numbers of seromucous glands and vascular dilatation:
 - The histologic findings are nonspecific.
 - The clinical impression of the atrophic appearance of nasal cavity tissues (e.g., turbinates) is important in trying to make the diagnosis.
 - Excluding evidence of other possible diseases is necessary.
- Medical therapy (e.g., antibiotics, nutritional supplements [vitamin A, iron, estrogen], and surgery) has been used to treat atrophic rhinosinusitis.
- No known cure; over time, the active disease may spontaneously arrest with disappearance of the nasal crusting and foul odor.

Aspirin Intolerance or Aspirin-Exacerbated Respiratory Disease (AERD)

- Also referred to as Samter triad or syndrome, which includes:
 - Aspirin intolerance
 - Sinonasal polyps
 - Asthma
- No gender predilection; often begins in the third to fourth decades of life
- Within hours of aspirin ingestion, patients may experience bronchoconstriction and rhinorrhea:
 - In some patients may also follow ingestion of nonsteroidal antiinflammatory medications
 - Symptoms may also include nausea, vomiting, diarrhea with gastrointestinal cramping.
 - Considered to be a pharmacologic effect with interference in the metabolism of arachidonic acid rather than an allergic response
- Polyps usually are bilateral:
 - Histology of polyps is similar to that of sinonasal inflammatory polyps not occurring in aspirin-intolerant patients.
- Presence of nasal polyps has a significant negative impact on patients with chronic rhinosinusitis:
 - Patients with nasal polyps have more severe symptoms with less improvement after operative intervention and a significantly higher need for revision surgery.

- Nonallergic rhinosinusitis with eosinophilia (NARES) syndrome may be precursor to the aspirin intolerance syndrome.
- Treatment includes:
 - Avoidance of instigating medications
 - Symptomatic relief
 - Polypectomy

Radiology of Rhinosinusitis

Acute Rhinosinusitis

- Air-fluid levels represent the best diagnostic clue characterized by bubbly appearing secretions within a sinus and mucosal thickening:
 - Most common in ethmoid and maxillary sinuses
 - Creates a “foam on water” appearance
 - Sinus lumen size remains normal without expansion or reduction in volume:
 - Sinus expansion can be seen in mucocoeles.
 - Sinus reduction in volume can be seen with chronic rhinosinusitis.
 - Not accurate in assessing extent of inflammation
- CT findings:
 - Peripheral soft tissue mucosal thickening within sinus
 - Inflammatory tissue obstructing drainage pathways of osteomeatal complex
 - Contrast-enhanced CT shows enhancement of inflamed mucosa but not central secretions.
- MR findings:
 - Not frequently performed for rhinosinusitis
 - Used to evaluate for orbital and intracranial complications
 - Can be used to differentiate fungal from other inflammatory diseases
 - Can be used to differentiate inflammatory lesions from neoplasms

Chronic Rhinosinusitis

- Mucosal thickening or soft tissue opacification of nonexpanded sinus with thickening and sclerosis of sinus bony walls:
 - Most common in ethmoid sinus followed by maxillary sinuses, frontal and sphenoid sinuses
 - Sinus lumen size remains normal or is decreased in volume.
- CT findings:
 - Mucosal thickening or opacification of sinus without sinus expansion
 - Variable density (isodense to hyperdense) of secretions depending on content (protein, water, fungi)
 - Better at detecting luminal sinus disease than endoscopic evaluation

- Lack of correlation between symptomatology and imaging findings

Pathology of Nonspecific Chronic Rhinosinusitis

Histology

- The histologic changes of nonspecific chronic sinusitis include:
 - Submucosal mixed inflammatory cell infiltrate, including mature lymphocytes with variable admixture of plasma cells, eosinophils, histiocytes, and neutrophils
 - Submucosal edema
 - Surface mucosa squamous metaplasia is often (but not uniformly) present.
 - Minimal fibrosis
 - Vascular proliferation may be present
 - In long-standing and/or recurrent/persistent disease, inflammatory epithelial hyperplasia may be present, characterized by:
 - Papillary appearance to the surface mucosa
 - Epithelium is bland appearing, lined by single layer of columnar cells and goblet cells.
 - Abundant inflammatory cells within lamina propria
 - May be referred to clinically as (hyperplastic) papillary sinusitis

Differential Diagnosis

- A more specific cause of sinusitis (see previous and subsequent sections)
- Sinonasal inflammatory polyp
- Neoplastic proliferation especially in the setting of inflammatory epithelial hyperplasia

Treatment and Prognosis

- Rhinosinusitis is a spectrum of diseases, and defining its various subtypes will alter management to include medical treatment (e.g., steroids, antibiotics) and surgery (e.g., functional endoscopic sinus surgery [FESS]).
- Management often involves combination of systemic and topical therapies, with surgery reserved for patients who fail medical therapy.
- FESS is among the most common surgeries performed for sinonasal disease refractory to maximal medical therapy.
- Optimal timing of FESS in treatment remains to be defined.
- Over the past decades, the average life expectancy for patients with cystic fibrosis has increased; with increasing survival and improved pulmonary management, otolaryngologists are now seeing increasing numbers of cystic fibrosis patients with chronic rhinosinusitis:

- For adult and pediatric cystic fibrosis patients with sinusitis, endoscopic sinus surgery yields clinical improvement measured primarily by sino-nasal symptoms and endoscopic findings.
- In general, sinusitis is not life threatening but depending on cause may result in ongoing and persistent morbidity.

SINONASAL INFLAMMATORY POLYPS (Figs. 2-7 through 2-12)

Definition: Non-neoplastic inflammatory swellings of the sinonasal mucosa.

Clinical

- No gender predilection; occur in all ages but are commonly seen in adults over 20 years of age and rarely seen in children less than 5 years of age:
- The exception to this age restriction occurs in patients with cystic fibrosis, who develop nasal polyps in the first and second decades of life.
- Most polyps arise from the lateral nasal wall or from the ethmoid recess; not infrequently, involvement of the nasal cavity and paranasal sinuses occurs:
 - Common occurrence along the lateral nasal wall probably relates to the fact that the normal physiologic parameters of lateral nasal cavity mucosa are such that prominent edema readily forms in the mucosal lamina propria.
- Polyps may be unilateral or bilateral, single or multiple.
- Symptoms include nasal obstruction, rhinorrhea, and headaches:
 - The triad of nasal polyps, asthma, and aspirin intolerance is well recognized and is referred to as Samter's triad.

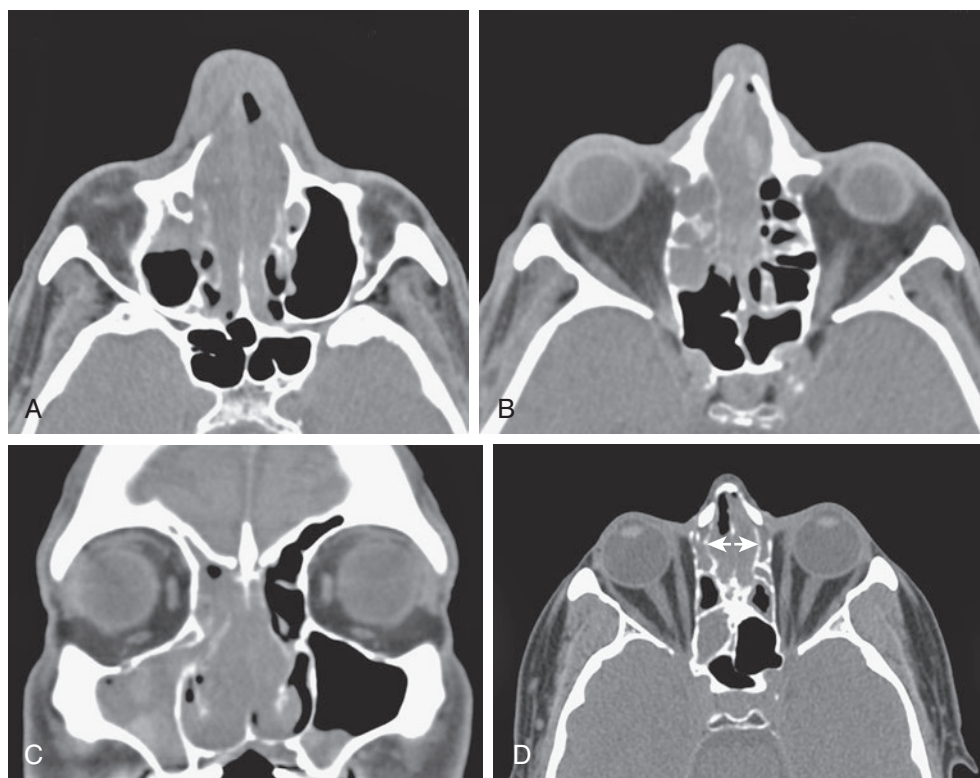
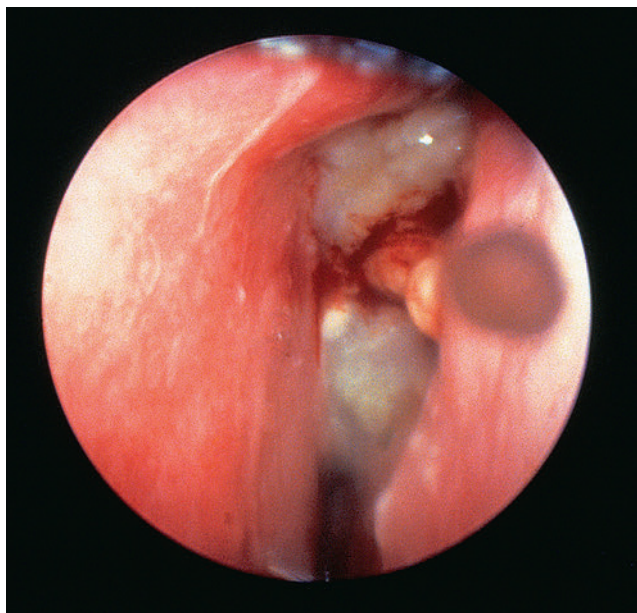


Fig. 2-7. Sinonasal inflammatory polyp.

Axial contrast-enhanced CT scans (**A, B**) and coronal CT scan (**C**) show bilateral nasal masses that have displaced the nasal bones anterolaterally and thinned part of the nasal septum. The upper nasal fossae are widened by the nasal masses, and the medial aspect of the each ethmoid complex has been displaced laterally. There are also inflammatory changes in the ethmoid, sphenoid, and maxillary sinuses. This patient had nasal polyposis and sinusitis. Axial CT scan (**D**) on another patient shows that nasal polyposis has widened the upper nasal cavity by pushing the medial ethmoid complex walls laterally (arrows). Inflammatory disease also is seen in the sphenoid sinuses in this patient with allergic sinusitis and polyposis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 199, Fig. 3-49.)

**Fig. 2-8.**

Endoscopic appearance of sinonasal inflammatory polyps appearing as multiple polypoid masses with a glistening mucoid appearance.

- Radiology:
 - Soft tissue densities, air-fluid levels, mucosal thickening, and opacification of the paranasal sinuses; when extensive, inflammatory polyps may expand and even destroy bone.
- Cause is linked to multiple factors, including allergy (atopy), infections, cystic fibrosis, diabetes mellitus, and aspirin intolerance.
- Mulberry turbinate is a clinical term that refers to swollen nasal turbinate tissue formed as a result of edema interspersed among the thick vessel walls of the prominent (essentially normal) turbinate vascularity; this appearance may clinically suggest a pathologic process such as a vascular malformation.

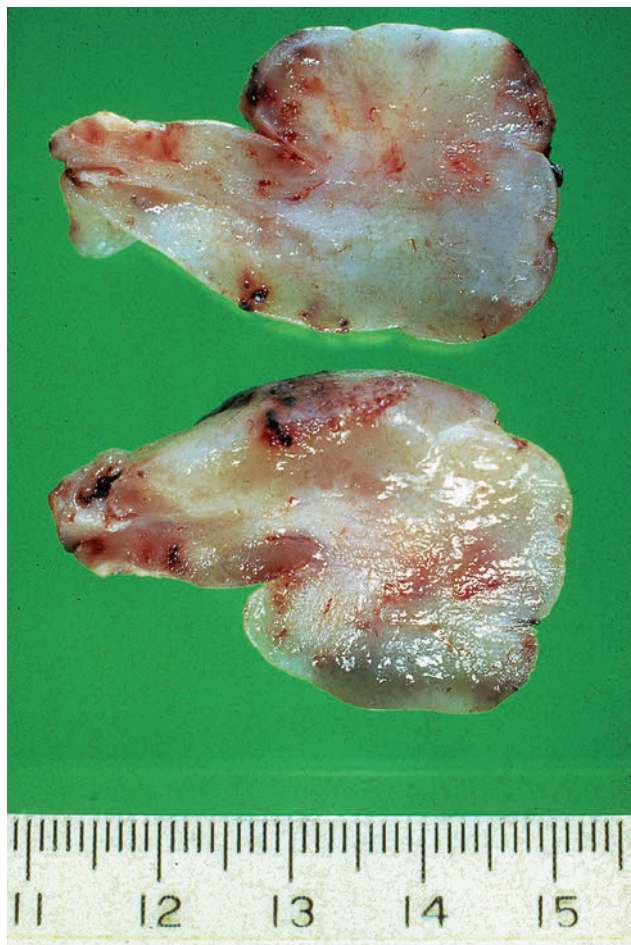
Pathology

Gross

- Sinonasal polyps are soft, fleshy, polypoid lesions with a myxoid or mucoid appearance.
- Polyps vary in size, ranging up to several centimeters in diameter.

Histology

- Surface epithelium is composed of intact respiratory epithelium but may show squamous metaplasia; the basement membrane may be thickened and eosinophilic in appearance.

**Fig. 2-9.**

Transected sinonasal inflammatory polyp appearing as tan-white, polypoid-shaped tissue with a shiny, myxoid/mucoid appearance.

- Stroma is markedly edematous and is noteworthy for the absence of seromucous glands; a mixed chronic inflammatory cell infiltrate is present and is predominantly composed of eosinophils, plasma cells, and lymphocytes; neutrophils may predominate in polyps of infectious origin.
- Stroma contains bland-appearing fibroblasts and small to medium-sized blood vessels.
- Secondary changes include surface ulceration, fibrosis, infarction, granulation tissue, deposition of an amyloid-like stroma, osseous and/or cartilaginous metaplasia, glandular hyperplasia, granuloma formation, and atypical stromal cells:
 - Granulomas result from ruptured mucous cysts, cholesterol granulomas, or as a reaction to medicinal intranasal injections (steroids) or inhalants.
- Occasionally small patches of stromal nonedematous collagen may be found scattered in a polyp that

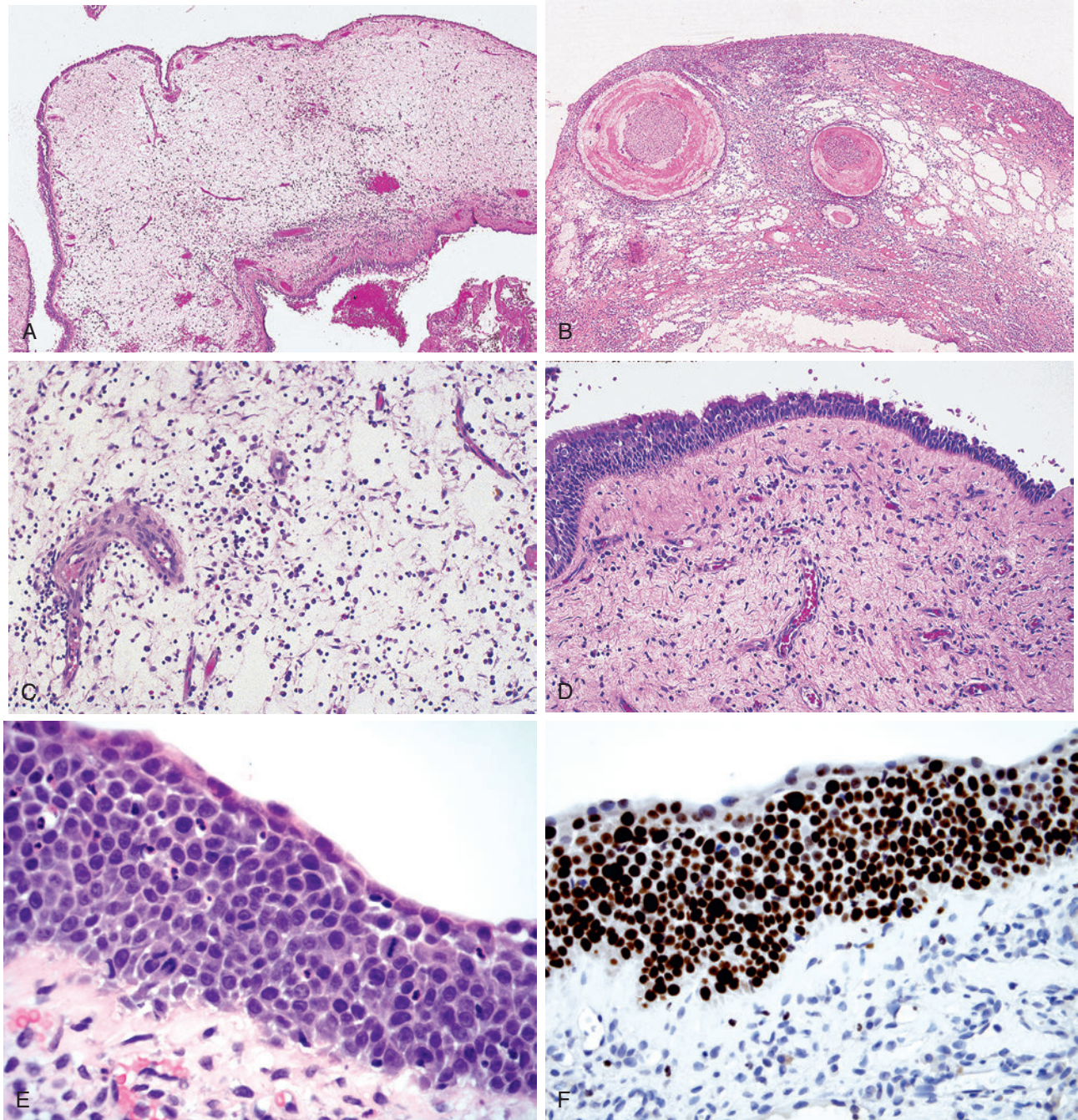


Fig. 2-10. Histologic features of sinonasal polyps.

A, Polypoid-appearing mass with intact surface (respiratory) epithelium with the underlying stroma characterized by edema, inflammatory infiltrate, and variable vascularity. **B**, Seromucous glands are typically absent but may be present and appear dilated (ecstatic), filled with mucinous material. **C**, The inflammatory infiltrate includes an admixture of lymphocytes, plasma cells, eosinophils, and neutrophils. **D**, Intact surface ciliated respiratory epithelium overlying an edematous stroma with associated chronic inflammation and thin-walled vascular spaces. **E**, In this patient's inflammatory polyp, an incidentally identified focus of high-grade intraepithelial dysplasia (i.e., carcinoma in situ) was focally identified. This is an extraordinarily rare occurrence. **F**, This focus of high-grade intraepithelial dysplasia shows increased proliferation rate by Ki67 staining throughout the epithelium. There was no immunoreactivity for p16 (not shown).

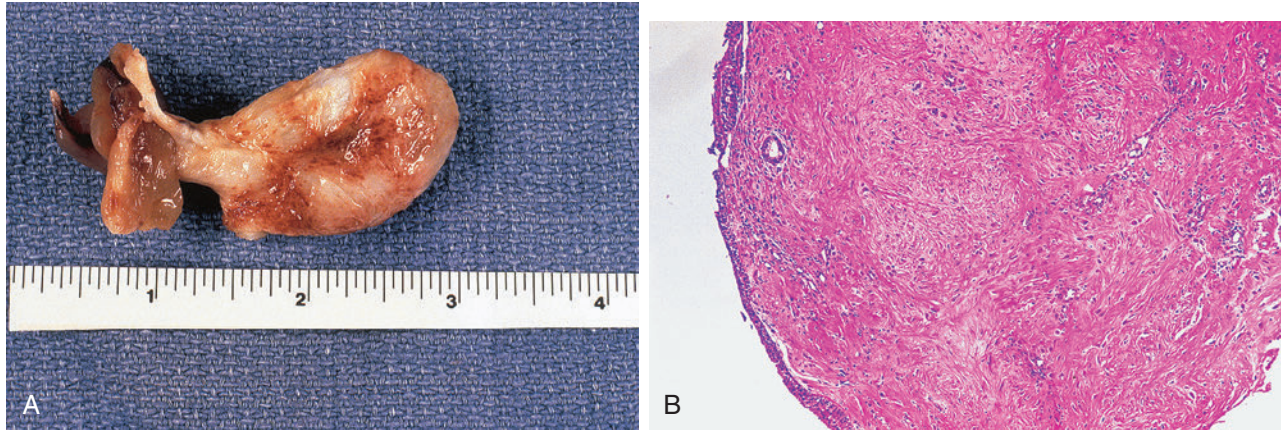


Fig. 2-11. Sinonasal inflammatory polyp.

A, Similar to the polyp depicted in Fig. 2-9, this polyp is pedunculated with a glistening appearance but had firmer consistency owing to increased fibrosis. **B**, Histologically, there is increased stromal fibrosis, a secondary (chronic) reactive alteration.

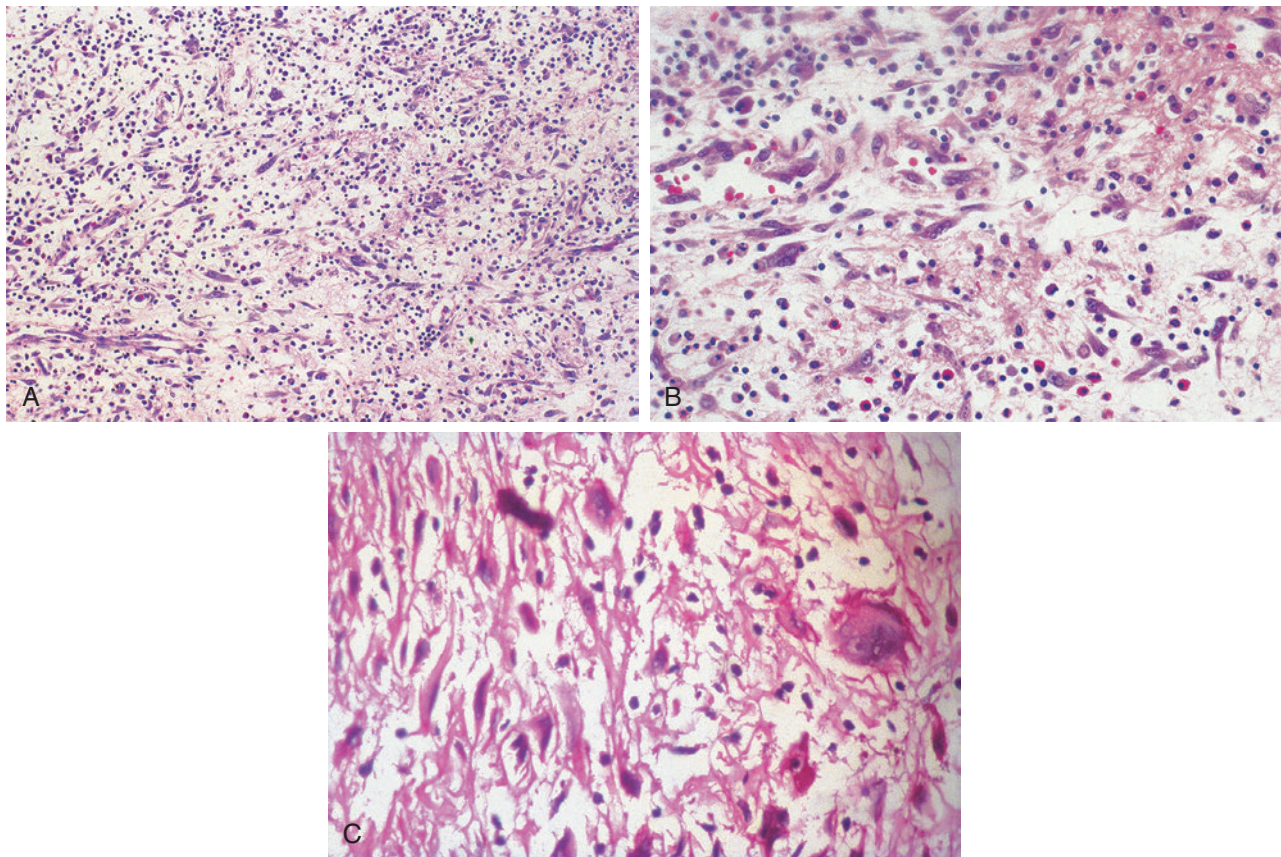


Fig. 2-12. Sinonasal inflammatory polyp with atypical stromal cells.

A, There is an increased number of inflammatory cells, including spindle-shaped and pleomorphic cells, which have been referred to as atypical stromal cells. **B**, The atypical stromal cells are myofibroblasts characterized by large vesicular-appearing nuclei with identifiable nucleoli and abundant cytoplasm with a basophilic and fibrillar appearance. **C**, In some examples the myofibroblasts can be disturbing in their appearance characterized by enlarged hyperchromatic nuclei raising concern for a malignant cellular infiltrate (e.g., rhabdomyoblasts); note the presence of ample amount of cytoplasm (low nuclear-to-cytoplasmic ratio) often seen in these cells and a feature that would support benignancy, albeit with atypical features.

may have inflammatory cells aggregated around its periphery, creating a “pseudogranuloma.”

- Stroma may have spaces containing a watery-appearing fluid and simulate the appearance of lymphatic spaces, which may suggest a diagnosis of lymphangioma; however, these spaces lack an endothelial cell lining.
- Atypical stromal cells (ASC) can be seen in sinonasal and antrochoanal polyps but tend to be more common in the latter:
 - ASC are bizarre-appearing cells with enlarged, pleomorphic, and hyperchromatic nuclei, indistinct to prominent nucleoli, and eosinophilic- to basophilic-appearing cytoplasm; typically, an ample amount of cytoplasm is present so that there is a low nuclear-to-cytoplasmic ratio, a feature usually associated with benignancy.
 - ASC tend to cluster near areas of tissue injury (e.g., near thrombosed vascular spaces).
 - ASC may be confused with malignant cells (e.g., rhabdomyoblasts), but their localization to limited areas of the lesion coupled with the absence of an increased nuclear-to-cytoplasmic ratio, increased mitoses, atypical mitoses, or cross-striations should preclude a diagnosis of malignancy.
 - ASC are of myofibroblastic origin and likely represent a component of wound healing.
 - Immunohistochemical staining of ASC may include reactivity for:
 - Vimentin, actins (smooth muscle and muscle specific), and cytokeratins; the presence of cytokeratin reactivity may result in the suggestion of a spindle cell squamous carcinoma (sarcomatoid carcinoma), but the overall histology points to an inflammatory polyp and not an epithelial malignancy.
 - No immunoreactivity for desmin, myoglobin, myogenin (myf4)
- Prominent vascular component, variably termed angiomatous or angioectatic nasal polyps, may clinically and histologically simulate a malignant tumor:
 - These lesions may undergo infarction or be associated with acellular eosinophilic material simulating amyloid deposition; Congo red staining is negative.
 - Papillary endothelial hyperplasia may be present.
- An extremely rare occurrence that may be seen in association with sinonasal inflammatory polyps (as well as in nonspecific chronic sinusitis) may be the presence of incidentally identified foci of intraepithelial high-grade dysplasia:
 - Such examples occur in the absence of invasive carcinoma.
 - Such examples are limited in extent, usually only focally identified in the resected tissue(s).

- Other than close clinical follow-up, there is no need for additional treatment if these foci of high-grade intraepithelial dysplasia are limited in extent.

Differential Diagnosis

- Infectious diseases (tuberculosis, sarcoid, others)
- Schneiderian papilloma:
 - May occur in the background of histologic changes of a sinonasal inflammatory polyp or, similar to sinonasal inflammatory polyps, may have marked stromal edema
 - Surface epithelial proliferation seen in association with Schneiderian papillomas is absent in inflammatory polyps.
- Nasopharyngeal angiofibroma (NPAF):
 - Histologic features including slit-like vessels lacking significant smooth muscle component and variably cellular fibrous stroma absent in sinonasal inflammatory polyps
- Sinonasal hamartomas (e.g., respiratory epithelial adenomatoid hamartoma, seromucinous hamartoma, others): see later in this section
- Heterotopic central nervous system tissue (HCNST) and acquired encephalocele:
 - Brain tissue in the setting of HCNST and acquired encephalocele may be histologically altered and/or associated with fibrotic tissue and may not readily be recognized as CNS tissue.
 - HCNST and acquired encephaloceles can be mistaken for inflammatory polyps.
 - Immunostains including GFAP may be required to assist in identifying CNS type tissue.
- Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)
- Squamous intraepithelial lesions (i.e., dysplasia, carcinoma in situ):
 - Rarely occurs as an isolated finding in the sinonasal tract in the absence of a coexisting invasive carcinoma
- Rhabdomyosarcoma (due to the presence of atypical stromal cells, which may be confused with rhabdomyoblasts; see Antrochoanal Polyp)
- Amyloidosis

Treatment and Prognosis

- Identification and treatment of possible etiologic factor(s) is the initial approach in the treatment of sinonasal polyps.
- Surgical excision includes polypectomy for nasal polyps and medial maxillectomy (Caldwell–Luc procedure) to include removal of the stalk for antrochoanal polyps.
- Approximately 50% of patients will have recurrence of their nasal polyps following surgery, recurrence

rates being highest in patients with aspirin intolerance and asthma.

- Development of functional endoscopic sinus surgery (FESS) has contributed to decreasing the morbidity of sinonasal surgery and the recurrence of nasal polypoidosis in patients with cystic fibrosis and in improving sinonasal-related symptomatology for patients with asthma.
- Sinonasal inflammatory polyps occurring in patients with cystic fibrosis may respond to medical therapy, but surgical resection may be required.
- Systemic steroid treatment effective in decreasing polyp size and in controlling mucosal inflammation:

- Steroid treatment results in decrease in nasal symptoms and polyp size.
- Systemic steroid treatment may also contribute to prevention of recurrence.

ANTROCHOANAL POLYP

(Figs. 2-13 through 2-16)

Definition: Clinically distinctive variant of sinonasal inflammatory polyp originating from within the maxillary sinus (medial wall area) and extending via a stalk through the ostium of the maxillary sinus into the nasal cavity; most of the growth occurs in the nasal cavity.

Synonym: Killian polyp

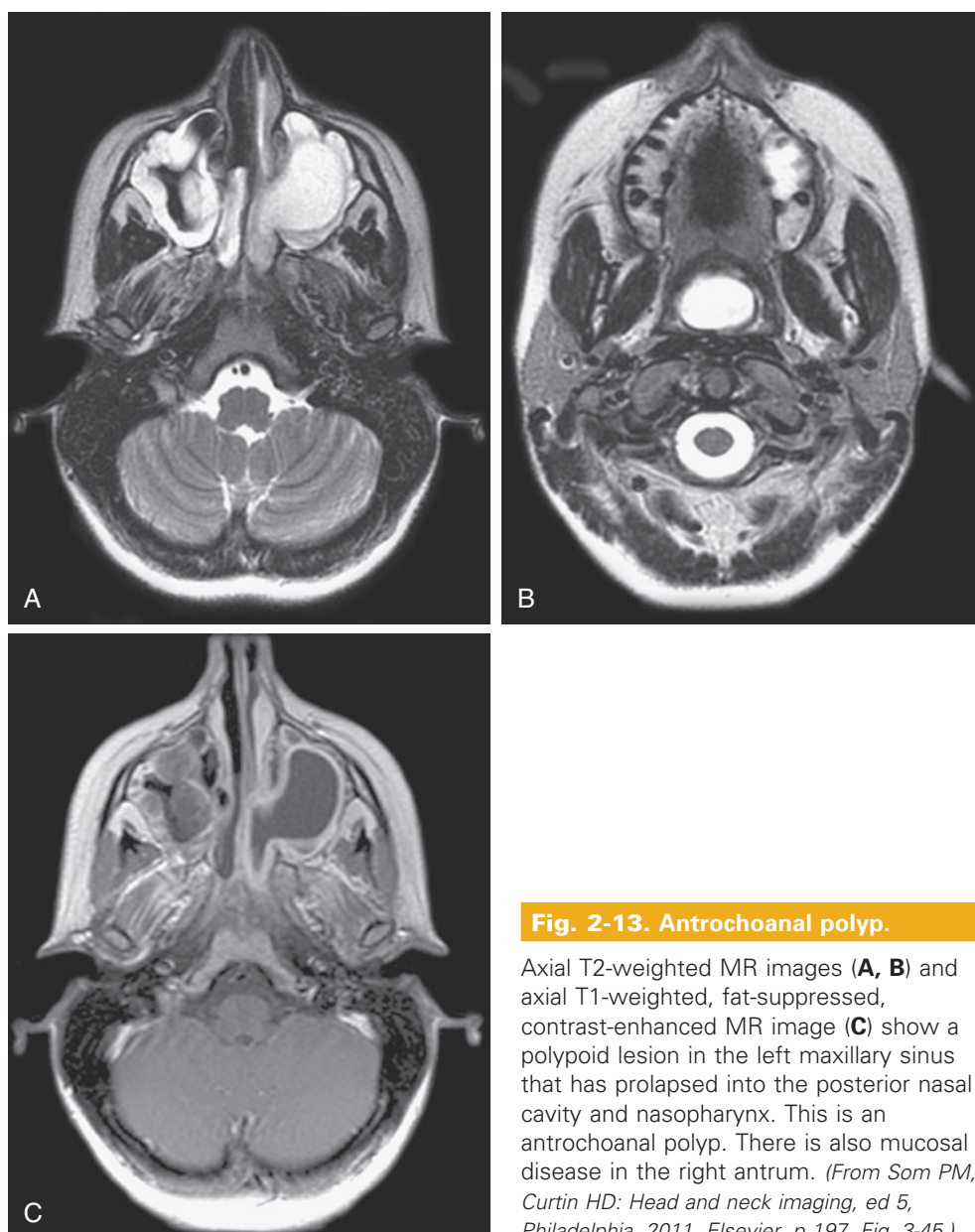


Fig. 2-13. Antrochoanal polyp.

Axial T2-weighted MR images (**A, B**) and axial T1-weighted, fat-suppressed, contrast-enhanced MR image (**C**) show a polypoid lesion in the left maxillary sinus that has prolapsed into the posterior nasal cavity and nasopharynx. This is an antrochoanal polyp. There is also mucosal disease in the right antrum. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 197, Fig. 3-45.)

**Fig. 2-14.**

Antrochoanal polyp appearing as polypoid mass of tan-pink tissue filling the nasal cavity grossly indistinguishable from other sinonasal polyps.

**Fig. 2-15.**

Resected antrochoanal polyp characterized by the presence of a pedicle generally absent from nonchoanal-derived sinonasal inflammatory polyps.

Clinical

- Represents approximately 3% to 6% of all sinonasal polyps
- More common in men than in women; tend to occur in patient populations that are younger (i.e., teenagers and young adults) as compared to patient population affected by nasal polyps
- Generally present as a single, unilateral polyp with nasal obstruction; however:
 - Posterior extension from the maxillary sinus toward the nasopharynx may result in obstruction of the nasopharynx and clinical suspicion of a primary nasopharyngeal tumor.
 - May extend (“hang”) into the oropharynx and be identifiable through the open mouth
- Often associated with bilateral maxillary sinusitis, and despite correlation in up to 40% of cases of associated allergies, the antrochoanal polyp is felt to be of an inflammatory cause.
- Antrochoanal polyps are often associated with bilateral maxillary sinusitis and may also be associated with more typical sinonasal polyps:

- Sphenchoanal polyps originate from the sphenoid sinus and extend through the sphenoid ostium, across the sphenothmoid recess, and into the choana (the boundary between the nasal cavity and nasopharynx):
 - Rarely, antrochoanal polyp may coexist with sphenchoanal polyp.
- In up to 40% of cases of antrochoanal polyps, there may be a documented history of allergies.
- Radiology:
 - Soft tissue density in the posterior choanal region or in the nasopharynx with clouding or opacification of the maxillary sinus

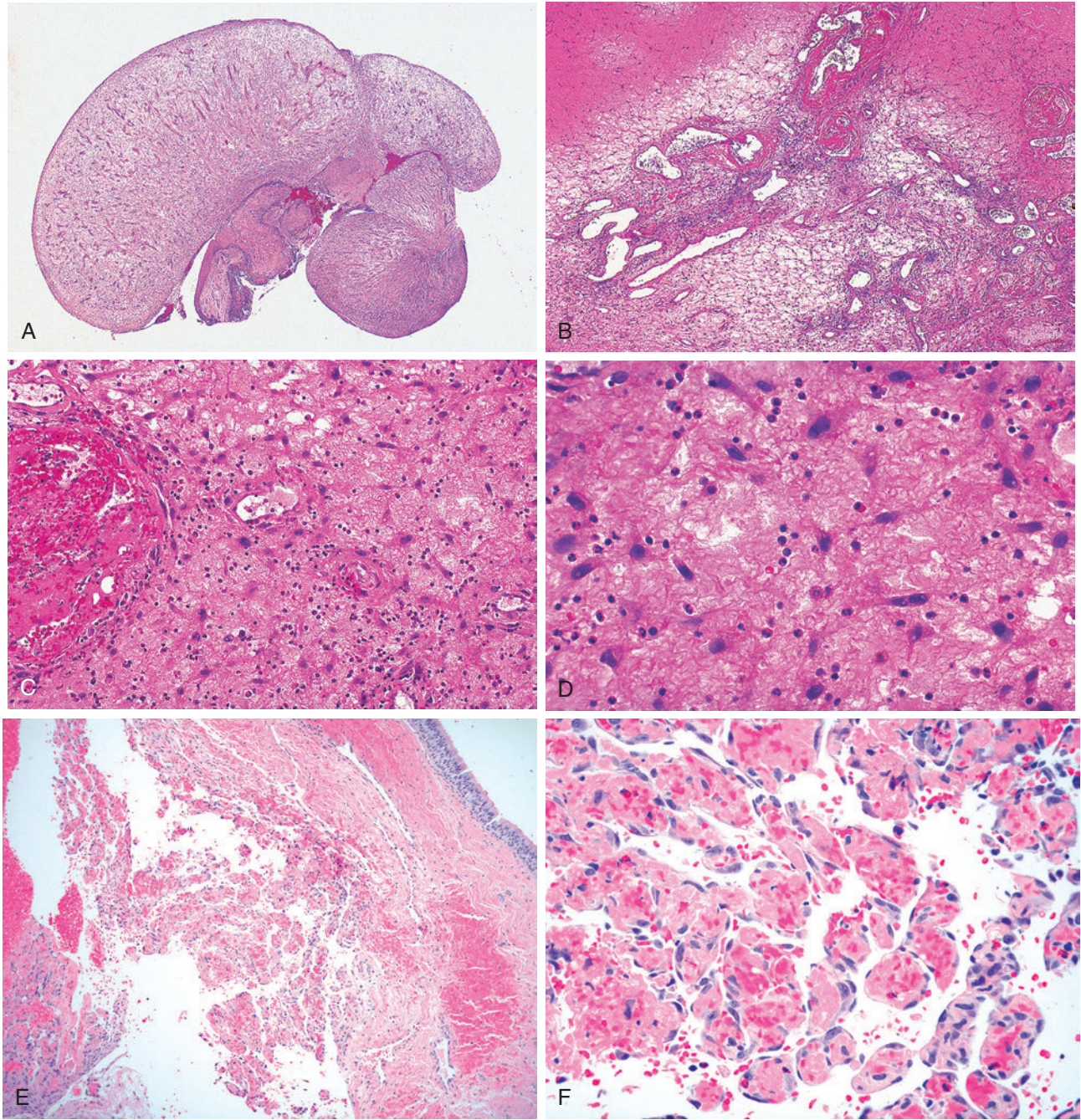
Pathology

Gross

- Identical to other nasal polyps except for the presence of a stalk with attachment to the maxillary sinus

Histology

- Similar to sinonasal polyps except for a relative lack of mucous glands and an eosinophilic inflammatory infiltrate
- Fibrotic stroma often present
- Because antrochoanal polyps extend via a stalk through the maxillary sinus ostium, a relatively small opening, these polyps often are subject to secondary changes resulting from chronic or subacute vascular compromise, including:
 - Presence of atypical stromal cells identical (in distribution and appearance) to those seen in sinonasal inflammatory polyps (see above)
 - Vascular thrombosis often is present:
 - Atypical stromal cells often cluster around thrombosed blood vessels.
 - Infarction, partial or complete:
 - Hemorrhage in the setting of infarction may be minimal or extensive.
 - Presence of hemorrhage and reactive changes may result in bone erosion of the lateral nasal cavity-medial maxillary sinus wall, which can be extensive.
 - Radiographic features of this process may raise the clinical concern for a malignant neoplasm.
 - Histologically, due to the presence of reactive changes, which may include extensive neovascularization, characterized by multiple, variably dilated vascular channels, confusion with a vascular neoplasm may arise; the presence of prominent neovascularization may be referred to or diagnosed as (pseudo)angiomatic polyp.
 - Papillary endothelial hyperplasia may occur in this setting in conjunction with organizing thrombus.

**Fig. 2-16.**

Antrochoanal polyp, owing to torsion in its passage through the antrum, often has associated reactive and degenerative changes. **A**, Polypoid mass with surface ulceration and associated granulation tissue-like reaction in the submucosa; there is squamous metaplasia of the surface epithelium along the lower portion of the image. **B**, Edema, hemorrhage, and vascular thrombosis may be present; although not shown, necrosis may be part of this histologic picture. **C**, Atypical stromal cells (i.e., myofibroblasts) tend to cluster in areas of injury as is seen here near to a thrombosed vascular space. **D**, Despite their atypical appearance, including hyperchromatic nuclei, myofibroblasts have a low nuclear-to-cytoplasmic ratio, have a fibrillar-appearing cytoplasm, are elongated with axonal-like extensions, and lack atypical mitoses. **E** and **F**, Reactive changes in antrochoanal (and other) polyps may also include papillary endothelial hyperplasia, which may suggest the presence of a vascular neoplasm.

Differential Diagnosis

- Nasopharyngeal angiofibroma
- Vascular proliferation/neoplasm:
 - Hemangioma
 - Angiosarcoma

Treatment and Prognosis

- Cured following complete surgical excision
 - Endoscopic approach for complete removal considered safe and effective procedure
 - A focus on the detection of the exact origin and the extent of the polyp considered key to prevent recurrence
- May recur if the polyp including the stalk is incompletely excised:
 - High recurrence rate also occurs in antrochoanal polyps, especially in patients with a history of allergies.
 - Endoscopic removal may result in a higher recurrence rate.
 - Surgical removal of the polyp with its stalk markedly decreases the likelihood of recurrence.
 - To prevent incomplete excision and recurrences, combined approaches (functional endoscopic sinus surgery and mini-Caldwell) have been advocated.

PARANASAL SINUS MUCOCELE

(Figs. 2-17 through 2-20)

Definition: A distinct clinicopathologic entity in which there is expansion of a sinus cavity due to obstruction of the outflow tract (ostium or duct) resulting in a cystic lesion of the paranasal sinus, in which the epithelium continuously produces mucus causing expansion of the bony walls of the sinus or air cell cavity.

NOTE: The diagnosis of a paranasal sinus mucocoele is a correlation between clinical, radiographic, and pathologic findings; diagnosis of a paranasal sinus mucocoele by histopathology alone may be extremely difficult given the nonspecific histologic features with the lining of (paranasal sinus) mucocoeles being the same as that of the normal paranasal sinus or the lining associated with nonspecific sinusitis. The expansion of the bony walls of the sinus is a *sine qua non* for paranasal sinus mucocoele.

Clinical

- No gender predilection; may occur in all age groups
- Occur most commonly in the frontal and ethmoid sinuses (>90%):
 - The fronto-nasal duct is relatively long and narrow and thus can relatively easily be obstructed, especially following surgery to this region.

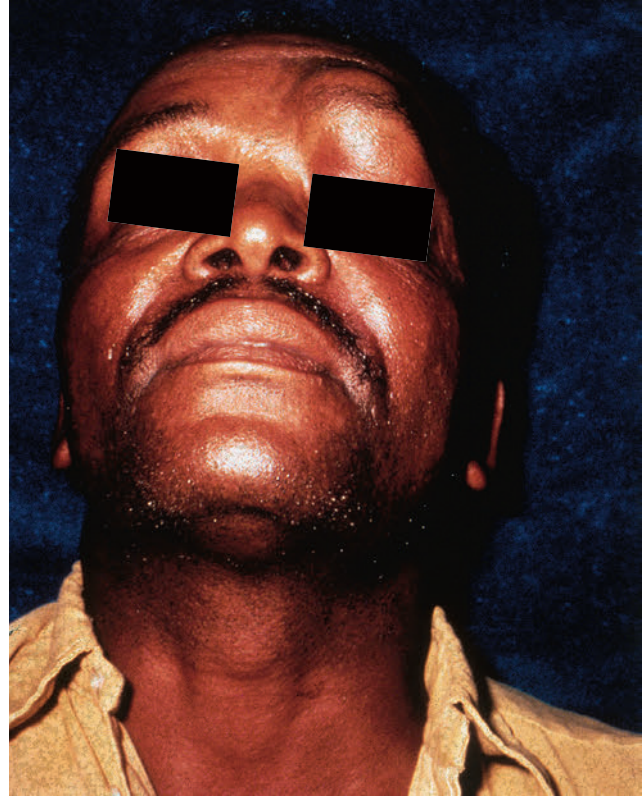
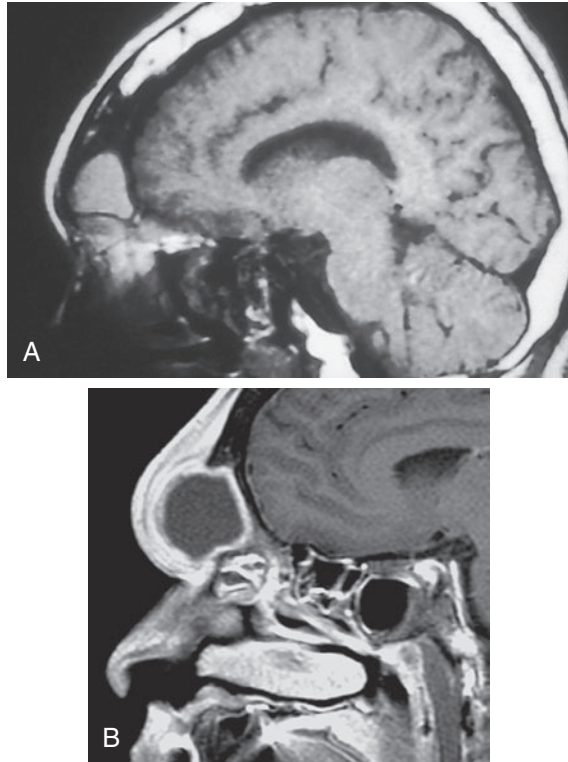
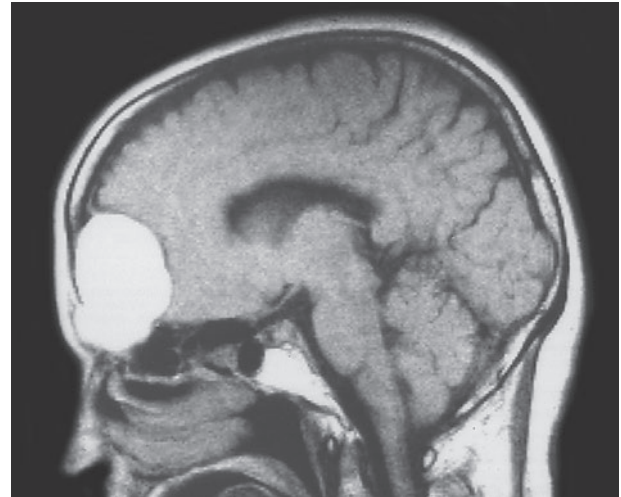


Fig. 2-17. Supraorbital swelling and enophthalmos caused by a large mucocoele.

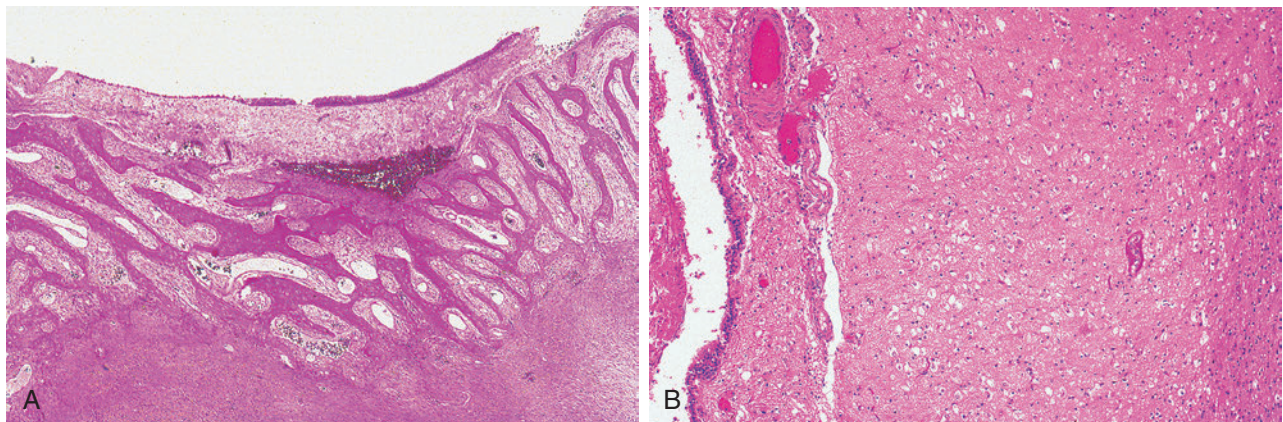
- The maxillary sinus may be involved but is uncommon (5% to 10%).
- Sphenoid sinus involvement occurs but is considered rare.
- Symptoms depend on the site of involvement as well as the direction and extent of expansion, and include pain, facial swelling or deformity, proptosis, enophthalmos, visual disturbances (e.g., diplopia, loss of vision, sudden blindness), optic neuropathy, rhinorrhea, nasal obstruction:
 - Overall this is a chronic process with signs and symptoms occurring over time rather than an acute process.
- Two types of mucocoeles are identified:
 - **Internal:** herniation of the cyst into submucosal tissue adjacent to the bony wall of the sinus
 - **External:** herniation of the cyst through the bony wall of the sinus with extension into subcutaneous tissue or into the cranial cavity
- Expansion of a mucocoele is in the direction of least resistance.
- Clinical picture may be mistaken for a neoplasm.
- Radiology:
 - Opacification of the involved sinus; with time there is increase in pressure resulting in:

**Fig. 2-18.**

Sagittal T1-weighted MR image (**A**) scan shows an expansile frontal sinus mass with an intermediate signal intensity. This mass had a high T2-weighted signal intensity. This patient had a frontal sinus mucocoele. Sagittal T1-weighted contrast enhanced MR image (**B**) shows uniform mucosal enhancement surrounding the secretions within an expanded frontal sinus. This patient had a frontal sinus mucocoele. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 207, Fig. 3-70.)

**Fig. 2-19.**

Sagittal T1-weighted MR image shows an expansile frontal sinus mass with high signal intensity. The mass has extended down into the medial orbit and back into the anterior cranial fossa. The mass also had a high T2-weighted signal intensity. This patient had a frontal mucocoele. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 208, Fig. 3-71.)

**Fig. 2-20.**

A, Internal mucocoele with herniation of the cyst lined by a respiratory epithelium into submucosal tissue adjacent to the bony wall of the sinus. **B**, External mucocoele with herniation of the cyst lined by a respiratory epithelium through the bony wall of the sinus with extension into the cranial cavity and identification of central nervous system tissue (identified in the majority of the image).

- Erosion and/or destruction of the sinus walls with loss of the typical scalloped outline along the mucoperiosteum
- Abnormal radiolucency due to loss of bone
- Sclerosis of adjacent bone
- The cavity manifests a smoothly contoured expanded wall with reactive bony thickening.
- Based on the strikingly rounded appearance and presence of homogeneous mucoid contents, the radiographic picture can be highly characteristic.
- Irrespective of the sinus involved, the pathogenesis of mucocoeles are thought to occur as a result of an increase in pressure within a given sinus secondary to blockage of the sinus outlet (ostium), most often the result of an inflammatory or allergic process:
 - Additional factors implicated in the development of a mucocoele include trauma, postsurgical or a neoplasm.

Pathology

Gross

- Cysts filled with thick mucoid or gelatinous secretions
- Contents are sterile.
- Cases complicated by infection (pyocoele) are filled with a purulent exudate.

Histology

NOTE: The histologic findings are usually nonspecific, and if one is not aware of this entity and/or the clinical-radiographic findings, then a descriptive diagnosis of essentially normal and/or reactive tissues may be preferred.

- Cysts lined by a flattened pseudostratified ciliated columnar epithelium:
 - In long-standing cases the cyst epithelium may demonstrate squamous metaplasia, but metaplastic changes are uncommon.
- Reactive bone formation can be seen lying in proximity or deep to the epithelial-lined cyst.
- A variable amount of inflammatory cells may be present.
- Additional reactive changes may include fibrosis, granulation tissue, hemorrhage, and cholesterol granuloma formation.

Differential Diagnosis

- Mucous retention cyst

Treatment and Prognosis

- Prognosis is excellent after complete surgical excision:
 - With the introduction of endoscopic sinus surgical instruments and techniques, there has been a

trend toward transnasal endoscopic management of sinus mucocoeles.

- Increasing evidence shows that endoscopic management of sinus mucocoeles results in long-term control with near zero recurrence rates.
- Complications include:
 - Superimposed infection (pyocoele)
 - Meningitis
 - Brain abscess

HETEROTOPIC CENTRAL NERVOUS SYSTEM TISSUE (HCNST) (Figs. 2-21 through 2-24)

Definition: Congenital (often midline) developmental, non-neoplastic displacement of neuroglial tissue in extracranial sites without connection to the cranial cavity.

Synonyms: Nasal glioma; glial heterotopia

NOTE: HCNST is non-neoplastic and therefore the term *glioma* is a misnomer.

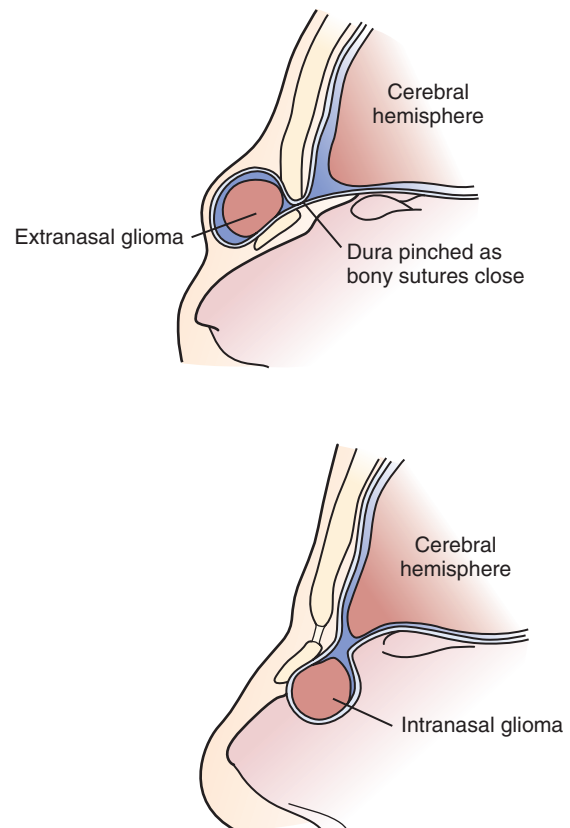


Fig. 2-21.

Schematic of the origin of (A) extranasal gliomas and (B) nasal gliomas. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 34, Fig. 1-26.)

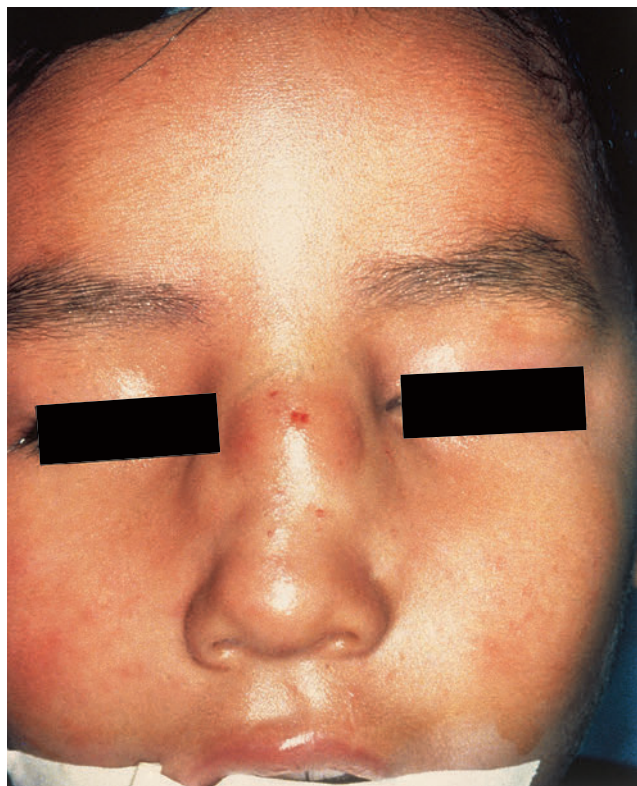


Fig. 2-22.

Extranasal heterotopic central nervous system tissue manifesting as a subcutaneous mass along the bridge of the nose.

Clinical

- Occurs in approximately one of 4000 births
- No gender predilection; generally presents at birth or within the first few years of life; however, may affect any age group
- Most commonly occurs in and around the nasal cavity, usually associated with the septum:
 - A midline location with swelling in the nasal bridge area is common.
 - Lesion is usually not strictly midline but may occur more laterally (paramidline), toward or near the inner canthus of the eye.
 - Other sites of involvement include the ethmoid sinus, palate, middle ear, tonsil, and pharyngeal area.
- No evidence of familial predisposition
- Extranasal lesions:
 - Most common, making up approximately 60% of cases
 - Present as a subcutaneous blue or red mass along the bridge of the nose; the skin overlying the swelling or mass may be slightly erythematous.

- Intranasal lesions:
 - Represent approximately 30% of cases
 - Present with obstruction and/or septal deviation
 - Clinically confused with nasal polyps
 - Nasal attachment occurs high within the nasal vault along the lateral wall of the nasal fossa or middle turbinate.
- Mixed extra- and intranasal:
 - Represents approximately 10% of cases
 - Communication occurs through a defect in the nasal bone.
- Negative Furstenberg test (swelling or pulsating lesion following pressure on the ipsilateral jugular vein; typically positive in an encephalocele)
- HCNST most often occurs sporadically but rarely may occur with other congenital abnormalities, including dermal sinus or overlying tuft of hair.
- Radiology:
 - Radiographic studies are indicated to rule out a bony defect that may identify communication to the cranial cavity (encephalocele).
- Prior to biopsy of a lesion in the superior portion of the nasal cavity or base of the nose, detailed clinical and radiographic evaluation of possible continuity with the central nervous system (CNS) is indicated; CNS involvement may be clinically apparent by evidence of meningitis, cerebrospinal fluid rhinorrhea, and anosmia.

Pathology

Gross

- Firm, smooth mass measuring from 1 to 3 cm in diameter appearing gray to yellow and often streaked with white bands
- Rarely described or recognized as brain tissue

Histology

- Composed of astrocytes and neuroglial fibers associated with a fibrous, vascularized connective tissue:
 - Cells in the glial tissue may resemble plump fibroblasts.
- May identify multinucleated or gemistocytic astrocytes
- Neurons are usually absent but may be sparse to few in numbers.
- In long-standing clinically undetected cases, a fibrous stroma may predominate and obscure the astrocytes and neuroglial fibers:
 - In this setting a finely fibrillary glial-type matrix may not be readily apparent.
 - Due to the presence of thick fibrous septa within the lesion and obscuring of neuroglial tissue the entire lesion may be considered as a fibrous proliferation.
 - Fibrous bands tend to circumscribe nodules of the glial tissue resulting in a lobular architecture.

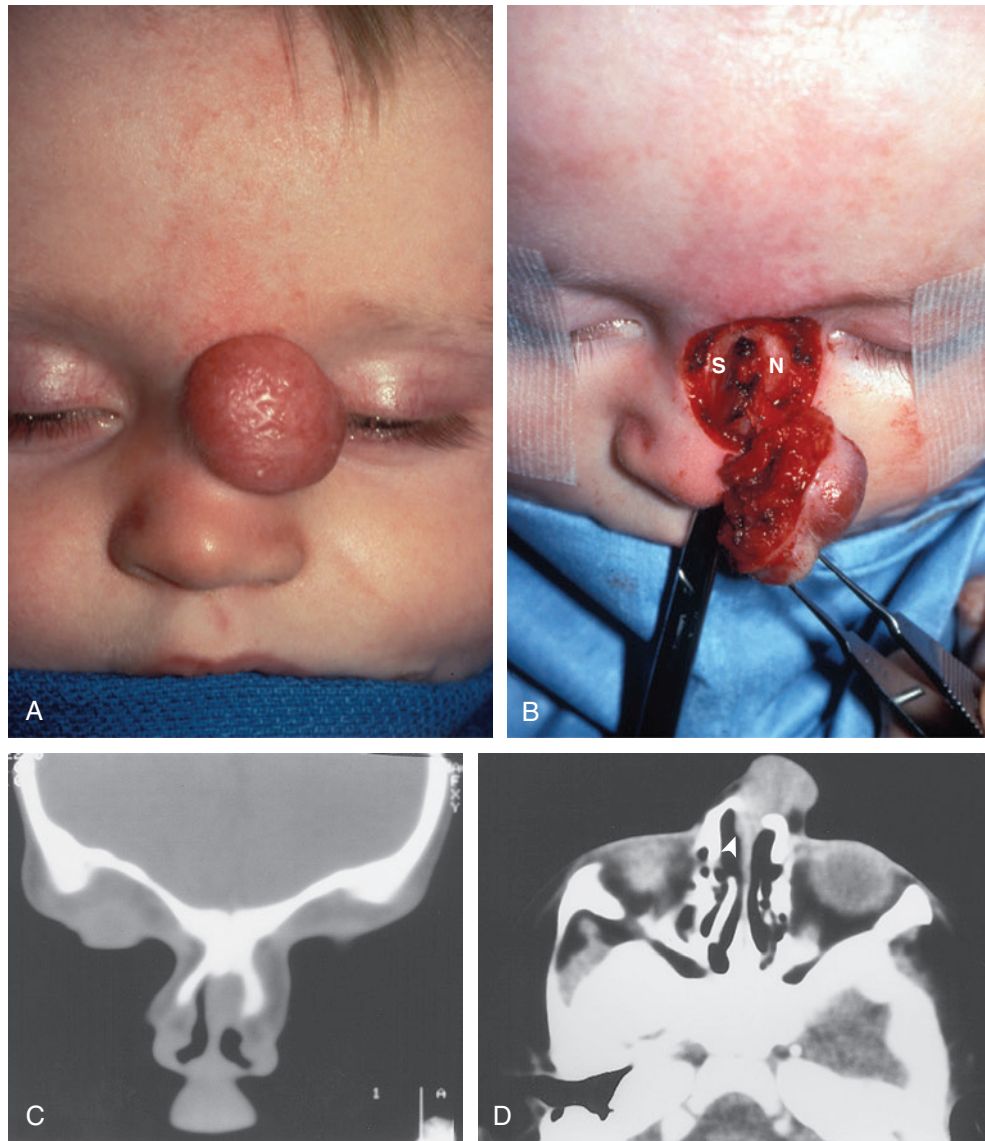


Fig. 2-23. Mixed extranasal-intranasal glioma in a 6-month-old boy.

A, The globular mass overlies the dorsum of the nose on the left. **B**, At surgery the lesion was found to have extended through the left nasal bones, bowed the septum (*S*) rightward, and bowed the residual left nasal bones (*N*) leftward. It was attached by a pedicle to the foramen cecum. **C** and **D**, Coronal and axial CT scans show that the mass extends through the resultant defect into the thickened nasal septum (*white arrowhead* in **D**). The crista galli and brain were normal. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 45, Fig. 1-40.)

- Immunohistochemistry:
 - Astrocytes are immunoreactive with glial fibrillary acidic protein (GFAP) and S-100 protein but are negative for cytokeratins and epithelial membrane antigen.

Differential Diagnosis

- Encephalocele (congenital or acquired):
 - Some consider HCNST to represent a variant of encephalocele in which the communication to the

central nervous system has closed, remains undetected, or has become fibrotic.

- Distinction from an encephalocele is important but may be difficult (see below):
 - The lobular architecture formed by circumscribing fibrous septa is more characteristic of the HCNST.
 - The presence of neurons would be more in favor of an encephalocele, but the absence of neurons does not exclude an encephalocele.

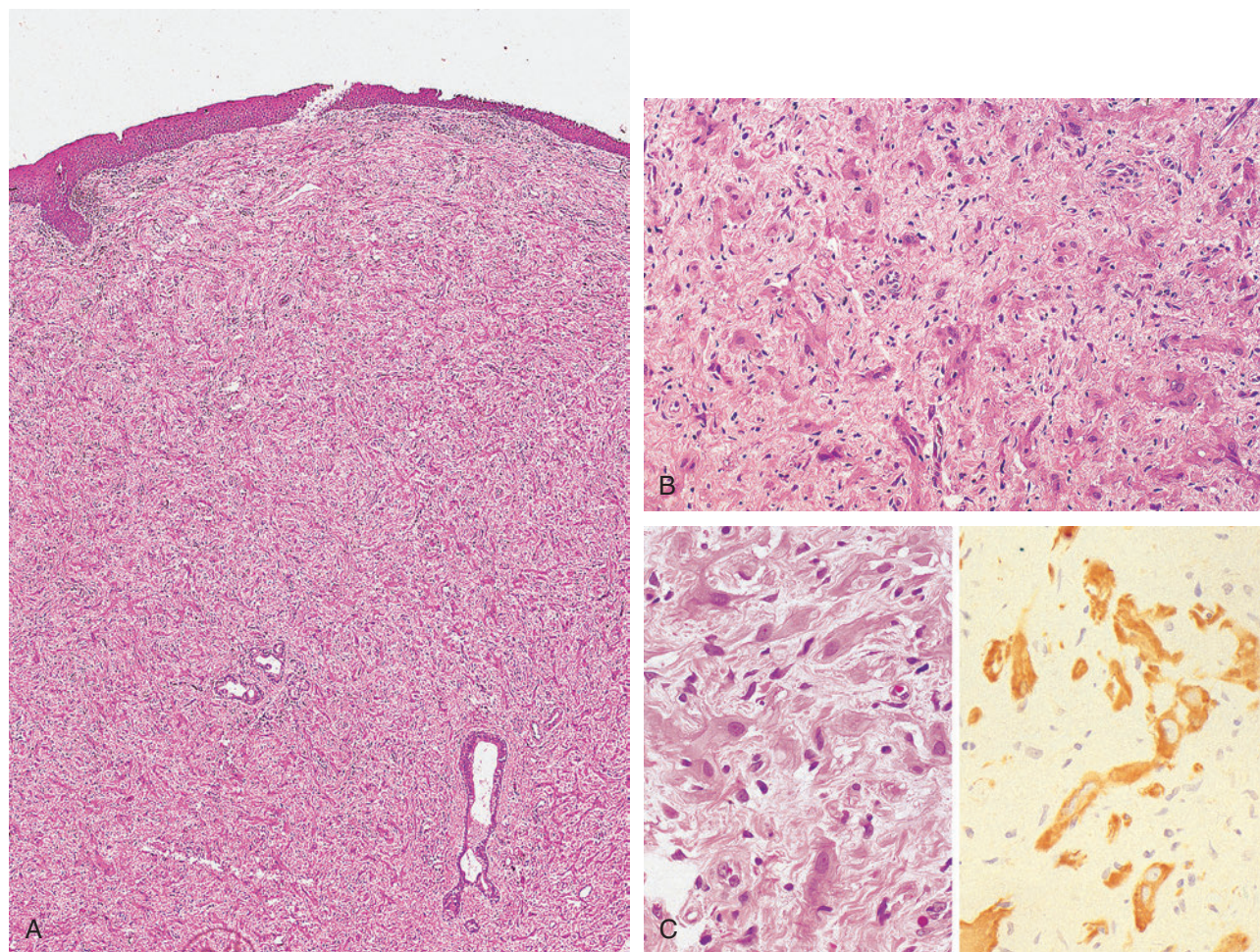


Fig. 2-24. Heterotopic central nervous system tissue.

A, Polypoid-appearing lesion with intact surface squamous epithelium and submucosal cellular proliferation that (**B**) at higher magnification is composed of astrocytes and neuroglial fibers associated with a fibrous and vascularized connective tissue; although not illustrated, the presence of a dense fibrous stroma may obscure the CNS tissue causing the diagnosis of HCNST to be overlooked. **C**, *Left*, irregularly shaped neuroglial cells composed of round to oval nuclei, eosinophilic nucleoli, and abundant granular-appearing cytoplasm; *right*, confirmation of neuroglial origin can be seen by the presence of glial fibrillary acidic protein (GFAP) immunoreactivity.

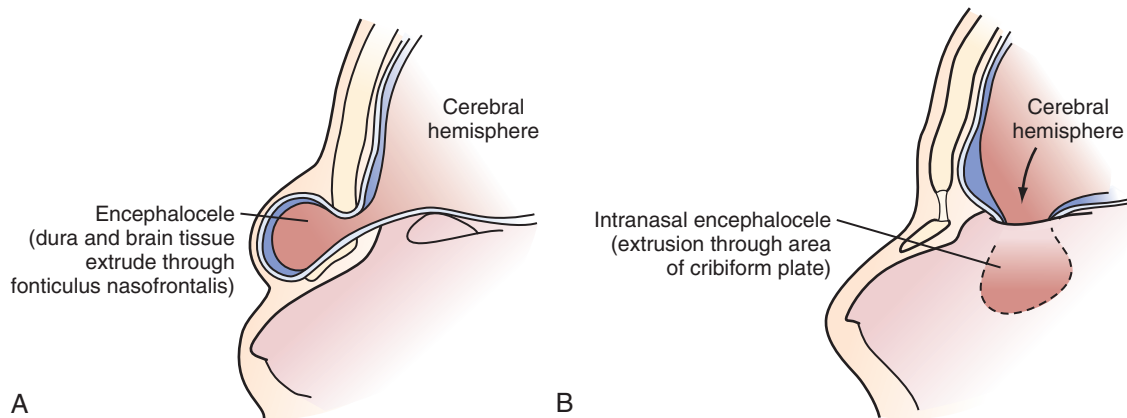
- In general, encephaloceles are composed of tissue that is more like brain.
- Sinonasal inflammatory polyps
- Teratoma
- Benign peripheral nerve sheath tumor (e.g., neurofibroma)
- Olfactory neuroblastoma
- Presence of gemistocytic astrocytes in the lesion may cause consideration for a malignant lesion.

Treatment and Prognosis

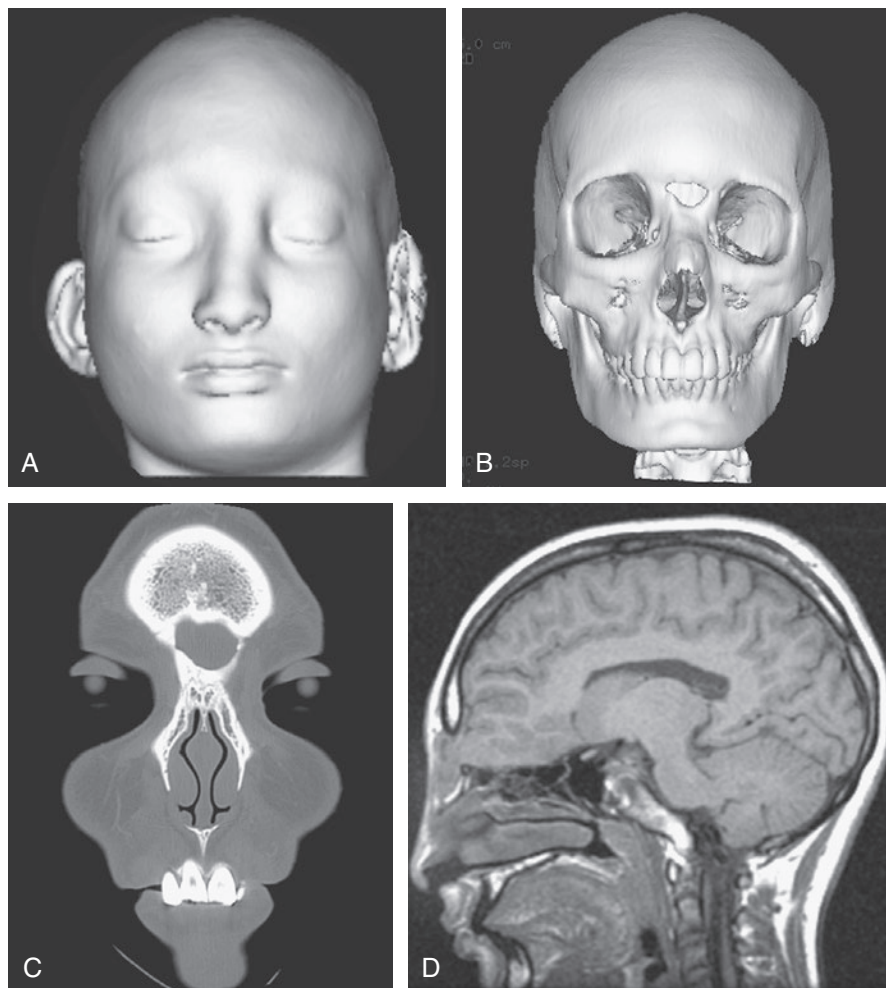
- Surgery is the preferred treatment and results in the cure of the patient:
 - HCNST does not regress and therefore requires management (i.e., surgery).
- 10% recurrence or persistence rate following incomplete excision
- Preoperative assessment for CSF communication is indicated and, if present (i.e., an encephalocele), communication with the CNS necessitates surgical repair.
- Prognosis is excellent.

SINONASAL ENCEPHALOCELE (Figs. 2-25 through 2-27)

Definition: Herniation of brain tissue beyond the confines of the cranial cavity
Synonym: Cephalocele

**Fig. 2-25.**

Schematic of the origin of **(A)** extranasal (glabellar) cephaloceles and **(B)** intranasal transtethmoidal cephaloceles. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 33, Fig. 1-25.)

**Fig. 2-26. Sincipital cephalocele, interfrontal type.**

Three-dimensional CT of the skin surface **(A)** and the bone **(B)** in a 9-year-old girl shows minimal swelling above the glabella with midline cranium bifidum and concavity of the external surface of the frontonasal suture. **C**, Direct coronal CT documents that the sharply margined defect lies superior to the nasofrontal suture, between the two frontal bones. **D**, Sagittal T1-weighted MR image shows fullness at the glabella and herniation of intracranial content through the cranial defect above and external to the nasal bones and nasal capsule. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 48, Fig. 1-42.)

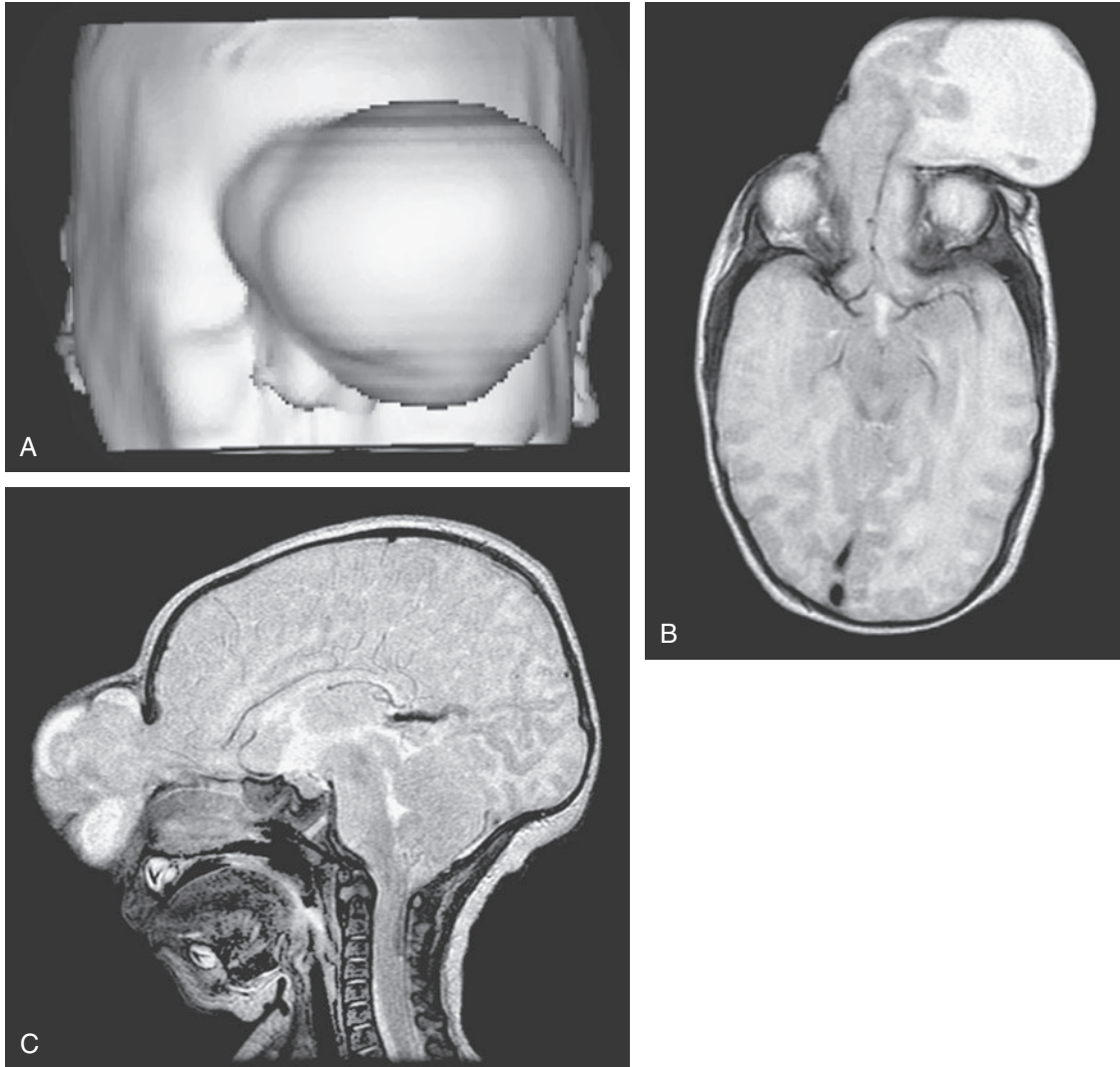


Fig. 2-27. Frontonasal form of frontoethmoidal cephalocele.

A, Three-dimensional CT of the skin surface. The asymmetric glabellar mass obscures the left orbit and projects over the bony and cartilaginous nose. T2-weighted MR images in the axial (**B**) and sagittal (**C**) planes demonstrate hypertelorism, anterior herniation of both frontal lobes into the cephalocele through a defect between the frontal bones and the nasal bones, and asymmetric distension of the sac by CSF. The medial frontal anatomy is distorted by the herniation. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 50, Fig. 1-46.)

Terms:

- Sincipital encephalocele refers to an encephalocele situated in the anterior part of the skull and includes:
 - Interfrontal (cranial defect lies between the two frontal bones)
 - Frontoethmoidal:
 - Nasofrontal
 - Nasoethmoidal
 - Naso-orbital
- Occipital encephaloceles include:
 - Cervico-occipital
 - Low occipital involving the foramen magnum
 - High occipital above the intact rim of the foramen magnum
- Basal encephaloceles may be categorized depending on their point of passage through the skull and the area to where they extend:
- Midline basal encephaloceles include:
 - Transsphenoidal type
 - Sphenoethmoidal type
 - Transethmoidal type
- Lateral basal encephaloceles include:
 - Sphenorbital and sphenomaxillary types

Clinical

- May be classified as congenital (developmental skull defect) or an acquired lesion:
 - Almost all encephaloceles appear to occur sporadically and are not associated with any genetic syndrome(s).
- Prevalence of congenital encephaloceles varies in different parts of the world from about 0.8 to 4 per 10,000 live births.
- More common in Asia than in the western hemisphere
- Ratio of sincipital to occipital lesions varies geographically:
 - Sincipital encephaloceles are about nine times more frequent than occipital ones in Southeast Asia.
 - In Europe and North America the occipital lesions are more common than sincipital ones.
 - Basal encephaloceles are rare (2% to 10% of cases) in all geographic regions.
- Sincipital congenital encephaloceles:
 - Usually form a visible midline or paramidline mass in the region of the bridge (root) of the nose and glabella and are almost always evident at birth
 - Tend to be larger than HCNST
 - Tend to be more compressible than HCNST
 - May be associated with hypertelorism
- Basal encephaloceles:
 - Do not produce a visible facial mass
 - Most involve the midface and may appear as a mass lesion in nasal cavity, nasopharynx, the posterior orbital region, or the sphenomaxillary fossa.
 - May not be evident during infancy and may not present until the patient is significantly older, accounting for a “second peak” of encephalocele incidence around the age of 5 to 10 years
 - Likely the lesions slowly enlarge and thus tend to eventually become more symptomatic.
 - May be clinically mistaken for an inflammatory nasal polyp
- Incidence of acquired sinonasal encephaloceles is unknown:
 - Tend to occur in adults
 - Generally occur as a postsurgical complication
 - May be misdiagnosed as “heterotopias,” and their true nature and genesis goes unrecognized.
 - Some probably related to head trauma other than surgery
 - The cause of some acquired encephaloceles is unclear.
- Radiographic assessment is an important component in the evaluation of these lesions and for detecting evidence of the connection to the central nervous system.

- Embryogenesis:
 - Occipital encephaloceles may be associated with other neural tube closure defects, such as myelomeningocele; associated anomalies may include cleft lip, cleft palate, nasal tip malformation, ocular abnormalities, craniosynostosis.
 - Sincipital encephaloceles are not linked with neural tube defects.
 - Basal encephaloceles may be associated with other anomalies, mostly of the midface, including cleft lip and cleft palate.

Pathology

Gross

- Firm, solid, and tan- to pink-appearing tissue surrounded by a pseudocapsule; small spaces or cystic areas may be identified.

Histology

- Histology is that of normal brain tissue, including neurons; however, due to nutritional impairment of the herniated brain tissue, degenerative and/or reactive changes may be present including gliosis and loss of neurons.
- Vascular congestion or hemorrhage may be present.

Differential Diagnosis

- Heterotopic central nervous system tissue
- CNS neoplasm:
 - Possibility of a neoplasm such as a low-grade astrocytoma may arise.
 - Primary intracranial neoplasm presenting in the sinonasal tract without obvious intracranial origin and extension into the sinonasal tract is highly unlikely.

Treatment and Prognosis

- Treatment for congenital sincipital-basal encephaloceles is surgical (transcranial) resection:
 - In the presence of gross hypertelorism, orbital translocation may be required.
 - Normal development in approximately 60% of cases
- Treatment for acquired encephaloceles is surgery:
 - Repair of a CNS leak may be required.
 - Prevention of meningitis is paramount.
 - Prognosis is very good.

NASAL DERMOID SINUS AND CYST (Figs. 2-28 and 2-29)

Definition: Nasal dermoid cysts are a congenital developmental lesion that are virtually identical to dermoid cysts found in other anatomic locations.

Synonym: Craniofacial dermoids

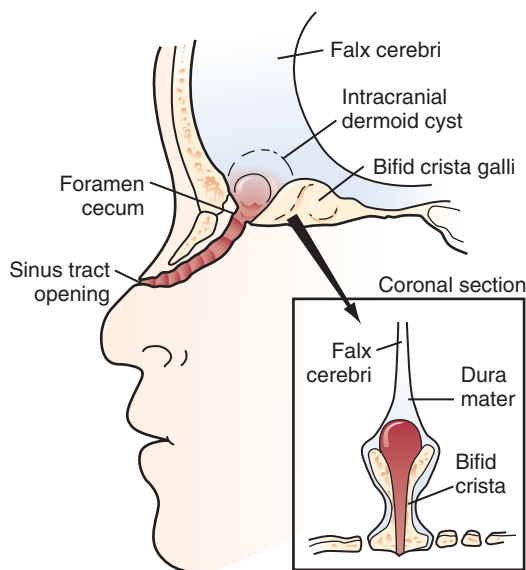
**Fig. 2-28.**

Diagram of a typical nasal dermal sinus and cyst traversing the prenasal space and the enlarged foramen cecum to form a mass anterior to and within a groove in the anterior concavity of the crista galli. *Inset:* The anatomic relationships of the leaves of the falx to the sides of the crista galli direct upward extension of the mass into the interdural space between the leaves of the falx. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 33, Fig. 1-24.)

Clinical

- Nasal dermoid cysts represent approximately 10% of all dermoids in the cervicofacial region.
- No gender predilection; usually present in infants or young children, but may occur in adults
- Majority are midline swellings at the root of the nose (nasal bridge), although a few may be found in the lower and lateral regions of the nose near the ala:
 - Small lesions or deeply seated cysts may not be apparent until after they become infected and inflamed.
 - Sinus tract with an epidermal opening may be present.
 - Intracranial extension may occur.
 - Rarely, may present with median upper lip fistula
- Radiology:
 - Preoperative evaluation is essential to rule out intracranial extension.
 - Computed tomography (CT) and/or magnetic resonance (MRI) is indicated to delineate deep tissue involvement and to exclude a possible associated intracranial extension.
- Predominance as a midline lesion in the nasal bridge, a similar location as the glial heterotopias, suggests that the development of these two lesions is related.

- May be associated with or coexist with other congenital developmental malformations and may be familial

Pathology

- Cyst with cutaneous appendages (e.g., hair follicles, sebaceous glands, sweat glands) identified in the connective tissue wall
- Lumen is filled with keratin or sebaceous material.
- Respiratory epithelium may be identified.

Differential Diagnosis

- Normal skin surface
- Due to marked alterations secondary to infection, the lesion may be obscured and overlooked.
- Distinction should be made between nasal dermoids and so-called nasopharyngeal dermoids; the latter are not cysts and are actually ectopic accessory auricles.

Treatment and Prognosis

- Curative treatment is surgical:
 - The most important treatment concern is the possibility of the associated existence of a deeply seated cyst or its related sinus tract involving the anterior midline skull base.
 - Radiographic examination to judge the deep extent of the lesion is obviously important in planning operative removal.
- Lesions with intracranial extension have traditionally been managed with lateral rhinotomy, midface degloving, or external rhinoplasty approaches combined with a frontal craniotomy; alternatively, a subcranial approach has been proposed that:
 - Offers excellent exposure
 - Minimizes frontal lobe retraction
 - Reduces the likelihood of cerebrospinal fluid leak
 - Provides for excellent cosmetic result
 - Shows long-term follow-up with no recurrence or negative effect on craniofacial growth
- Low recurrence rates

PRIMARY CILIARY DYSKINESIA (PCD) (Figs. 2-30 and 2-31)

Definition: Primary ciliary dyskinesia (PCD) is a multi-system disease caused by ultrastructural defects of respiratory cilia and sperm tails and characterized by recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility, associated in about 50% patients with situs inversus totalis (Kartagener syndrome).

Synonyms: Immotile cilia syndrome; ciliary dysfunction

Clinical

- PCD is a heterogenetic disorder, usually inherited as an autosomal recessive trait, but pedigrees showing autosomal dominant or X-linked recessive modes of inheritance have been reported.
- Majority of cases are congenital due to an inborn genetic error, but some are acquired, usually the result of epithelial alterations subsequent to inflammatory disease:
 - Acquired forms of the disorder are referred to as secondary ciliary dyskinesia.
- Ciliopathies are a category of diseases caused by disruption of the physiologic functions of cilia:
 - Ciliary dysfunction results in a broad range of phenotypes, including renal, hepatic, and pancreatic cyst formation; situs abnormalities, retinal degeneration, anosmia, cerebellar or other brain anomalies, postaxial polydactyly, bronchiectasis, and infertility.
- Specific clinical features are dictated by the subtype, structure, distribution, and function of affected cilia.
- Presentation for PCD is typically in the early neonatal period:
 - If the diagnosis is considered in older children or in adults and a reasonably reliable clinical history is devoid of evidence of prominent and persistent respiratory tract problems dating from early infancy, the diagnosis is probably not feasible.
- Virtually all patients manifest sinusitis and otitis media, and an associated persistent mucopurulent rhinorrhea is often striking:

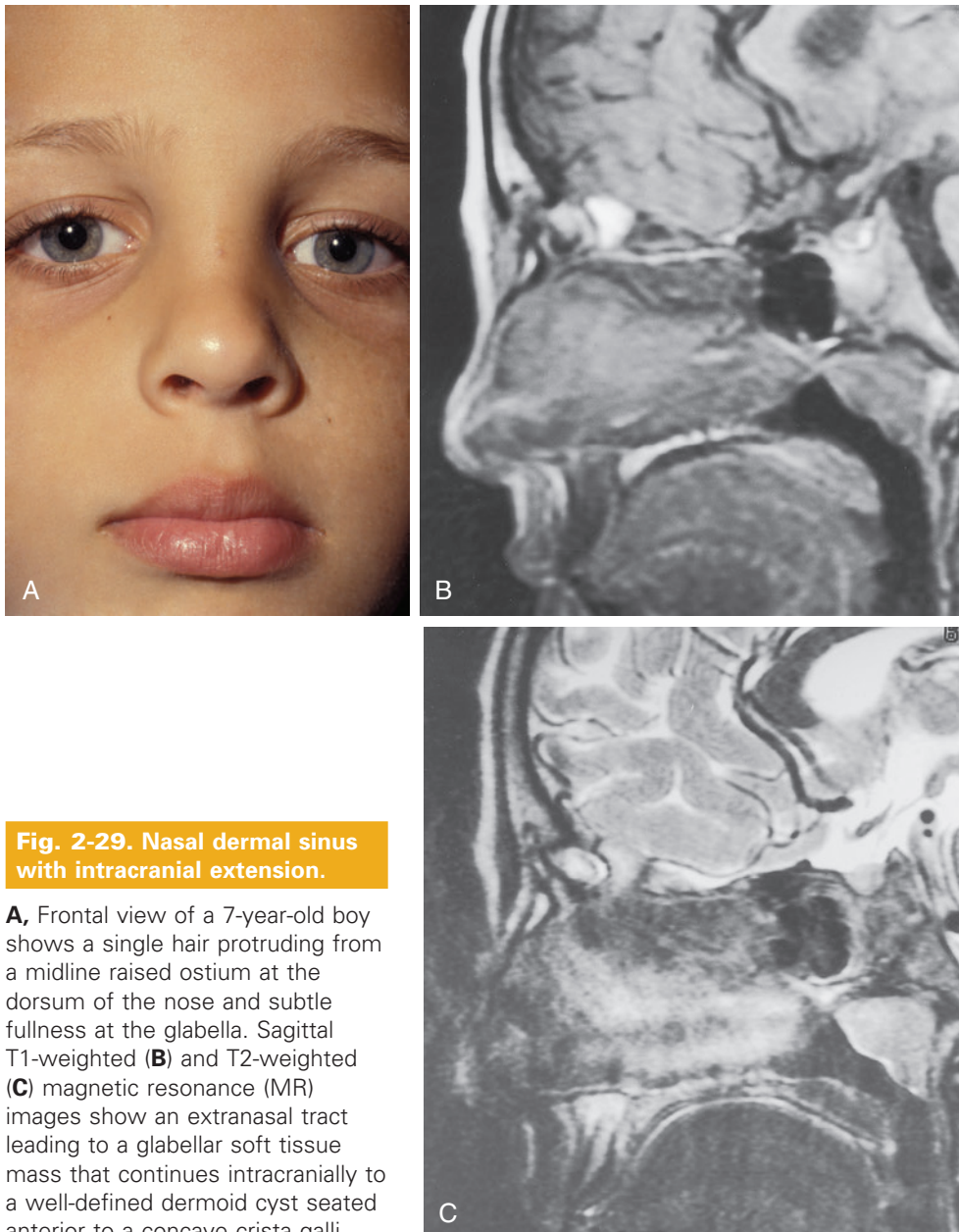
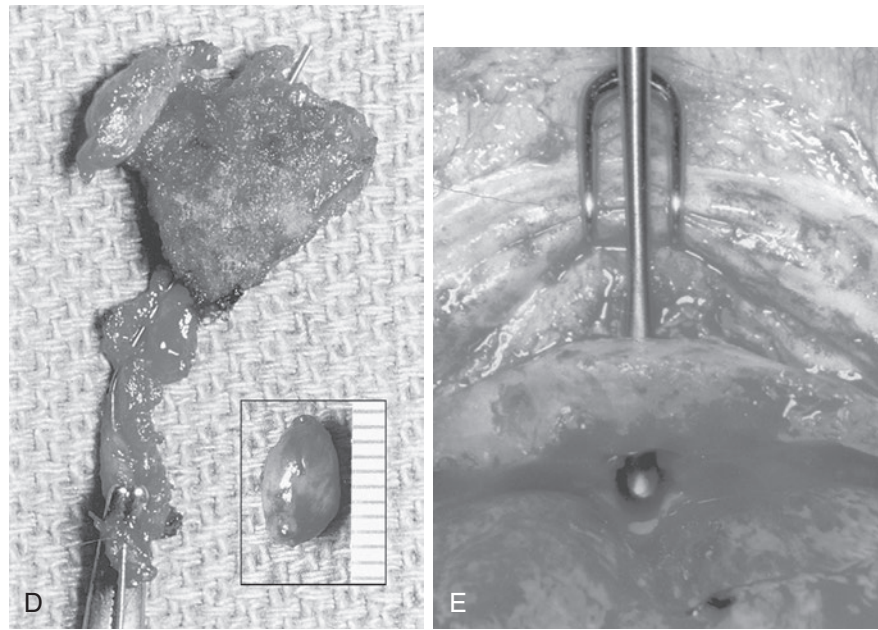
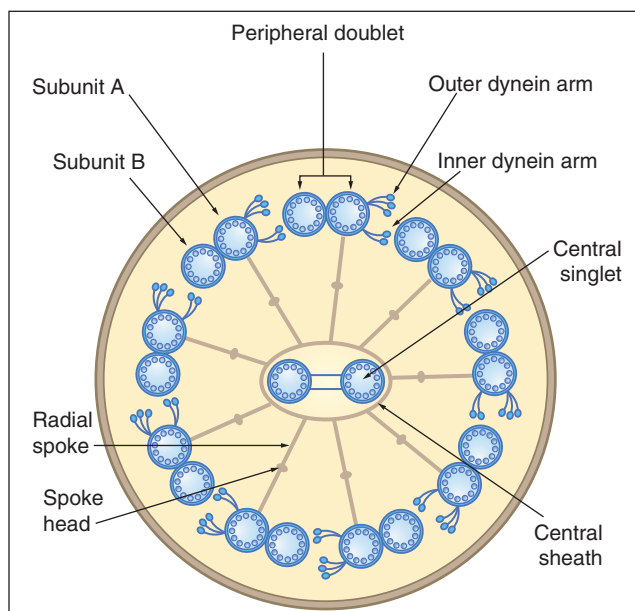


Fig. 2-29. Nasal dermal sinus with intracranial extension.

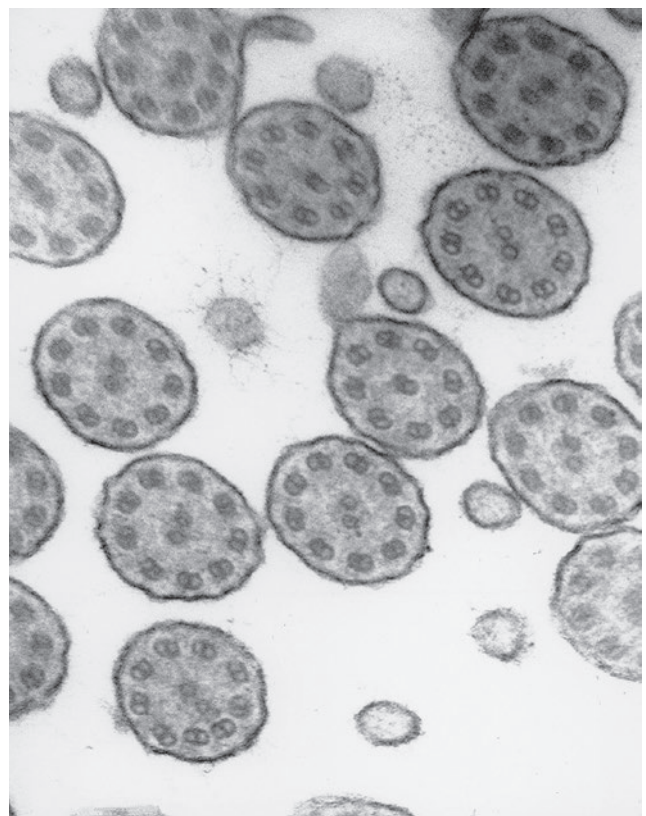
A, Frontal view of a 7-year-old boy shows a single hair protruding from a midline raised ostium at the dorsum of the nose and subtle fullness at the glabella. Sagittal T1-weighted (**B**) and T2-weighted (**C**) magnetic resonance (MR) images show an extranasal tract leading to a glabellar soft tissue mass that continues intracranially to a well-defined dermoid cyst seated anterior to a concave crista galli.

**Fig. 2-29. cont'd**

D, The probe demonstrates the course of the excised tract in relation to the mass and the dermoid. *Inset*: Close-up of the dermoid that nested in the anterior concavity of the crista galli. **E**, Intraoperative photograph, from above, shows the probe passing from the surgical defect in the nasal bones, through the tract, to the intracranial space anterior to the crista, between the two layers of dura that constitute the falx (see *inset*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 38, Fig. 1-34.)

**Fig. 2-30.**

Schematic representation of a cross-section of a ciliary axoneme (main body of the organellum) detailing the normal ciliary structures.

**Fig. 2-31. Primary ciliary dyskinesia.**

Electron microscopic evaluation showed complete absence of dynein arms that confirmed the clinical suspicion for primary ciliary dyskinesia.

- Chronic bronchitis, recurrent pneumonia, and atelectasis are common.
- Presence of situs inversus in association with chronic bronchitis, recurrent pneumonia, and atelectasis is virtually pathognomonic for Kartagener's syndrome, and this clinical scenario generally does not require cilia evaluation for the diagnosis.
- Approximately 50% of patients lack situs inversus, and in this setting ultrastructural examination of cilia is required for diagnostic purposes.
- Exhaled and nasal nitric oxide (NO) measurements have been used to detect PCD in children:
 - Nasal NO is significantly lower in children with proven PCD compared with those with negative biopsy results and healthy control subjects.
 - Nasal NO below a cut-off level of 105 ppb has a reported specificity of 88% for PCD and positive predictive value of 89%.
 - Nasal NO above a cut-off level of 105 ppb excluded PCD with a 100% certainty.
 - Measurement of nasal NO appears to be a useful tool to screen children for PCD and to exclude this disease in those with high nasal NO levels.
- Most patients are currently diagnosed with PCD based on the presence of defective ciliary ultrastructure; however:
 - Diagnosis often remains challenging due to variability in the clinical phenotype and ciliary ultrastructural changes.
 - Some patients with PCD have normal ciliary ultrastructure, further confounding the diagnosis.
 - A genetic test for PCD exists but is of limited value because it investigates only a limited number of mutations in only two genes.
 - Genetics of PCD is complicated owing to the complexity of axonemal structure that is highly conserved through evolution, which is composed of multiple proteins.
 - Identifying a PCD-causing gene is challenging due to locus and allelic heterogeneity.
 - There are a limited number of known PCD-causing genes that combined explain approximately 50% of PCD cases; therefore more genes must be identified.
- For ultrastructural analysis:
 - A nasal cavity biopsy is usually the most easily obtained specimen.
 - Anterior ends of the nasal turbinates are a readily accessible biopsy location, but these areas are where epithelial metaplastic changes are common. In patients with the chronic rhinitis as occurs in PCD, the presence of squamous metaplasia of the anterior turbinate regions is likely and a biopsy from these areas will in all probability contain no cilia. In such a situation, a specimen is best obtained more toward the posterior part of the nasal cavity.
 - If lower respiratory tract endoscopy is done as a part of the patient's evaluation, obtaining a tracheal mucosal brushing or biopsy has a much higher chance of producing a specimen with abundant cilia.
- Gene mutations in PCD:
 - PCD is genetically heterogeneous.
 - PCD-causing mutations have been identified in 20 genes, but collectively they account for only approximately 65% of all PCDs.
 - Ciliary gene mutations are now known to cause single organ disease as well as complex syndromes.
 - Different genes are involved in different patients.
 - Loss-of-function mutations in *ARMC4* cause PCD with situs inversus and cilia immotility, associated with a loss of the distal outer (but not inner) dynein arms.
 - Biochemical analysis in *Chlamydomonas* spp. revealed that the C21orf59 ortholog FBB18 is a flagellar matrix protein that accumulates specifically when cilia motility is impaired:
 - *Chlamydomonas* *ida6* mutant identifies CCDC65/FAP250 as an essential component of the nexin-dynein regulatory complex.
 - Two genes associated with PCD-causing mutations elucidated two distinct mechanisms critical for motile cilia function:
 - Dynein arm assembly for C21orf59
 - Assembly of the nexin-dynein regulatory complex for CCDC65
 - Mutations in SPAG1 cause PCD with ciliary outer dynein arm and inner dynein arm defects.
 - Exome sequencing has identified loss of function mutations in *CCDC114* as a cause of PCD.
 - *ZMYND10* is a cytoplasmic protein required for inner dynein arm and outer dynein arm assembly, and its variants cause ciliary dysmotility and PCD.
 - Loss-of-function *DYX1C1* mutations, a newly identified dynein axonemal assembly factor (DNAAF4) found in patients with PCD
 - *RSPH1* mutations appear as a major cause for this PCD phenotype, including central complex and radial spoke defects.
 - Founder mutation in *RSPH4A* identified as a common cause of PCD without situs abnormalities in patients of Hispanic (Puerto Rican) descent
 - Mutations in *CCDC39* and *CCDC40* are the major cause of primary ciliary dyskinesia with axonemal disorganization and absent inner dynein arms.

- Combining ultrastructural analysis and molecular genetics, the diagnostic yield can be increased:
 - Ciliary biopsy is unreliable as the sole criteria for a definitive diagnosis.
 - Molecular genetic analysis can be used as a complementary test to increase the diagnostic yield.
- In the presence of dynein arms the diagnosis essentially excludes the condition of “absence of dynein arms.”
- The evaluation of dynein arm abnormality is problematic:
 - To make the diagnosis of “absent dynein arms” requires that the sample has multiple ciliary cross-sections that have clear structural detail; otherwise, one cannot be sure that the lack of perception of the arms is not just artifactual.
 - Even in the most technically excellent photographic results one does not see arms on every peripheral tubule doublet because the arms are spaced along the longitudinal axis.
 - If the technical results are mediocre or poor (as most seem to be), it is difficult to clearly see any arms even if the cilia are entirely normal.

Pathology

Electron Microscopy

- The difficulties with interpreting ultrastructural studies of clinical specimens increases the importance and applicability of fresh specimen “wet-prep” examinations of ciliary function as a low-cost effective means of excluding PCD.
- Having abundant cilia in the specimen is critical because it is often difficult to discern dynein arms; the latter is partly due to the fact that:
 - The arms are tiny structures that are focally spaced along the ciliary axonemal tubules and therefore the quantity of electron dense material presented by the tiny arm is meager.
 - The arms are tiny, so relatively high magnification is required.
 - Combined with the meager density of the arm, the need for high magnification results in only a faint image with consequent visual resolution problems.
- Achieving technical results satisfactory for interpretation is a significant challenge.

Normal Cilia

- Internal structure of the axoneme of cilia has classic 9 + 2 microtubular pattern:
 - Pair in center is composed of single microtubules (singlets).
 - Peripheral row of 9 are double-barrelled (doublets) composed of subunits A and B.
 - Two short diverging arms (dynein arms) project clockwise from subunit A of each doublet toward the next doublet.
 - Radial spokes connect subunit A to a central sheath surrounding the central singlets.

Findings in Immotile Cilia Syndrome

- The structural abnormality that is most confidently diagnosable by ultrastructural examination is absence of dynein arms:
 - Dynein arms are necessary for the translational movement of ciliary peripheral doublet tubules with respect to one another (via a biochemico-physical “ratcheting-walking” mechanism); the absence of the arms results in lack of capability for kinetic (i.e., dynamic) movement.

- In the presence of dynein arms the diagnosis essentially excludes the condition of “absence of dynein arms.”
- The evaluation of dynein arm abnormality is problematic:
 - To make the diagnosis of “absent dynein arms” requires that the sample has multiple ciliary cross-sections that have clear structural detail; otherwise, one cannot be sure that the lack of perception of the arms is not just artifactual.
 - Even in the most technically excellent photographic results one does not see arms on every peripheral tubule doublet because the arms are spaced along the longitudinal axis.
 - If the technical results are mediocre or poor (as most seem to be), it is difficult to clearly see any arms even if the cilia are entirely normal.
- The above problems make the diagnosis of “partial absence of arms” or “shortened” or “defective” arms extremely difficult and of suspect validity in most instances; this is especially true of “absent inner arms” because the inner arms usually are seen less well than the outer arms.

Differential Diagnosis

- Diagnosis and differential diagnosis is essentially normal cilia versus abnormal cilia:
 - Avoidance in diagnosing a ciliary abnormality with its implication of an incurable genetic defect should be avoided as an error; such a diagnosis sentences a patient to an unwarranted pessimistic prognosis that could be of major negative emotional impact.
 - If the results strongly suggest a structural defect, it is probably best to obtain another sample from a different anatomic location to see if the same results are obtained.

Treatment and Prognosis

- Presence of ciliary abnormality represents a universal and permanent genetic defect in all of the patient’s cilia and is permanent.
- Early recognition and initiation of otolaryngologic and pulmonary management may reduce potential long-term morbidities.

SINONASAL HAMARTOMAS

- Classification of sinonasal hamartomas is listed in [Box 2-3](#).
- Hamartomas of the sinonasal tract are uncommon:
 - Majority of hamartomas of this region are of the pure epithelial type.
 - Mesenchymal hamartomas or mixed epithelial-mesenchymal hamartomas may occur.

BOX 2-3 Classification of Sinonasal Hamartomas

- Epithelial
 - Respiratory epithelial adenomatoid hamartoma
 - Seromucinous hamartoma
- Mixed epithelial and mesenchymal
 - Chondro-osseous and respiratory epithelial (CORE) hamartoma
- Mesenchymal
 - Nasal chondromesenchymal hamartoma (NCH)

- [Table 2-1](#) details the comparison of various features among sinonasal hamartomas.
- Owing to cases showing histologic features of respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma, these lesions may represent a spectrum of the same lesion instead of different lesions.
- On the basis of the presence of increased fractional allelic loss reported in respiratory epithelial adeno-

TABLE 2-1 Comparison of the Sinonasal Hamartomas

	REAH	SH	CORE	NCH
Age/gender	M > F; third to ninth decades, median sixth decade	M > F; second decade to ninth decade	M = F; second to eighth decades	M > F; most occur in newborns within the first 3 months of life but may occur in the second decade of life, and occasionally in adults
Site(s) of occurrence	Nasal cavity, in particular posterior nasal septum; involvement of other intranasal sites occurs less often and may be identified along the lateral nasal wall, middle meatus, and inferior turbinate; other sites of involvement include the nasopharynx, ethmoid sinus, and frontal sinus	Posterior nasal septum although may occur in the lateral nasal wall, paranasal sinuses, and nasopharynx	Nasal cavity most common; other sites include nasopharynx, ethmoid sinus, and sphenoid sinus	Intranasal mass or facial swelling; may erode into the cranial cavity (through the cribriform plate area)
Histology	Glandular proliferation composed of widely spaced, small to medium glands separated by stromal tissue; glands arise in direct continuity with the surface epithelium, which invaginate downward into the submucosa; glands are round to oval; composed of multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells; characteristic finding is the presence of stromal hyalinization with envelopment of glands by a thick, eosinophilic basement membrane; atrophic glands may be lined by a single layer of flattened to cuboidal-appearing epithelium; reactive seromucinous gland proliferation present in between glandular proliferations can be seen	Dense serous gland proliferation with back-to-back appearance resemble a cribriform pattern of growth; glands are lined by low cuboidal to flat epithelium cells with round to oval nuclei and a variable amount of basophilic to eosinophilic to clear appearing cytoplasm; invagination of the surface respiratory epithelium may be seen with at least focal merging with the glandular proliferation; periglandular hyalinization may also be present; lack a significant mucinous cell component, although focal mucinous change may be found; residual seromucinous glands with retention of their lobular architecture and haphazard growth of glands represent important findings that allow for differentiation from sinonasal low-grade adenocarcinoma	Histologic features of REAH (although adenomatoid components tend to be of less prominent) and intimate association with cartilaginous and/or osseous trabeculae	Nodules of cartilage varying in size, shape, and contour; loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma present at the periphery of the cartilaginous nodules; other patterns include a myxoid to spindle cell stroma, fibro-osseous proliferation with cellular stromal component and ossicles or trabeculae of immature (woven) bone; additional findings may include focal osteoclast-like giant cells in the stroma, and erythrocyte-filled spaces resembling those of the aneurysmal bone cyst; mature adipose tissue can be present; proliferating epithelial elements are not a prominent feature

TABLE 2-1 Comparison of the Sinonasal Hamartomas—cont'd

	REAH	SH	CORE	NCH
IHC	Cytokeratin positive (AE1/AE3, CAM 5.2, CK7); negative for CK20 and CDX2; p63 and CK903 (34βE12) staining of basal (myoepithelial) cells but may be absent; S100 may or may not be positive; low proliferation rate	Seromucinous glands reactive for cytokeratins (CK7, CK17, CK19), HMWK; negative for CK14, CK20; p63, calponin, MSA typically negative but in any given case may be positive; S100 protein staining is limited to the seromucinous glands; collagen type IV and laminin staining present around the glandular proliferation; low proliferation rate	None reported	Cartilaginous nodules and mesenchymal stromal component S100 protein staining (more intense staining in cartilaginous components); spindle cell stroma vimentin and smooth muscle actin reactivity; muscle specific actin (HHF35) may be present
Molecular findings	Increased fractional allelic loss (as compared with chronic sinusitis but less than that for adenocarcinoma)	Higher mutation rate in comparison with normal seromucinous glands	None reported	None reported
Associated lesions	Sinonasal inflammatory polyps; hyperplasia and/or squamous metaplasia of the surface epithelium unrelated to the adenomatoid proliferation; osseous metaplasia; rare association with inverted type Schneiderian papilloma, and solitary fibrous tumor; reported instances of low-grade adenocarcinomas associated with REAHs	Sinonasal inflammatory polyps; REAH	None reported	None reported

CORE, Chondro-osseous and respiratory epithelial (CORE) hamartoma; *HMWK*, high molecular weight keratin; *IHC*, immunohistochemistry; *MSA*, muscle specific actin (HHF35); *NCH*, nasal chondromesenchymal hamartoma; *REAH*, respiratory epithelial adenomatoid hamartoma; *SH*, seromucinous hamartoma.

matoid hamartomas, it remains an open issue whether these lesions are non-neoplastic or neoplastic.

- Because our understanding of the nature of these hamartomas is still evolving, this text retains the classification of these lesions as being non-neoplastic and describe respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma as separate lesions, although any given case may show histologic features of both types of hamartomas.

RESPIRATORY EPITHELIAL ADENOMATOID HAMARTOMA (REAH) (Figs. 2-32 and 2-33)

Definition: Benign acquired non-neoplastic overgrowth of indigenous glands of the nasal cavity, paranasal sinuses, and nasopharynx arising from the surface

epithelium and devoid of ectodermal, neuroectodermal, and/or mesodermal elements.

Synonyms: Glandular hamartoma; nasal hamartoma

Clinical

- Predominantly occur in adult patients with a decided male predominance; patients range in age from the third to ninth decades of life with a reported median age in the sixth decade of life.
- Majority occur in the nasal cavity, in particular the posterior nasal septum:
 - Involvement of other intranasal sites occurs less often and may be identified along the lateral nasal wall, middle meatus, and inferior turbinate.
 - Other sites of involvement include the nasopharynx, ethmoid sinus, and frontal sinus.
- Majority of lesions are unilateral but occasionally bilateral lesions may occur.

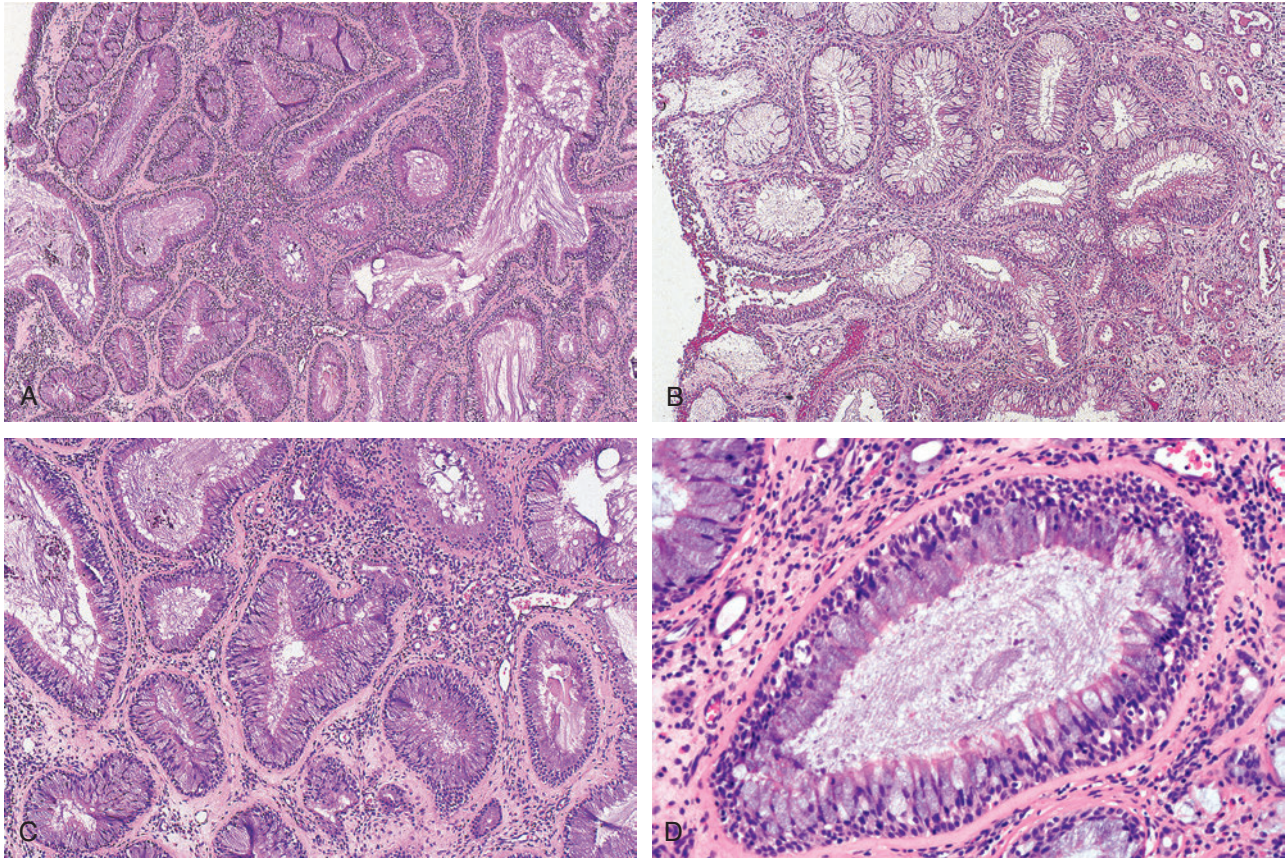


Fig. 2-32. Respiratory epithelial adenomatoid hamartoma.

Respiratory epithelial adenomatoid hamartoma. **A** and **B**, The histopathologic changes are dominated by the presence of a glandular proliferation composed of widely spaced, small to medium-size glands separated by stromal tissue; in areas the glands can be seen arising in continuity with the surface epithelium invaginating downward into the submucosa; glandular dilatation distended with mucus is present. **C** and **D**, The glands are round to oval, composed of multilayered ciliated respiratory epithelium often with admixed mucin-secreting (goblet) cells; a characteristic feature is the presence of stromal hyalinization with envelopment of glands by a variably thickened, eosinophilic basement membrane. The stroma is edematous or fibrous containing a mixed chronic inflammatory cell infiltrate, and scattered residual seromucinous glands are present.

- Clinical presentation may include one or more of the following symptoms:
 - Nasal obstruction, nasal stuffiness, epistaxis, and chronic (recurrent) rhinosinusitis
 - Symptoms may occur over months to years.
 - Associated complaints include allergies.
 - Nondestructive
- No association with any specific etiologic agent such as environmental or occupational exposure, tobacco use, or alcohol abuse
- Arise in the setting of inflammatory polyps, raising a possible developmental induction secondary to the inflammatory process

Pathology

Gross

- Typically polypoid or exophytic lesions with a rubbery consistency, tan-white to red-brown appearance measuring up to 6 cm in greatest dimension

Histology

- Histopathologic changes are dominated by the presence of a glandular proliferation composed of widely spaced, small to medium-sized glands separated by stromal tissue.

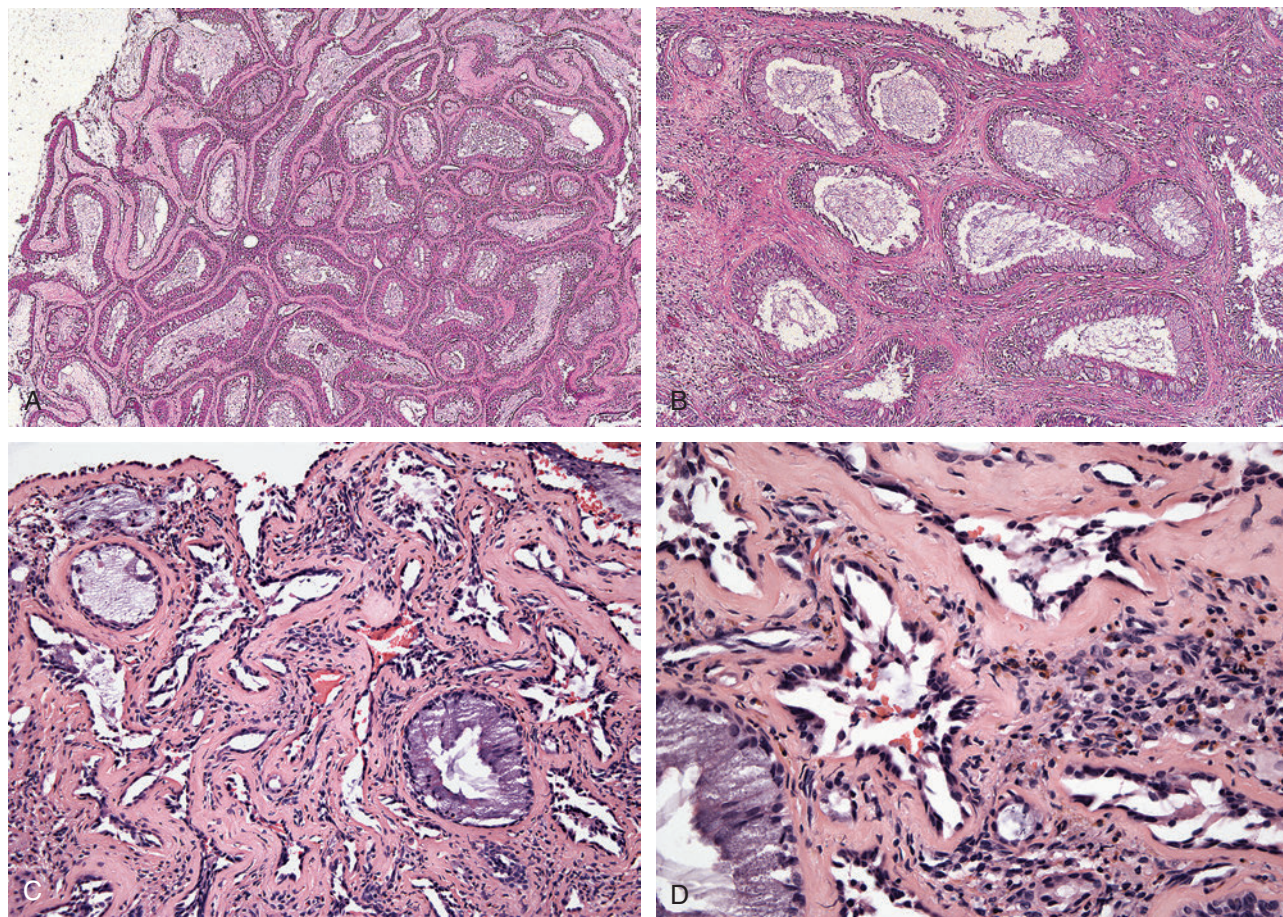


Fig. 2-33. Respiratory epithelial adenomatoid hamartoma.

A and **B**, More prominent stromal hyalinization as compared with Fig. 2-32. This finding is consistent and characteristic of REAH. **C** and **D**, Additional alterations that may be present include the presence of atrophic changes of the surface epithelium and glands, which are lined by a single layer of flattened to cuboidal-appearing epithelium; mucinous metaplasia of glandular epithelium is focally seen and residual seromucinous glands are present.

- In areas the glands are seen arising in direct continuity with the surface epithelium, which invaginate downward into the submucosa.
- Glands are round to oval, composed of multilayered ciliated respiratory epithelium, often with admixed mucin-secreting (goblet) cells.
- Glandular dilatation distended with mucus can be seen.
- A characteristic finding is the presence of stromal hyalinization with envelopment of glands by a thick, eosinophilic basement membrane.
- Atrophic glandular alterations may be present in which glands are lined by a single layer of flattened to cuboidal-appearing epithelium.
- Small reactive-appearing seromucinous glands can be seen; however, some cases may show marked proliferation of seromucinous glands with features of the seromucinous hamartoma (see below).
- Stroma is edematous or fibrous, containing a mixed chronic inflammatory cell infiltrate.
- In addition to the glandular proliferation, additional findings that can be found in association with REAHs include:
 - Histologic alterations of sinonasal inflammatory polyps
 - Hyperplasia and/or squamous metaplasia of the surface epithelium unrelated to the adenomatoid proliferation
 - Osseous metaplasia
 - Rare association with inverted type Schneiderian papilloma, and rare association with a solitary fibrous tumor

- Reported instances of low-grade adenocarcinomas associated with REAHs prompting the consideration that REAHs are a precursor lesion for at least a subset of sinonasal low-grade adenocarcinomas:
 - No definitive proof linking REAH as a precursor lesion to sinonasal adenocarcinoma
- Immunohistochemistry:
 - Glandular proliferation (surface and/or submucosal):
 - Reactive for cytokeratins, including AE1/AE3, CAM 5.2, CK7
 - Negative for CK20 and CDX2
 - p63 and CK903 (34βE12) staining of basal (myoepithelial) cells but in any given case or in areas of any given lesion such staining may be absent:
 - Absence of p63-positive myoepithelial/basal cells does not confer a diagnosis of adenocarcinoma unlike in other organ systems, including the breast and prostate gland, where in conjunction with appropriate light microscopic findings the absence of myoepithelial/basal cells by immunohistochemical staining with p63, smooth muscle actin, and/or smooth muscle myosin heavy chain would support a diagnosis of adenocarcinoma.
 - S100 protein may or may not be reactive.
 - Ki67 (MIB1) staining either is absent or shows a very low proliferation rate (1% to 2%).
 - Molecular genetics:
 - Increased fractional allelic loss (FAL) of 31% falling in between an FAL of 1% for chronic sinusitis and 64% for sinonasal adenocarcinoma:
 - Based on the appreciable allelic loss within hamartomas considered unusually high for a non-neoplastic entity, the possibility that REAHs may be a benign neoplasm rather than a hamartoma has been suggested.
 - Possibility that REAHs are benign neoplasms remains uncertain

Differential Diagnosis

- Sinonasal inflammatory polyp:
 - REAHs may appear polypoid and be mistaken for nasal polyps.
 - Origin of REAHs from the posterior edge of the nasal septum contrasts with the origin of most inflammatory polyps from the lateral portions of the sinonasal tract and rare (if ever) occurrence of inflammatory polyp from the septum.
 - REAHs tend to be firmer than inflammatory polyps; this feature is noted by clinicians who may comment that “this lesion is funny for a inflammatory polyp.”

- Seromucinous hamartoma: see subsequent section
- Schneiderian papillomas
- Nasopharyngeal angiofibroma
- Sinonasal adenocarcinoma, low-grade, nonintestinal, nonsalivary gland type

Treatment and Prognosis

- Conservative, but complete surgical excision is curative.

SEROMUCINOUS HAMARTOMA (SH) (Figs. 2-34 and 2-35)

Definition: Benign acquired non-neoplastic overgrowth of indigenous glands of the sinonasal tract, and rarely of the nasopharynx, arising from submucosally situated seromucinous glands.

Synonym: Glandular hamartoma

Clinical

- Slight male predilection; occurs over a wide age range, including second to ninth decades of life
- Most commonly occurs as an incidental finding seen in surgical material from patients removed for clinical diagnoses such as chronic sinusitis and/or sinonasal inflammatory polyps.
- Symptomatic patients may present with nasal obstruction and epistaxis.
- Most common site of occurrence is the posterior nasal septum, although may occur in the lateral nasal wall, paranasal sinuses, and nasopharynx.
- Generally limited in extent but may extend into adjacent sinuses (e.g., maxillary, ethmoid)
- No known etiologic factors, although some patients have been reported in association with chronic sinusitis, inflammatory polyps, rheumatoid arthritis, and Parkinson disease.
- Radiographically, may appear as polypoid lesion without evidence of aggressive growth such as bone destruction

Pathology

Gross

- Polypoid to exophytic-appearing lesions measuring from 6 mm to 4 cm in greatest dimension

Histology

- Covered by benign ciliated respiratory epithelium that may show squamous metaplasia and often have an associated hypocellular edematous, myxoid, and/or fibrous stroma similar to that seen in sinonasal inflammatory polyps
- Characteristic finding is presence of a submucosal epithelial proliferation of small glands, serous acini

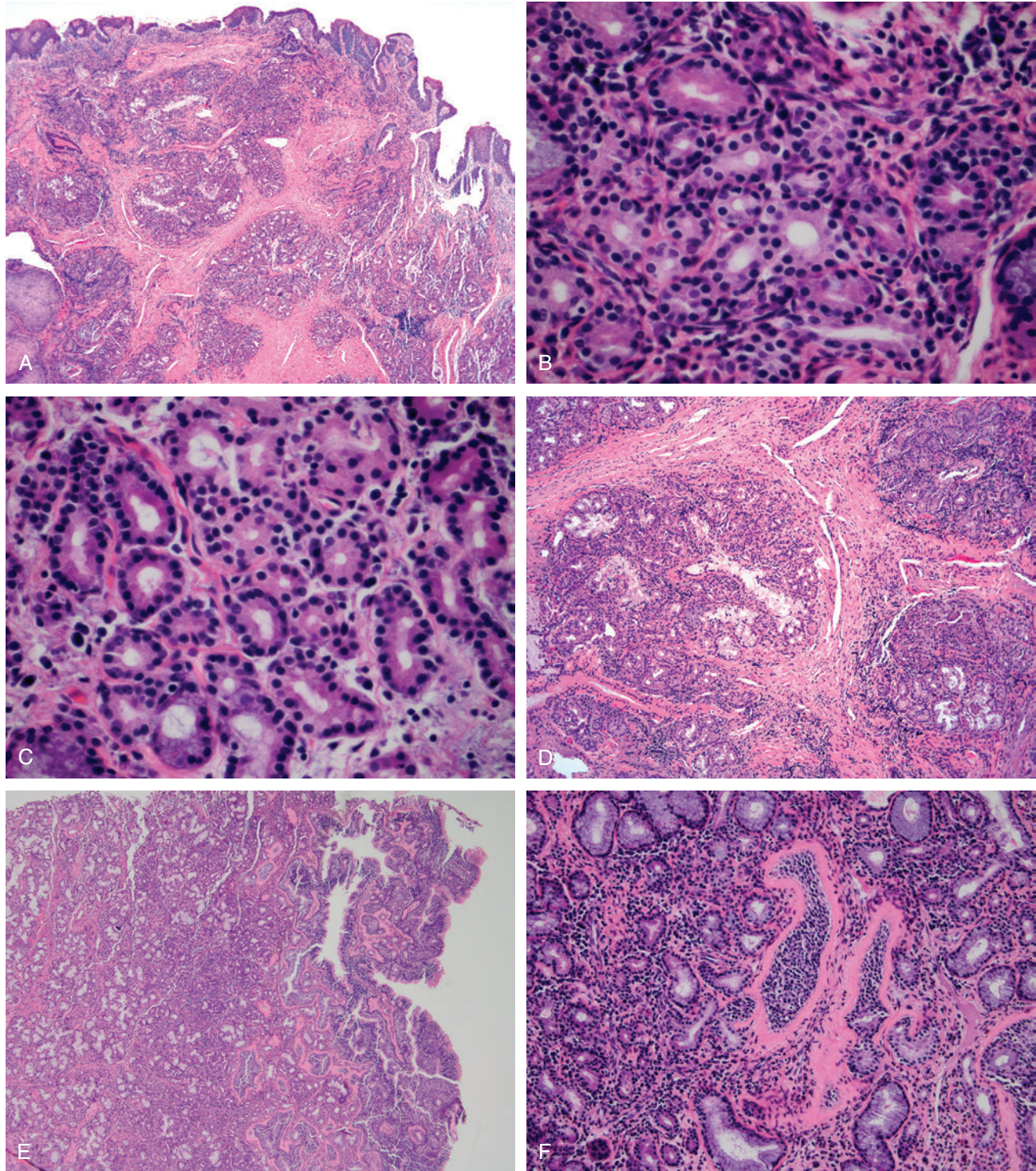


Fig. 2-34. Seromucinous hamartoma.

A, Polypoid to exophytic-appearing lesion with submucosal epithelial proliferation of small glands, serous acini, and tubules growing in clusters and lobules. **B**, In some cases the serous glands may be densely packed with a back-to-back appearance that may resemble a cribriform pattern of growth. **C**, Glands are lined by relatively bland, appearing low cuboidal to flat epithelium cells with round to oval nuclei and a variable amount of basophilic to eosinophilic-appearing cytoplasm. **D**, Residual seromucinous glands with retention of lobular architecture and/or haphazard growth of glands represent important findings that allow for differentiation from sinonasal low-grade adenocarcinoma. **E**, Invagination of the surface respiratory epithelium may be seen with at least focal merging with the glandular proliferation. **F**, Periglandular hyalinization may also be present.

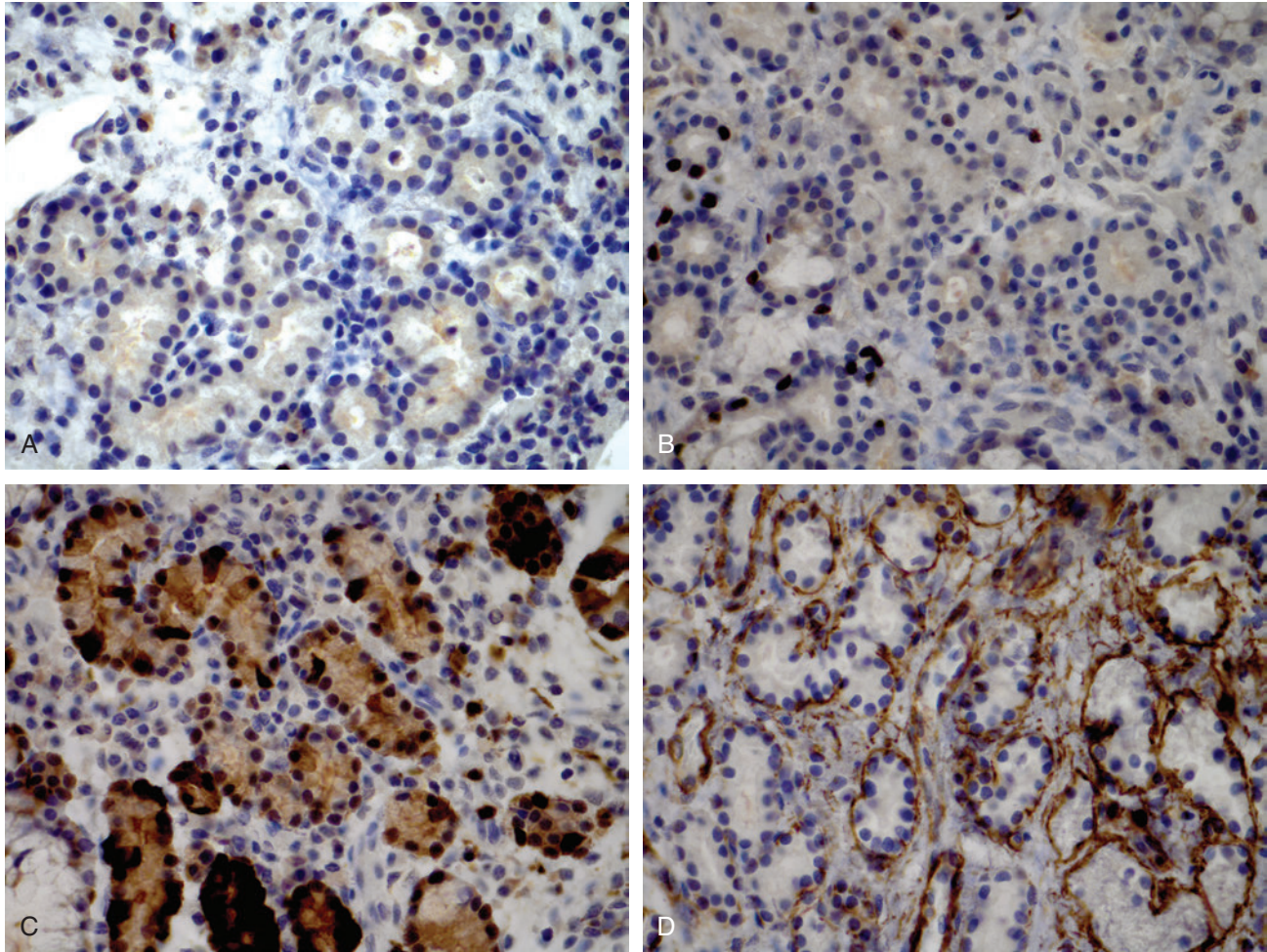


Fig. 2-35. Seromucinous hamartoma.

Immunohistochemical findings. **A**, Most of these lesions are p63 negative. **B**, Some of these lesions are p63 positive. **C**, S100 protein staining is limited to the seromucinous glands. **D**, Collagen type IV is present around the glandular proliferation.

and tubules growing in clusters, and lobules, although haphazard arrangements with larger glands and cysts are seen.

- In some cases the serous glands may be densely packed with a back-to-back appearance that may resemble a cribriform pattern of growth.
- Glands are lined by low cuboidal to flat epithelium cells with round to oval nuclei and a variable amount of basophilic to eosinophilic to clear-appearing cytoplasm.
- There is an absence of significant nuclear pleomorphism, increased mitotic activity, and necrosis.
- Glands vary in appearance from round to oval to angulated to branching and stellate containing luminal mucin material.
- Lack a significant mucinous cell component, although focal mucinous change may be found
- In any given case histologic changes similar to those of respiratory epithelial adenomatoid hamartoma may be present, including:
 - Invagination of the surface respiratory epithelium with at least focal merging with the glandular proliferation
 - Periglandular hyalinization
- Residual seromucinous glands with retention of their lobular architecture and haphazard growth of glands represent important findings that allow for differentiation from sinonasal low-grade adenocarcinoma.
- A mixed chronic inflammatory cell infiltrate composed of mature lymphocytes and plasma cells can be seen, but a significant population of eosinophils is not typically present.

- Immunohistochemistry:
 - Surface epithelium and the seromucinous glands are reactive for cytokeratins, including CK7, CK17, CK19, and high molecular weight cytokeratin (HMWK) but negative for CK14 and CK20.
 - Surface respiratory epithelium show p63-positive basal cells.
 - Myoepithelial/basal cell markers:
 - p63:
 - Seromucinous glands are typically negative but in any given case may be positive.
 - Calponin and muscle-specific actin:
 - Negative in the surface respiratory epithelium and the seromucinous glands but in any given case may be positive
 - Absence of myoepithelial/basal cells by immunohistochemical staining does not confer a diagnosis of adenocarcinoma unlike in other organ systems, including the breast and prostate gland, in which in conjunction with appropriate light microscopic findings the absence of myoepithelial/basal cells by immunohistochemical staining with p63, smooth muscle actin, and/or smooth muscle myosin heavy chain would support a diagnosis of adenocarcinoma.
 - S100 protein staining is limited to the seromucinous glands.
 - Collagen type IV and laminin staining present around the glandular proliferation
 - Ki67 (MIB1) staining is either absent or shows a very low proliferation rate (1% to 2%).
- Molecular genetics:
 - DNA mutation analysis on SH reported to show a higher mutation rate in comparison with normal seromucinous glands, which exhibited a lower mutation frequency (0.83%):
 - Supportive of SH as representing a benign process, although no indications whether such findings support non-neoplastic or neoplastic lesion
 - Suggested similarities between SH and microglandular adenosis of the breast

Differential Diagnosis

- REAH (Table 2-1)
- Schneiderian papillomas
- Sinonasal adenocarcinoma, low-grade, nonintestinal, nonsalivary gland type

Treatment and Prognosis

- Conservative but complete surgical excision is curative.
- No reported recurrences over extended periods of time

CHONDRO-OSSEOUS AND RESPIRATORY EPITHELIAL (CORE) HAMARTOMA (Fig. 2-36)

Definition: Considered to be related to REAHs, but they have the additional feature of chondroid tissue that can be histologically atypical.

Clinical

- Patients range in age from 11 to 73 years.
- Present as polypoid mass most commonly affecting the nasal cavity; other sites of occurrence may include the nasopharynx, ethmoid sinus, and sphenoid sinus.

Pathology

Histology

- In addition to the histologic features of REAH, although the respiratory epithelial adenomatoid components tend to be less prominent, the CORE hamartomas have an intimately associated admixture of cartilaginous and/or osseous trabeculae.
- A spectrum of chondro-osseous differentiation can be found, with some cases manifesting “immature-appearing” mesenchyme, in which cartilaginous plates display a zonal phenomenon resembling endochondral ossification in fetal skeletal development, to cases with well-developed bony trabeculae in a myxoid to fibrous stroma.

Differential Diagnosis

- REAH (Table 2-1)
- Seromucinous hamartoma (see Table 2-1)
- Sarcoma due to the presence of immature-appearing mesenchyme or cartilage

Treatment and Prognosis

- Conservative but complete resection should be curative, although rarely recurrence may occur.

NASAL CHONDROMESENCHYMAL HAMARTOMA (NCH)

(Figs. 2-37 and 2-38)

Definition: Nasal chondromesenchymal hamartoma is a tumefactive process of the sinonasal tract composed of an admixture of chondroid and stromal elements with cystic features that are analogous to chest wall hamartoma. These lesions have some histologic similarities to REAH and CORE hamartoma and they may be within the spectrum of the same type of lesion.

Synonyms: Chondroid hamartoma; nasal hamartoma

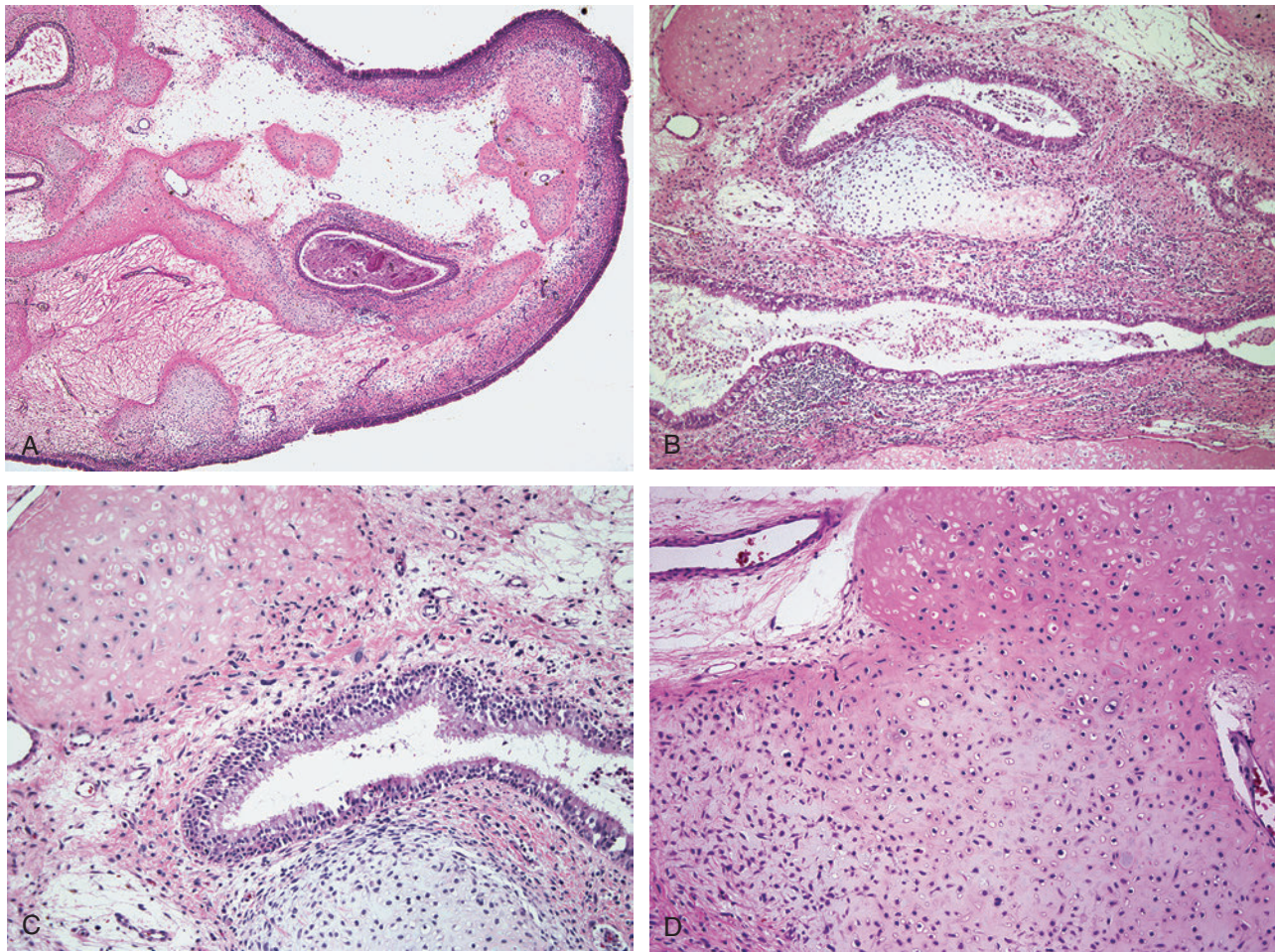


Fig. 2-36. Chondro-osseous and respiratory epithelial (CORE) hamartoma.

A and B, Polypoid lesion with intact surface epithelium and a submucosal proliferation of glands (less prominent as compared with the REAHs) and lighter colored areas that represent cartilage. **C,** At higher magnification CORE hamartomas show an admixture of glands and cartilaginous nodules. **D,** A zonal type phenomenon resembling endochondral ossification in fetal skeletal development may be seen.

Clinical

- Rare lesion, with less than 30 cases reported to date
- Male predilection; most of these lesions occur in newborns within the first 3 months of life but may occur in the second decade of life, and occasionally in adults.
- Patients present with respiratory difficulty and an intranasal mass, or facial swelling may be present; some of these tumors have eroded into the cranial cavity (through the cribriform plate area), a finding that may clinically simulate the appearance of a meningoencephalocele.
- Association with pleuropulmonary blastoma reported in a small subset of patients

- Radiology:
 - CT may demonstrate a partially calcified soft-tissue mass obstructing the nasal cavity.

Pathology

Gross

- Firm, polypoid-appearing, tan-yellow mass; cut section may reveal identifiable bone and blue-grey glistening nodules

Histology

- Characterized by the presence of nodules of cartilage varying in size, shape, and contour:
 - Degree of differentiation varies, with some nodules appearing similar to the chondromyxomatous

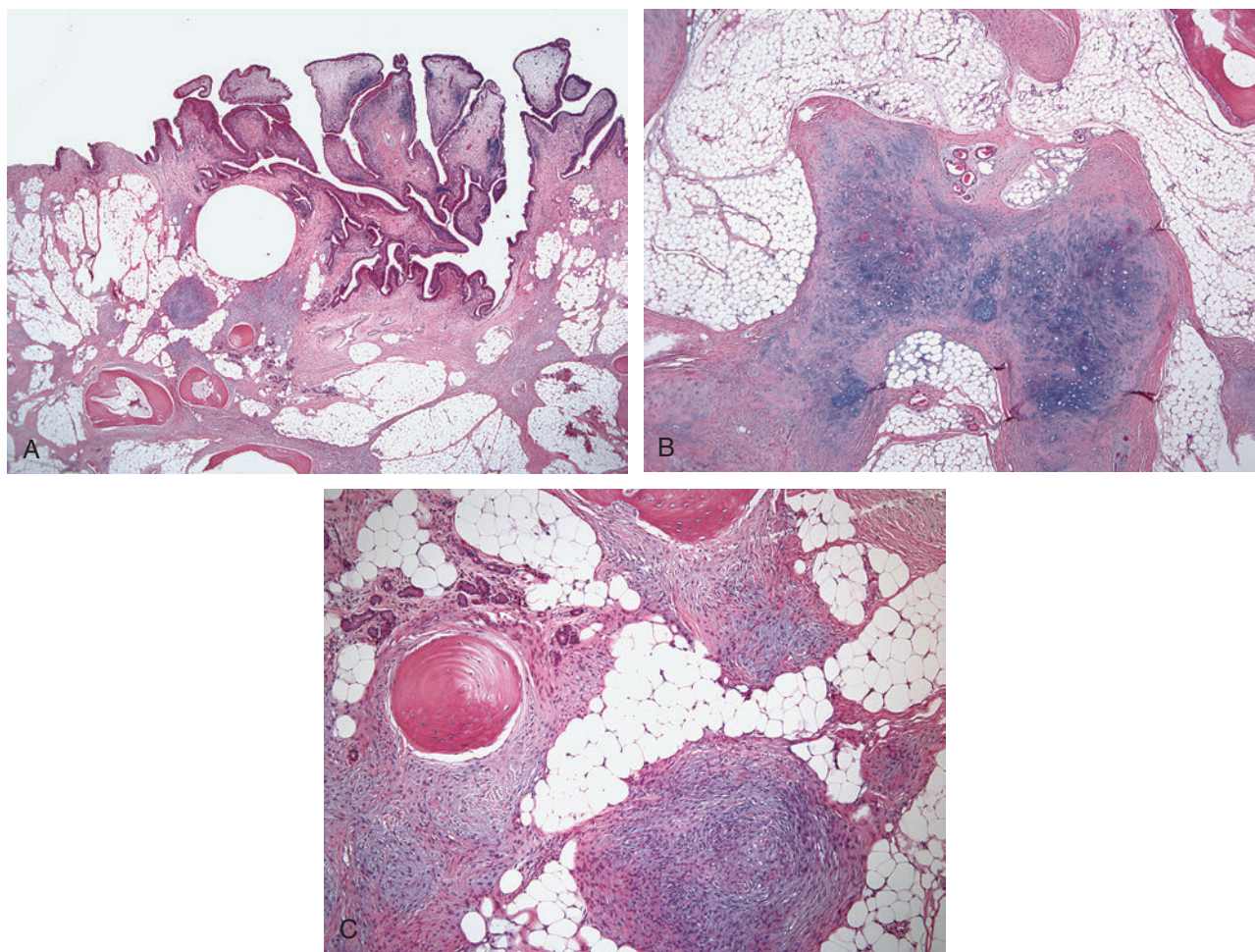


Fig. 2-37. Chondromesenchymal hamartoma.

A, Low power shows polypoid-appearing sinonasal mucosa with submucosal proliferation of adipose tissue, bony trabeculae, and round (cellular) nodules. **B**, Cartilaginous nodule surrounded by adipose tissue and bone (*upper right*). **C**, Rounded myxochondroid-appearing cellular nodules surrounded by adipose tissue as well as bone and scattered seromucous glands.

- nodules of chondromyxoid fibroma to nodules of well-differentiated cartilage.
 - Chondromesenchymal elements are relatively cellular and “immature,” probably reflecting the immature ages of the patients.
- A loose spindle cell stroma or abrupt transition to hypocellular fibrous stroma is present at the periphery of the cartilaginous nodules.
- Other patterns include a myxoid to spindle cell stroma, fibro-osseous proliferation with cellular stromal component, and ossicles or trabeculae of immature (woven) bone.
- Additional findings may include focal osteoclast-like giant cells in the stroma and erythrocyte-filled spaces resembling those of the aneurysmal bone cyst.
- Mature adipose tissue can be present.
- Proliferating epithelial elements are not a prominent feature.
- Immunohistochemistry:
 - Cartilaginous nodules and mesenchymal stromal component show S100 protein staining:
 - More intense staining in cartilaginous components
 - Spindle cell stroma shows vimentin and smooth muscle actin reactivity; muscle-specific actin (HHF35) may be present:
 - Presence of actin reactivity supports myofibroblastic differentiation.
 - Epithelial membrane antigen (EMA) reactivity has been reported, likely representing nonspecific staining.

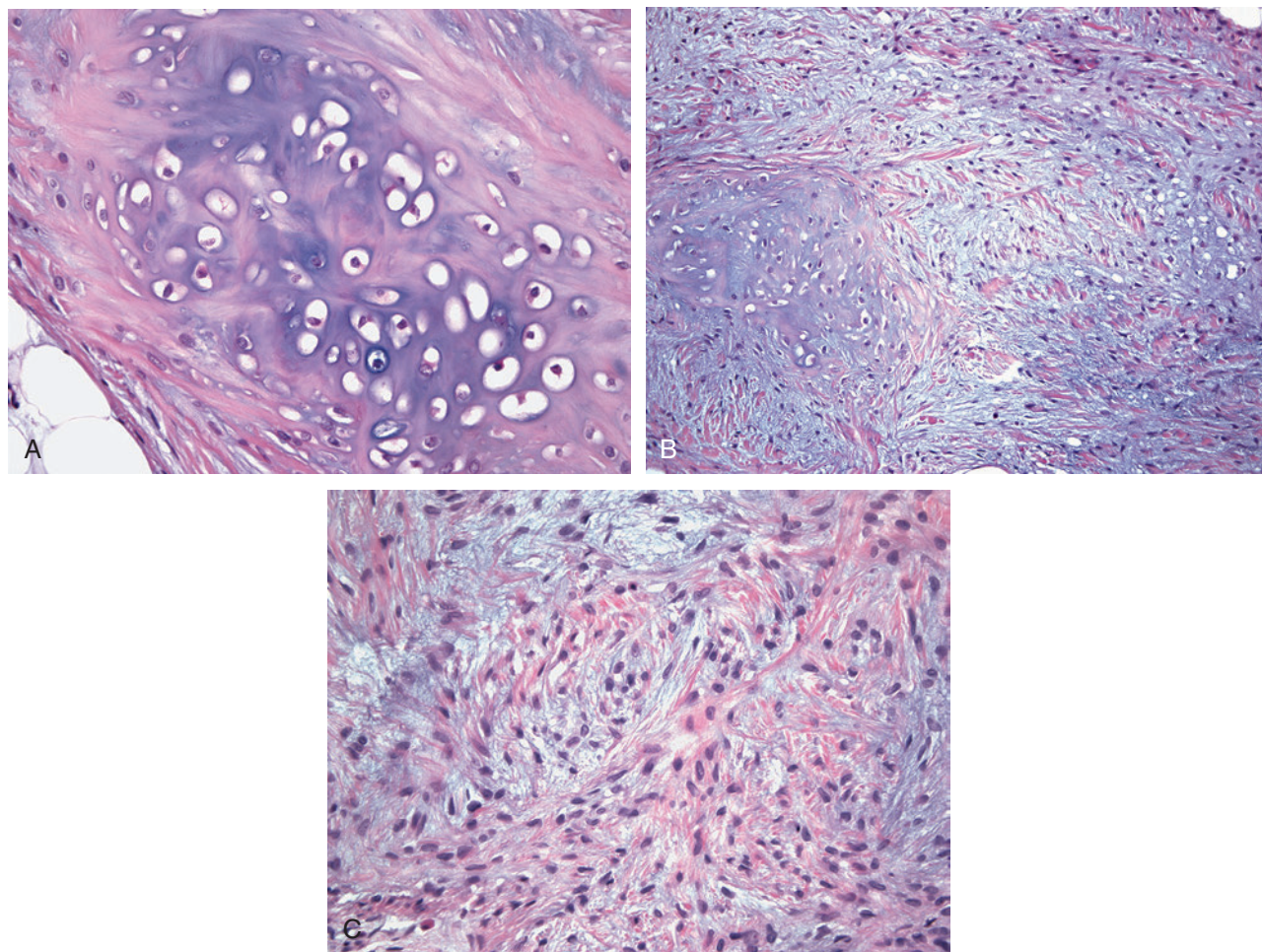


Fig. 2-38. Chondromesenchymal hamartoma.

A, Delineated nodular focus of cartilage. **B**, Transitional area between cartilaginous nodule and loosely cellular myxochondroid area. **C**, Cellular myxochondroid area composed of bland spindle-shaped cells.

- Cytogenetics and molecular biology
 - Novel 12;17 translocation, t(12;17)(q24.1;q21) identified as sole reported anomaly
 - Occurred in a single patient (11-year-old boy) with past medical history of pleuropulmonary blastoma

Differential Diagnosis

- REAH, seromucinous hamartoma, and CORE hamartoma (Table 2-1):
 - Nasal chondromesenchymal hamartoma is distinguished from these hamartomas by mostly

presenting in the neonatal age group and by a tendency to be larger and more aggressive than these other hamartomas.

Treatment and Prognosis

- Surgical resection is the treatment of choice that may necessitate combined intranasal and intracranial approach.
- Report of malignant transformation in an adult

INFECTIOUS-RELATED DISEASES OF THE SINONASAL TRACT

FUNGAL DISEASES

(Figs. 2-39 and 2-40)

Aspergillosis

- Sinonasal disease associated with *Aspergillus* sp. is divided into three distinct entities:
 - Allergic fungal sinusitis (AFS)
 - *Aspergillus mycetoma* (“fungus ball”)
 - Invasive fungal sinusitis
- Although most often seen in association with *Aspergillus* species, the above sinonasal fungal diseases may occur with any fungus.

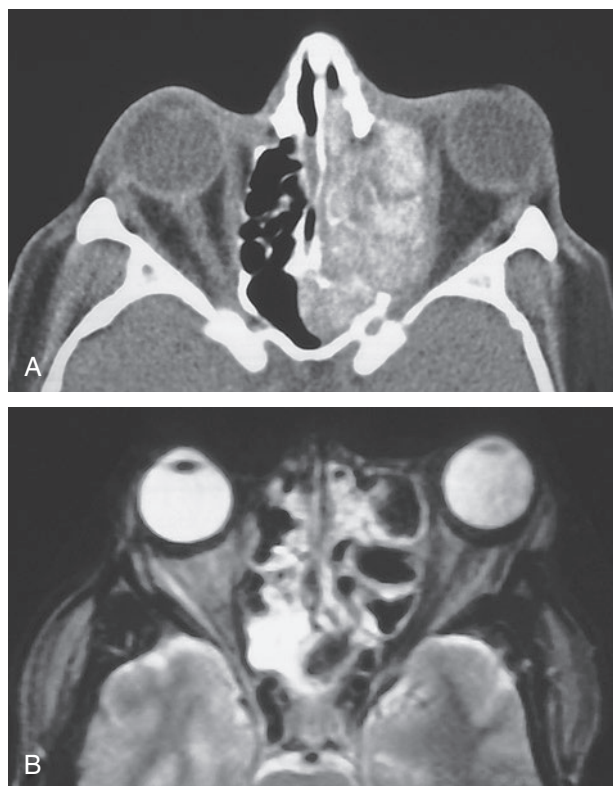


Fig. 2-39.

Axial CT scan (**A**) shows a mass in the left ethmoid and sphenoid sinuses that has broken out into the left orbit. There are discrete areas of high attenuation. The localized areas of high density on this non-contrast-enhanced CT makes an inflammatory process likely. However in **B**, a T2-weighted MR image, the areas of high attenuation in **A** have signal voids. This indicates that they are most likely either desiccated secretions or mycetomas. This patient had aspergillosis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 203, Fig. 3-60.)

- *Aspergillus* sp. is histologically characterized by relatively thin (2 to 5 μ m) hyphae with acute angle (45 degrees) branching and septation.
- *Aspergillus* is a member of the Moniliaceae family, Hyphomycetes class, Deuteromycota phylum:
 - *Aspergillus* spp. are abundant in soil and in decaying matter.
 - Mode of transmission is via inhalation.

Allergic Fungal Sinusitis (AFS)

Definition: Noninvasive collection(s) of impacted mucus and cellular debris; similar to allergic bronchopulmonary aspergillosis, the pathologic findings result from an allergic response to the presence of a topical fungal colonization within a sinus cavity. The amount of fungal elements is variable and often is quantitatively scanty. Nevertheless, the presence of fungus, irrespective of quantity, elicits an allergic response resulting in a significant pathologic process.

Synonyms: Inspissated mucus; allergic sinonasal aspergillosis; allergic fungal rhinosinusitis; eosinophilic fungal rhinosinusitis; eosinophilic mucin rhinosinusitis; “snotoma”

Clinical

- No gender predilection; may occur in all ages but is most commonly seen in children or young adults
- Tends to be more common in the south and south-west regions of the United States
- Primarily involves the maxillary and ethmoid sinuses but may involve any sinus
- Clinical presentation includes headaches and airway obstruction.
 - Sinus-obstructing inspissates of a characteristic extramucosal “peanut buttery” viscoelastic material
- Patients commonly present with chronic rhinosinusitis with nasal polyps, inhalant atopy, history of asthma, aspirin insensitivity, blood eosinophilia, and elevated total serum immunoglobulin E (IgE) levels.
- Recent studies implicated superantigens and nonimmunoglobulin E (IgE)-mediated mechanisms in the development of AFS:
 - Higher prevalence of *S. aureus* found in patients with AFS versus patients with non-AFS, supporting a potential role for *S. aureus* in the pathogenesis of AFS
- Originally considered solely due to *Aspergillus* species, but other fungi have been found also to be causative, including:
 - Dematiaceous fungi such as *Bipolaris*, *Exserohilum*, *Curvularia*, *Drechslera*, and *Alternaria*

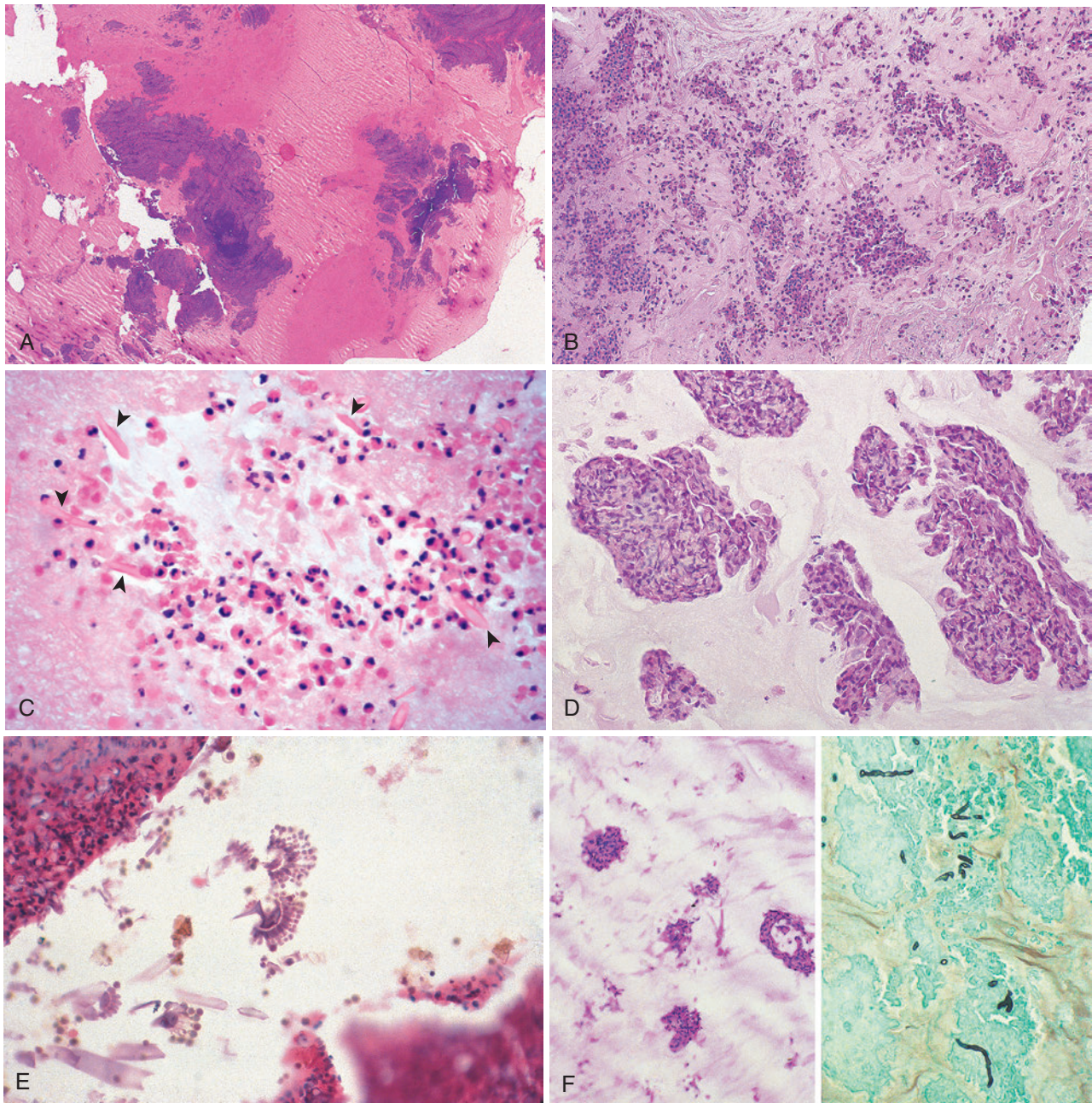


Fig. 2-40. Allergic fungal sinusitis.

A, Inspissated mucus ("allergic mucin") composed of amorphous eosinophilic material associated with nests of inflammatory cells. **B** and **C**, The inflammatory cells predominantly are composed of eosinophils, and Charcot-Leyden crystals can be seen. **D**, The combination of clusters of cohesive cells and homogeneous-appearing chondroid-like matrix may be mistaken for a pleomorphic adenoma; the cohesive cellular nests are inflammatory cells and not epithelial cells. **E**, Rarely, fruiting head of *Aspergillus* sp. may be identified. **F**, (left and right) More typical is the absence of readily identifiable fungal forms that require special stains (GMS) for identification of the fungi that include septated hyphae and acute angle branching.

- Schizophyllum commune, a basidiomycetous fungus, rare cause of AFS confirmed by sequence analysis
- Radiology:
 - Sinus CT is always abnormal, showing findings of chronic rhinosinusitis that often include central areas of increased contrast (“hyperattenuation”).
 - On rare occasions may be associated with bone destruction

Pathology

Gross

- Material removed from the involved sinus is thick, rubbery to firm, translucent to brown or greenish-brown:
 - Secretions may variably be described as greasy, putty-like, peanut butter-like.
 - May be foul smelling
- Material can attain large size, completely filling a sinus, and be quantitatively abundant.

Histology

- Histologic findings are similar irrespective of the fungal organism involved.
- AFS is characterized by the presence of “allergic mucin” composed of amorphous chondroid-like material associated with a prominent inflammatory cell infiltrate:
 - Amorphous material represents inspissated, gelatinized mucus; the material may have a laminated appearance.
 - Inflammatory component is most often composed of eosinophils and neutrophils; scattered plasma cells, lymphocytes, and histiocytes may also be seen.
 - Charcot-Leyden crystals may be seen among the eosinophilic infiltrate:
 - Elongated and needle-like in appearance
 - Composed of lysophospholipase
 - Stain purple-red on trichrome
 - Desquamated respiratory cells can be identified within this amorphous material.
 - Histologic appearance may suggest:
 - Necrotic debris, but on closer inspection necrotic tissue/cells are not identified
 - Epithelial neoplasm such as a pleomorphic adenoma
- Histochemistry:
 - Fungal hyphae may be seen by Gomori methenamine silver (GMS) or periodic acid Schiff (PAS) staining:
 - May be readily identifiable, very limited, or absent
 - Chondroid-like material is mucin positive.

- Fungal forms may be identifiable by special stains, but at times they are scarce; microbiologic culture for speciation is an important diagnostic tool in the identification of a fungal organism.
- Presence of “allergic mucin” is virtually diagnostic for allergic fungal sinusitis, even in the absence of fungal identification by special stains.
- Immunohistochemistry:
 - Epithelial markers (cytokeratins, p63, EMA, others) are negative.
- In situ hybridization (ISH) for abundant fungal rRNA sequences may provide a means for detecting dematiaceous fungi and prove useful for differentiating dematiaceous fungi from other filamentous fungi in fungal rhinosinusitis.

Differential Diagnosis

- Fungus ball (mycetoma) or invasive fungal sinusitis (see below)
- Pleomorphic adenoma
- Misinterpretation of “allergic mucin” as necrotic tissue may suggest the presence of a (necrotic) tumor.
- Rhabdomyosarcoma

Treatment and Prognosis

- Treatment includes surgical debridement and evacuation of involved sinus(es) with postoperative steroid therapy augmented by immunotherapy directed toward the patient’s specific allergen sensitivities:
 - Primary rationale for immunotherapy is to control the allergic diathesis that may be contributing to the patient’s chronic sinus inflammation.
- Antifungal agents are not used unless there is invasion into the tissue; although local topical antifungal agents could be used to reduce antigen load, the efficacy of such measures has not been determined.
- For some patients, recurrences even after clinically adequate initial therapy may occur.
- Approximately 20% of patients may demonstrate paranasal sinus expansion and bone erosion involving surrounding anatomic structures:
 - Such patients may have clinical findings involving the orbit and cranial vault.

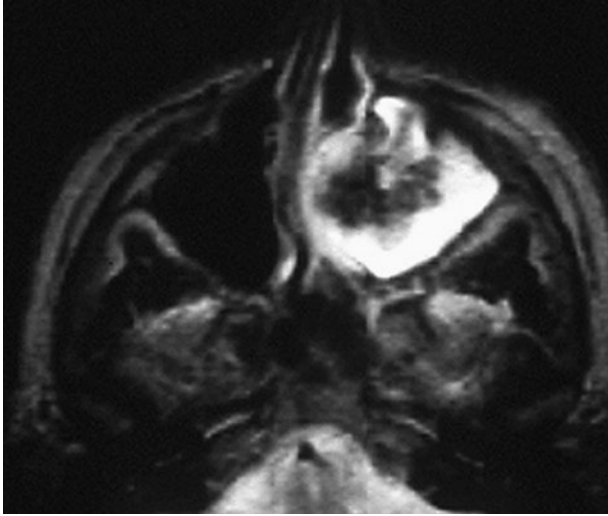
Mycetoma (“Fungus Ball”)

(Figs. 2-41 and 2-42)

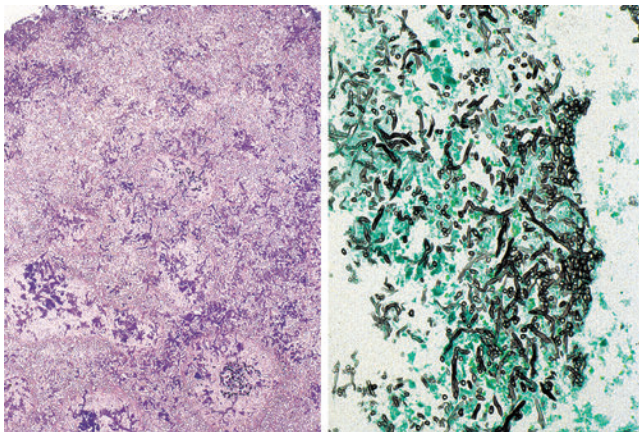
Definition: Indolent growth of fungal hyphae in a sinus cavity to the point at which a mass is formed.

Clinical

- Symptoms are similar to those of nonspecific chronic sinusitis, except that the symptoms usually are relatively unremitting.

**Fig. 2-41.**

Axial T2-weighted MR image shows inflammatory disease with a high signal intensity in the left maxillary sinus. Centrally within the sinus is a region of low signal intensity and signal void. This was an aspergilloma. This patient had aspergillosis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 204, Fig. 3-61.)

**Fig. 2-42. Mycetoma (aspergilloma or fungus ball).**

A, The fungal hyphae are so densely packed that they are somewhat distorted and may not be recognized immediately as a mass of hyphae; closer inspection should make it apparent that the material is packed fungal elements. **B**, GMS stain delineates the fungal spores and hyphae.

- Maxillary sinus is by far the most common site of occurrence.
- Radiographs demonstrate sinus opacification:
 - Calcium oxalate deposition commonly accompanies growth of aspergillus, which may be detected radiographically.

- Because the mass of fungal growth is extensive in a fungus ball, this calcium compound may be detected radiographically.

Pathology

- Histologically, the fungal hyphae are so densely packed that they are somewhat distorted and may not be recognized immediately as a mass of hyphae; closer inspection should make it apparent that the material is packed fungal elements.
- Histochemistry:
 - Special stains for fungi (e.g., GMS, PAS) delineate the fungal forms.
- Mucosal-based dense chronic inflammation may be present.
- Tissue invasion by fungi is not present.
- Calcium oxalate crystals appear as radiating clusters of birefringent crystals:
 - Characteristics of *Aspergillus niger* and may be seen in association with *Aspergillus flavus*.
- Differential diagnosis
 - Allergic fungal sinusitis
 - Invasive fungal sinusitis

Treatment and Prognosis

- Conservative treatment, usually consisting of surgical removal of the fungal mass and some increased aeration of the sinus, may be all that is necessary to prevent recurrence of the mycetoma.

Invasive Fungal Sinusitis (Fig. 2-43)

Definition: Acute, fulminant fungal infestation of the sinonasal tract often resulting in destruction of the involved sinus(es) within days.

Clinical

- Typical clinical scenario is the occurrence in immunocompromised patients.
- Presentation includes nasal discharge and sinus pain:
 - Swelling of the face (maxillary area and periorbital region) may be present.
 - With progression of disease, blindness may occur.
- The clinical picture of fulminant infection may be more similar to the clinical picture associated with “mucormycosis” than to the clinical features of the other forms of sinonasal aspergillosis.
- Patients may require immediate surgical debridement, which in turn may necessitate intraoperative consultation (i.e., frozen section) to determine the cause of the fulminant clinical picture:
 - Pathologists are tasked to histologically evaluate for the presence of fungi.
 - In addition to immediate histologic assessment, intraoperative samples should be sent for

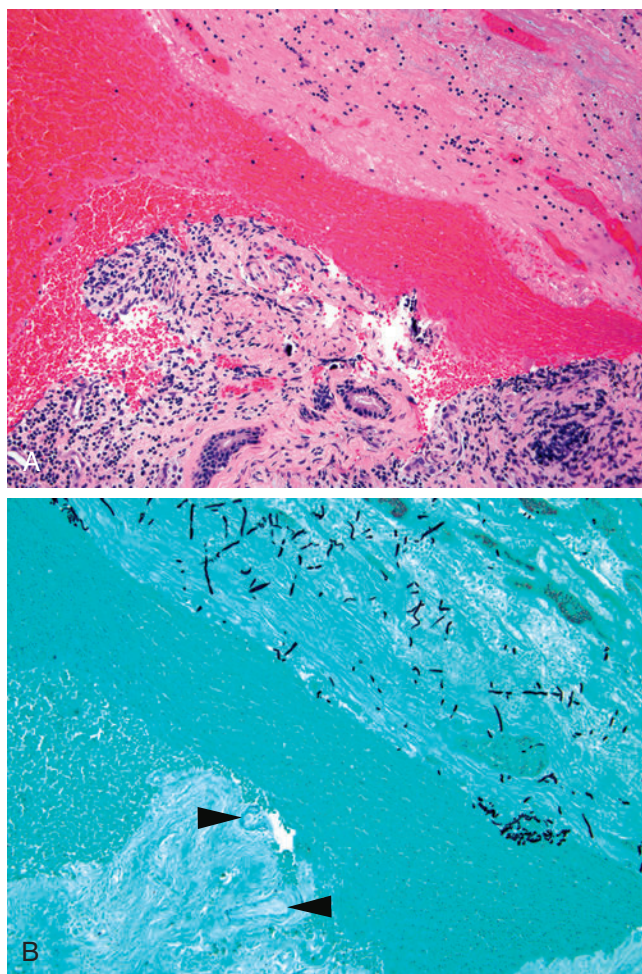


Fig. 2-43. Invasive fungal sinusitis.

A, Sinonasal mucosa showing hemorrhage and tissue necrosis with residual identifiable seromucous glands (lower portion of image). **B**, GMS stain shows extensive fungal invasion of sinonasal mucosa within necrotic tissue (upper portion of image); the outlines of viable seromucous glands are present (arrowheads).

microbiologic culture to be sure of the causative fungus.

Pathology

Histology

- Fungal forms are identified throughout resected tissue; when intact, fungi can be seen within mucosal and submucosal tissues, as well as in and around vascular spaces (angioinvasion).
- Tissue necrosis is evident, but an inflammatory response often is limited.
- Histochemistry:
 - Stains for fungi (e.g., GMS, PAS) delineate the fungal forms.

- In situ hybridization (ISH) using specific fungal probes (biotin-labeled oligonucleotide probes targeting *Aspergillus* sp., *Fusarium* sp., *Rhizopus* sp., and a sequence identified in dematiaceous fungi) can effectively identify fungi in (acute) invasive fungal sinusitis as well as in species identification in specimens with negative cultures.

Differential Diagnosis

- Mucormycosis

Treatment and Prognosis

- Treatment requires surgical intervention with anti-fungal chemotherapy:
 - Amphotericin B
 - Triazoles, including itraconazole, posaconazole, and voriconazole
- Increased morbidity and mortality unless prompt therapy is initiated; even with prompt therapy, the prognosis remains guarded:
 - Overall mortality remains high; only half of the patients survive.
 - Patients with diabetes appear to have a better overall survival rate than patients with other comorbidities.
 - Patients who have intracranial involvement or who do not receive surgery as part of their therapy have a poor prognosis.

Sinonasal Mucormycosis

(Figs. 2-44 through 2-46)

Definition: Acute, rapidly evolving fungal infection of the sinonasal region caused by the Zygomycetes class of primitive fungi.

Synonyms: Mucormycosis; zygomycosis; rhinocerebral or rhinorbitocerebral mucormycosis

- Human pathogens in the Zygomycetes class include the orders Mucorales and Entomophthorales.
- Three fungal genera designated *Rhizopus*, *Mucor*, and *Absidia* are included within the order Mucorales, family Mucoraceae.
- These infections are also sometimes labeled after the higher level class grouping of Zygomycetes, formerly Phycomycetes.
- Some species in the order Entomophthorales can cause mild infections, but this is not the severe clinicopathologic entity generally implied by mucormycosis.
- Mucorales sp. appear as relatively large/broad in diameter (10 to 20 μ m), nonseptated hyphae with branching at haphazard angles. Very rare septations may be seen, and the presence of septation does not exclude the diagnosis. Partially distorted hyphae are often seen and frequently appear twisted.

**Fig. 2-44.**

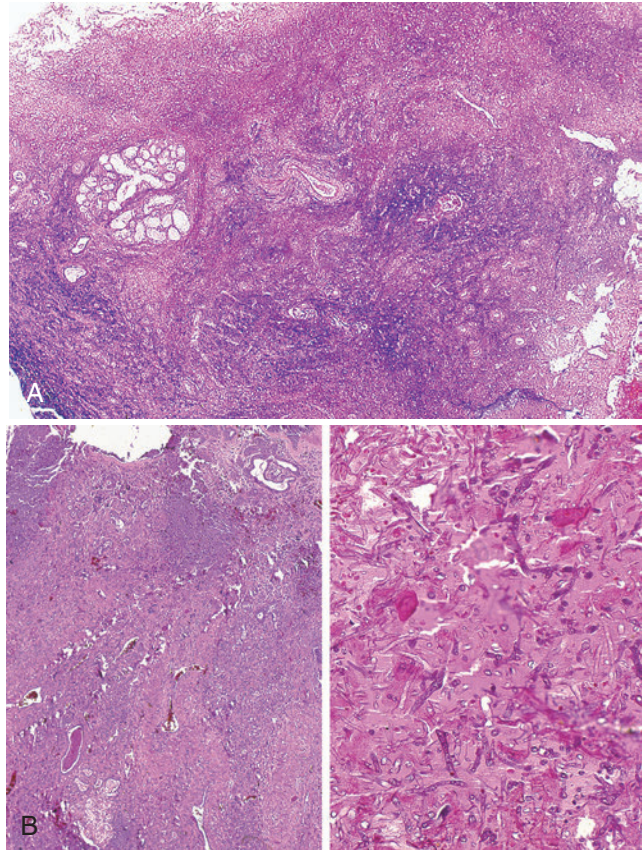
Sinonasal mucormycotic infection in this relatively young immunosuppressed patient resulted in an erosive nasal cavity mass with nasal septal perforation, black necrotic crusts, and gangrenous change.

**Fig. 2-45. Sinonasal mucormycosis.**

In this patient treatment was not immediately initiated and the infectious process spread to facial skin, the eyes, and periorbital tissues, necessitating orbital exenteration.

Clinical

- Mode of transmission is thought to occur via inhalation.
- Patients may present with the signs of an ordinary “cold” with blood-tinged nasal discharge.
- Primarily occurs in adult immunocompromised patients but rarely occur in pediatric immunocompromised patients
- Typical occurrence is in patients with diabetes mellitus, particularly those with the complication of diabetic ketoacidosis and/or immunocompromised patients, including patients with AIDS:

**Fig. 2-46. Sinonasal mucormycosis.**

A, At low magnification the appearance is that of an “ischemic type” geographic necrosis with effacement of the normal mucosal architecture, although residual seromucous glands are focally present; the ischemic type necrosis is due to the angiotropism of the fungi with thrombosis of the involved vessel(s) and subsequent tissue necrosis. **B**, *Left panel*, although there is minimal inflammation the tissue is infested by (*right panel*) innumerable fungi that in contrast to *Aspergillus* sp. are relatively large/broad in diameter and have nonseptated hyphae with branching at haphazard angles.

- Due to immunosuppression or diabetic acidosis, body defenses are not sufficient to ward off the invading organism.
- Black necrotic crusts appear on the nasal mucosa.
- Nasal septal perforation may ensue.
- Gangrenous change may develop rapidly and, unless aggressive therapeutic intervention ensues, the process may spread to facial skin, the eyes and periorbital tissues, and into the central nervous system; spread to distal anatomic sites may occur.
- *Rhizopus* sp. is the most commonly cultured species of the three genera that cause sinonasal mucormycosis.

- Radiology:
 - Extension of disease from the nasal cavity and paranasal sinus may include orbital involvement resulting in extension of the inflammatory process along the infraorbital fissure into the infratemporal fossa and extension into the cavernous sinus.
 - Clinically, orbital involvement may include proptosis, ptosis, ophthalmoplegia, loss of vision, and orbital cellulitis.

Pathology

Gross

- Tissue fragments often are hemorrhagic and dark in appearance owing to tissue necrosis.
- Given the need for aggressive surgical debridement, the tissue fragments may include bone.

Histology

- Diagnostic finding is the presence of fungal hyphae within resected tissues; the fungi are usually identifiable by hematoxylin and eosin staining (see above for description of the fungal forms).
- Fungi are angiotropic, including perivascular localization and angioinvasion; the latter includes through the vessel wall and into the lumen:
 - Luminal involvement may result in complete obstruction and thrombosis that may result in tissue necrosis (“gritty” type necrosis) in a geographic pattern; similar findings can be seen in aspergillosis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and nasal type NK/T cell lymphoma.
- Surrounding tissues include a mixed inflammatory cell infiltrate, hemorrhage, and necrosis; rarely, foreign body–type multinucleated giant cells may be identified, within which fungi may be identified.
- Histochemistry:
 - Stains for fungi (e.g., GMS, PAS) delineate the fungal forms.

Differential Diagnosis

- *Aspergillus* sp. or an aspergillus-like fungus:
 - In comparison to *Mucor* sp., *Aspergillus* and aspergillus-like fungi are generally smaller, more uniform in size, more uniformly show acute angle branching of the hyphae, and show the presence of septations.
- Granulomatosis with polyangiitis (formerly Wegener granulomatosis)

Treatment and Prognosis

- Therapy includes surgical removal of necrotic or gangrenous tissue and administration of amphotericin B.

- Increased morbidity and mortality unless prompt therapy is initiated; even with prompt therapy, the prognosis remains guarded:
 - Overall mortality remains high, with only half of the patients surviving.
 - Patients with diabetes appear to have a better overall survival than patients with other comorbidities.
 - Patients who have intracranial involvement or who do not receive surgery as part of their therapy have a poor prognosis.

Rhinosporidiosis (Figs. 2-47 and 2-48)

Definition: Chronic infectious disease of the upper respiratory tract (nasal cavity and nasopharynx) characterized by formation of polypoid masses and caused by the sporulating organism *Rhinosporidium seeberi* (*R. seeberi*).

Clinical

- Endemic in India, Sri Lanka, and Brazil with only sporadic occurrence in the United States
- More common in men than in women; affects all ages but most common in the third and fourth decades of life
- Thought to be a zoonotic organism, as rhinosporidiosis seen in cattle, horses, and mules
- Mode of transmission is thought to occur via water or dust from which the endospore penetrates the



Fig. 2-47. Rhinosporidiosis.

The resected specimen is a polypoid mass that grossly resembles sinonasal inflammatory polyps.

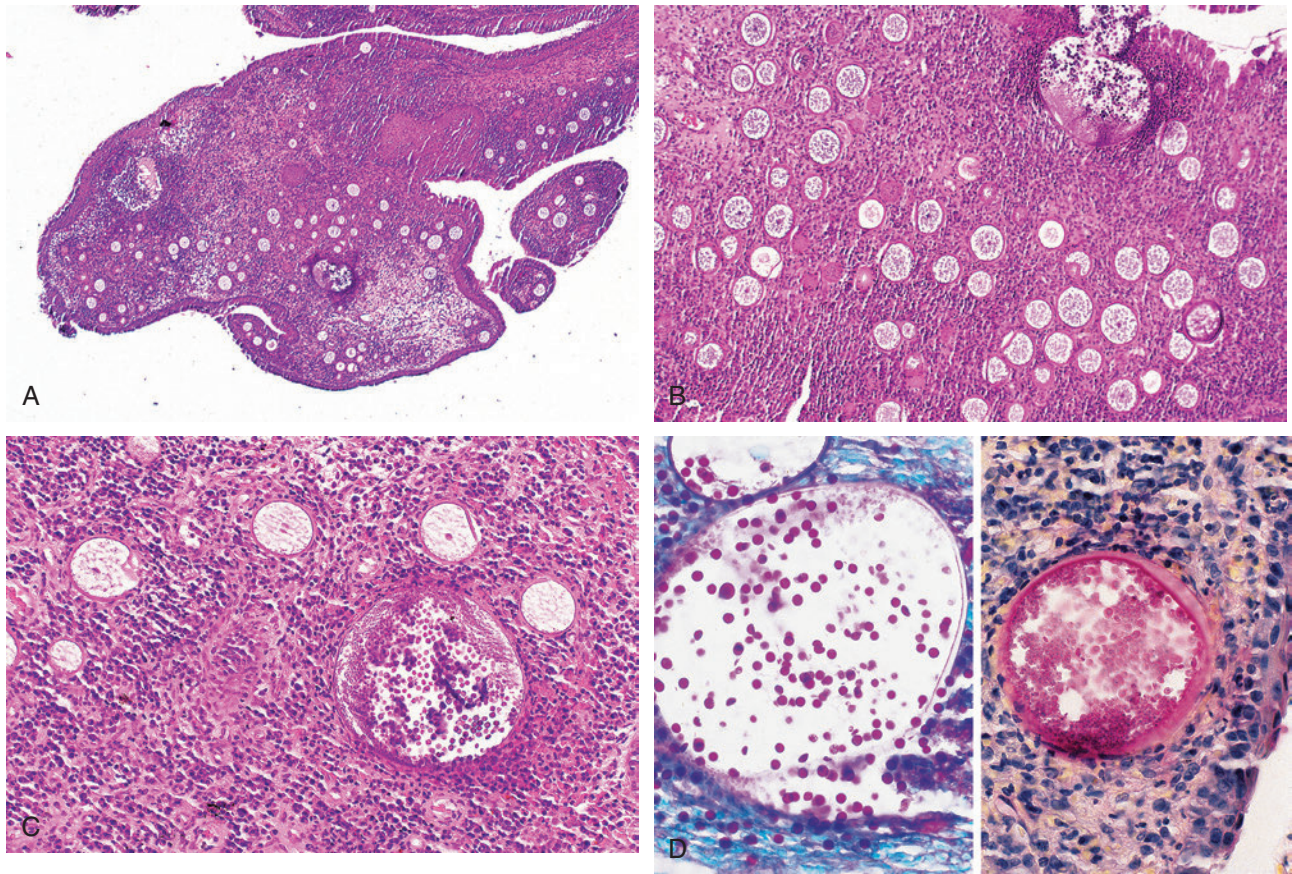


Fig. 2-48. Rhinosporidiosis.

A, Sinonasal rhinosporidiosis appearing as a polypoid lesion characterized by the presence of multiple submucosal cysts (sporangia); the overlying epithelium is hyperplastic with associated squamous metaplasia. **B**, Submucosa with multiple, variably sized sporangia. **C**, The sporangia contain innumerable endospores; an associated chronic inflammatory response consisting of lymphocytes, plasma cells, and eosinophils accompany the microorganisms; cysts may rupture, resulting in a microabscess formation (not shown), but usually a granulomatous reaction is not present. **D**, Although the microorganisms (*R. seeberi*) are readily identifiable by hematoxylin and eosin staining, additional stains may be used to detail these fungi, including, *left*, periodic acid-Schiff (PAS), and *right*, mucicarmine.

nasal cavity mucosa, matures into sporangium within the submucosal compartment, and following maturation the sporangia burst with release of endospores into surrounding tissue.

- Most common sites of involvement are the nasal cavity (inferior turbinate along the lateral nasal wall) and the nasopharynx:
 - Infection may involve the mucosa of the larynx, tracheobronchial tree, esophagus, pharyngeal-oral, palpebral conjunctiva, and ears.
- Most common symptoms include nasal obstruction, epistaxis, and rhinorrhea.
- Infection is a chronic, indolent one, and the causative organism does not seem to be contagious; patients are usually healthy.
- *R. seeberi* is a fungal organism that does not grow on synthetic media (although it has been propagated in cell culture media).

Pathology

Gross

- Single or multiple polypoid, pedunculated, or sessile masses:
 - Grossly resemble sinonasal inflammatory polyps
- Cut section shows pink to purplish-appearing tissue with glistening mucoid surface; microcysts may be seen in the submucosal stroma.

Histology

- Mucosal and submucosal cysts (sporangia) ranging in size from 10 to 300 μ m in diameter
- Sporangia contain innumerable sporangiospores (endospores) seen by hematoxylin and eosin; two sizes of sporangiospores may be seen, including:
 - Smaller spores measuring approximately 1 to 2 μ m in diameter

- Larger spores measuring approximately 5 to 10 μm in diameter
- Larger spores are the more mature forms.
- Larger spores tend to congregate toward the center with the smaller being more peripheral, creating a zonated appearance relative to spore size.
- Smaller cystic structures (without sporangiospores) ranging from 10 to 100 μm are also seen:
 - These smaller cystic structures are called trophocysts.
 - Considered to result from autoinfection via mature sporangiospores released from ruptured sporangia
 - Sporangia and trophocysts have eosinophilic walls measuring several μm in thickness.
- A chronic inflammatory response consisting of lymphocytes, plasma cells, and eosinophils accompanies the microorganisms.
- Rupture of the cysts induces an acute inflammatory response; however, a granulomatous reaction is not seen.
- Overlying epithelium may be hyperplastic and/or demonstrate squamous metaplasia.
- Histochemistry:
 - Microorganisms stain with periodic acid-Schiff (PAS) and mucicarmine.

Differential Diagnosis

- Coccidioidomycosis infection (*Coccidioides immitis*):
 - *R. seeberi* is usually much larger than *C. immitis*.
 - The wall of *R. seeberi* stains with mucin.
 - *C. immitis* does not stain with mucin.
- Schneiderian papilloma, cylindrical cell type:
 - Surface epithelial neoplastic proliferation that occasionally can be confused with rhinosporidiosis:
 - Histologically characterized by epithelial neoplastic proliferation (see next chapter)
 - Intraepithelial cysts are seen in Schneiderian papilloma, cylindrical cell type, whereas the cysts associated with rhinosporidiosis are intraepithelial and submucosal.

Treatment and Prognosis

- Surgical excision
- Recurrences, necessitating additional surgical excision, may occur in up to 10% of cases.
- No antibiotic therapy is effective.

Other Fungi (Fig. 2-49)

- Other fungal diseases of the sinonasal tract include sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis.
- Sinonasal infection by these fungal diseases is rare.

- *Sporotrichum schenckii* is the causative organisms in sporotrichosis and may be the cause of a primary nasal cavity infection.
- Sinonasal blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis rarely infect the sinonasal tract; infection of other sites (especially the lungs) often is part of the clinical picture.
- Infection with these fungi may result in pseudoepitheliomatous hyperplasia that clinically and pathologically may suggest an epithelial neoplasm.

BACTERIAL INFECTIONS

Rhinoscleroma (Fig. 2-50)

Definition: Chronic granulomatous infectious disease primarily occurring in the upper respiratory tract (nasal cavity and nasopharynx) caused by *Klebsiella rhinoscleromatis*.

- *K. rhinoscleromatis* is a gram-negative diplobacillus of the family Enterobacteriaceae:
 - Organism measures about 2.5 μm in length and is encapsulated.
 - Can be cultured on simple media
 - Not considered contagious (or is only minimally so)

Synonyms: Scrofulous lupus; scleroma; organism also referred to as “Frisch bacillus,” named for Anton von Frisch who identified organism in 1882

Clinical

- No gender predilection; can occur in all ages but tends to be more common in young age groups, including the first three decades of life
- Disease of lower socioeconomic class in which poor living conditions and malnutrition fosters the growth and spread of disease
- Endemic in Egypt, parts of Central and South America, North and Central Africa, and Eastern Europe
- Occurs but considered uncommon in the United States
- Infection manifests initially in the nasal cavity (nasal septum) and spreads posteriorly to the nasopharynx; other sites of involvement include the paranasal sinuses, orbit, larynx, tracheobronchial tree, and middle ear.
- Three clinical phases/stages, including:
 1. Rhinitic, exudative, or catarrhal stage:
 - Characterized by mucopurulent nasal discharge
 - This stage can continue for many months or even years; appearance of a granular nasal mucosa can herald the progression to the next stage.

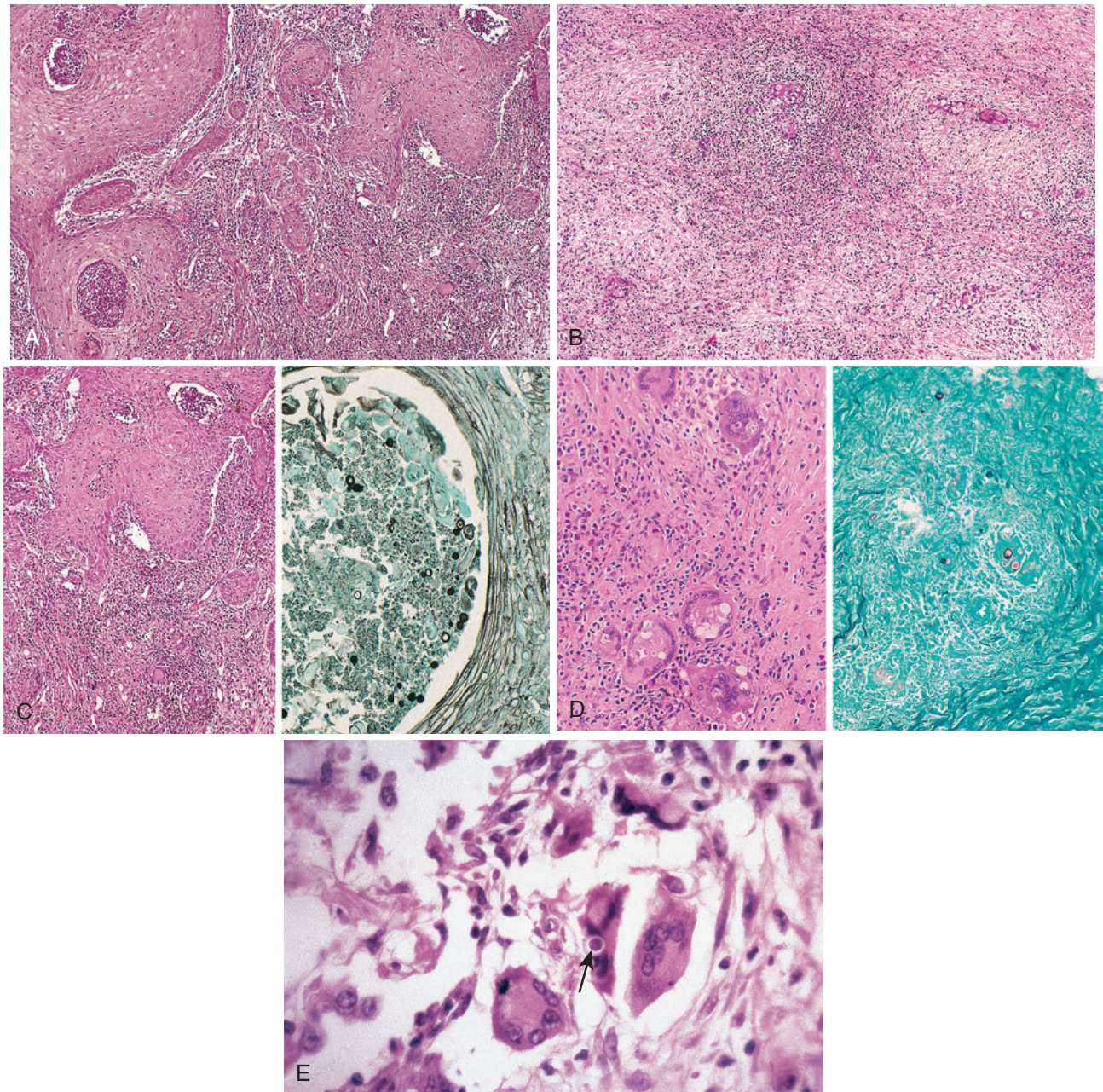


Fig. 2-49. Sinonasal blastomycosis.

A, The induction of a pseudoepitheliomatous hyperplasia in the face of blastomycotic infection may suggest an epithelial neoplasm; intraepithelial microabscesses including giant cells and giant cells within the submucosa are present.

B, Numerous multinucleated giant cells are present within the submucosa. **C**, *Left panel*, intraepithelial giant cells contain (*right panel*) fungi (GMS stain). **D**, *Left panel*, submucosal giant cells contain (*right panel*) fungi (GMS stain).

E, Under oil immersion the microorganism is encapsulated and located within a giant cell.

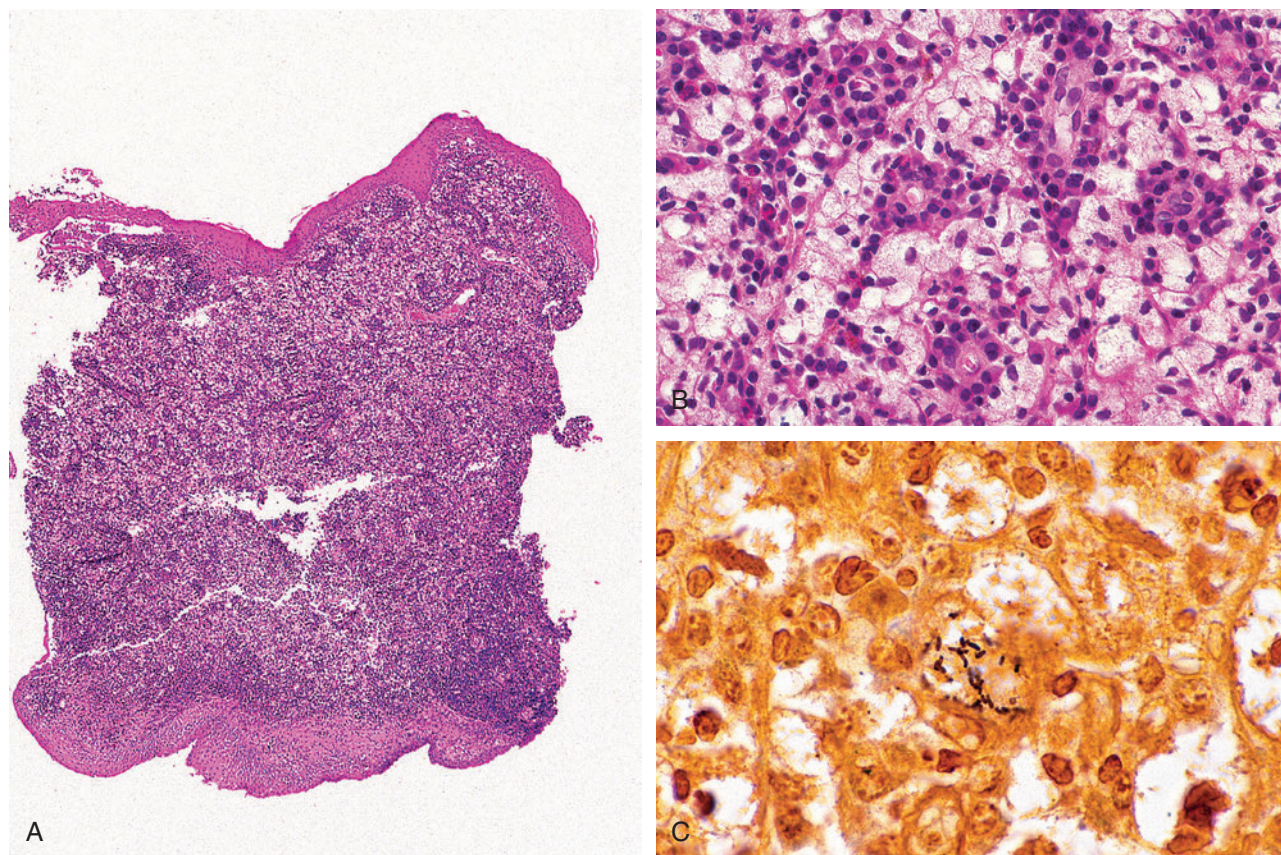


Fig. 2-50. Sinonasal rhinoscleroma.

A, A diffuse submucosal infiltrate is present, replacing seromucous glands with squamous metaplasia of the overlying epithelium; although not depicted here, rhinoscleroma may be associated with pseudoepitheliomatous hyperplasia. **B**, The cellular infiltrate in rhinoscleroma includes an admixture of mature lymphocytes, plasma cells, scattered eosinophils, and neutrophils, but the predominant cell type is macrophages with clear to foamy cytoplasm (Mikulicz cells). **C**, Warthin-Starry silver stain demonstrates the presence of the *K. rhinoscleromatis*, a gram-negative bacteria, within the macrophages.

2. Florid or proliferative stage:
 - Marked by mucosal thickening, which may result in nasal obstruction; diagnosis is usually made in this phase.
 - Results in a mass-like growth composed of firm nodules (consistency of cartilage) and a reddish appearance
 - Mass lesion may cause nasal expansion and deformity with some facial mutilation.
 - Bone erosion may contribute to radiographic findings, raising suspicion for a malignancy.
3. Fibrotic or cicatricial stage:
 - Represents resolution of disease
 - Generally follows therapy initiated during the second stage
 - Results in “burnt-out” fibrosis causing deformity but nasal discharge abates (relatively dry nose) and without further progression locally
 - Spread to other areas of the respiratory tract may occur during this phase.

- Reported in association with extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

Pathology

Gross

- Typically, in the florid or proliferative phase the infected mucosa is pale in appearance and demonstrates diffuse nodular thickening.

Histology

- Characteristic lesion seen in the florid or proliferative phase consists of a submucosal granulomatous infiltrate composed of macrophages with clear to foamy cytoplasm (Mikulicz cells) intimately associated with an admixture of lymphocytes and numerous plasma cells:
 - Macrophages (Mikulicz cells) harbor the bacteria
 - Number of Mikulicz cells varies with the stage of the disease; in the proliferative stage they are plentiful and readily identifiable.

- Overlying epithelium may demonstrate a squamous metaplasia or pseudoepitheliomatous hyperplasia; rarely, ulceration is seen.
- Characteristic Mikulicz cells may be difficult to identify in the fibrotic phase.
- Histochemistry:
 - Organisms (bacterial rods) are best detected by silver stain (Warthin-Starry stain).
 - Tissue Gram stain and Giemsa stain may also reveal the microorganisms but may be falsely negative.
- Immunohistochemistry:
 - Macrophages (Mikulicz cells) are CD68 positive but negative for S100 protein, CD1a, and Langerin.
- Primarily occurs as a skin-related lesion; rarely affects viscera (e.g., lung, liver, kidney, bowel, brain, orbit, spleen, lymph nodes, tonsil, sinonasal tract)
- Localized lesion that may clinically simulate the appearance of an aggressive neoplasm:
 - May occur in healthy individuals, patients with chronic disease or immune compromised conditions (e.g., cystic fibrosis, diabetes mellitus, chronic granulomatous disease, AIDS, other)
 - Patients with sinonasal disease may present with persistent headache, bulging eye.
 - Radiographic evidence of an expansile paranasal sinus-based lesion with bony erosion may be present.
- Histopathology includes:
 - Presence of amorphous, acellular material with deposition of proteinaceous material and inorganic compounds
 - Separate, rounded eosinophilic grains or granules associated with a neutrophilic infiltrate:
 - Grains or granules contain the causative bacterial organisms.
 - Club-like or radiating projections form along the periphery and are referred to as the Splendore-Hoepli phenomenon:
 - Considered to represent an antigen-antibody reaction
 - Can be seen in association with other organisms including actinomyces, fungi, bacteria, helminthes, mycetoma, phycomycosis, as well as in association with silk sutures
 - Filamentous gram-negative bacilli morphologically compatible with *P. aeruginosa* identified, but bacteria may not be readily identifiable, and if this diagnosis is not considered and/or if the pathologist is not familiar with this entity, the diagnosis may be overlooked.
 - Histochemical bacterial stains (Gram, Brown and Hopps) delineate the presence of bacteria.

Differential Diagnosis

- Syphilis
- Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
- Inflammatory (pseudo)tumor/plasma cell granuloma
- Clinically, may be suggestive of granulomatosis with polyangiitis (formerly Wegener granulomatosis) or a malignant lymphoma

Treatment and Prognosis

- Treatment of choice is long-term antibiotic therapy (tetracycline, streptomycin, thiopenicol, ciprofloxacin) followed by surgical debridement.
- Surgical resection may be necessary where airway obstruction may be life threatening.
- CO₂ laser surgery may represent an alternative means of therapy.
- Prognosis is good following initiation of antibiotic therapy, although may be high recurrence rates:
 - High rates of recurrence necessitate long-term follow-up.

Miscellaneous Sinonasal Bacterial Infections

Pseudomonas aeruginosa (Botryomycosis) (Fig. 2-51)

- Botryomycosis is a chronic bacterial infection analogous to a “fungus ball,” except the mass of microorganisms is composed of bacteria, usually *Pseudomonas* sp., that usually is a cutaneous (skin and subcutaneous tissue) lesion and uncommonly is mucosal based.
- Term *botryomycosis* is used to describe a lesion resembling mulberry or a “bunch of grapes” (Greek *botryos*), which was initially believed to be caused by a true fungus.
- **Synonym:** Also referred to as “bacterial ball”

- Microbiologic cultures confirm *Pseudomonas* infection.
- Surgical evacuation is curative.
- Botryomycotic lesions are generally resistant to antimicrobial therapy:
 - Due to associated fibrosis and the compactness of the granules characteristic of botryomycotic lesions, therapeutic drug levels may not reach the microorganisms.

Mycobacteria leprae (Fig. 2-52)

- Leprosy, also referred to as Hansen disease, is an infection caused by *Mycobacterium lepra*.
- Leprosy is characterized by cutaneous, mucosal, and peripheral nerve involvement.
- The microorganism:

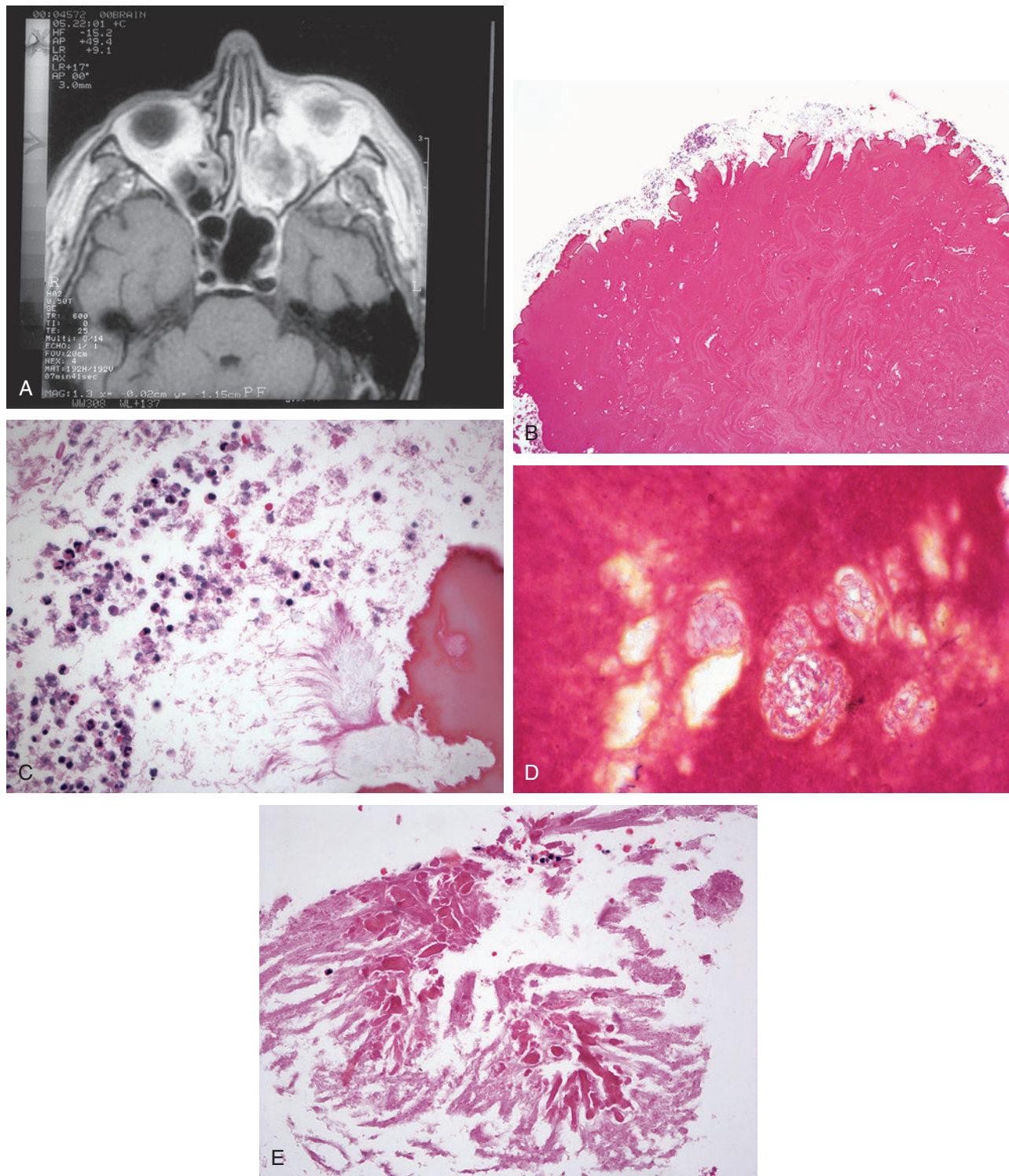


Fig. 2-51. Sinonasal botryomycosis (bacterial ball).

A, T1-weighted, gadolinium-enhanced axial MRI showing left sinus opacification with mass-like extension into the ethmoid sinus and nasal cavity. **B**, Amorphous, acellular material with deposition of proteinaceous material and inorganic compounds. **C**, At higher magnification separate, rounded eosinophilic grains or granules associated with a neutrophilic infiltrate are seen; the grains or granules contain the causative bacterial organisms. **D**, Filamentous gram-negative bacilli morphologically compatible with *P. aeruginosa* are present (Gram stain). **E**, Splendore-Hoeppli phenomenon characterized by the presence of club-like or radiating projections forming along the periphery can be seen in botryomycosis but is not unique to this lesion and can be seen in association with other organisms, including actinomyces, fungi, bacteria, helminthes, mycetoma, phycomyces, as well as in association with silk sutures.

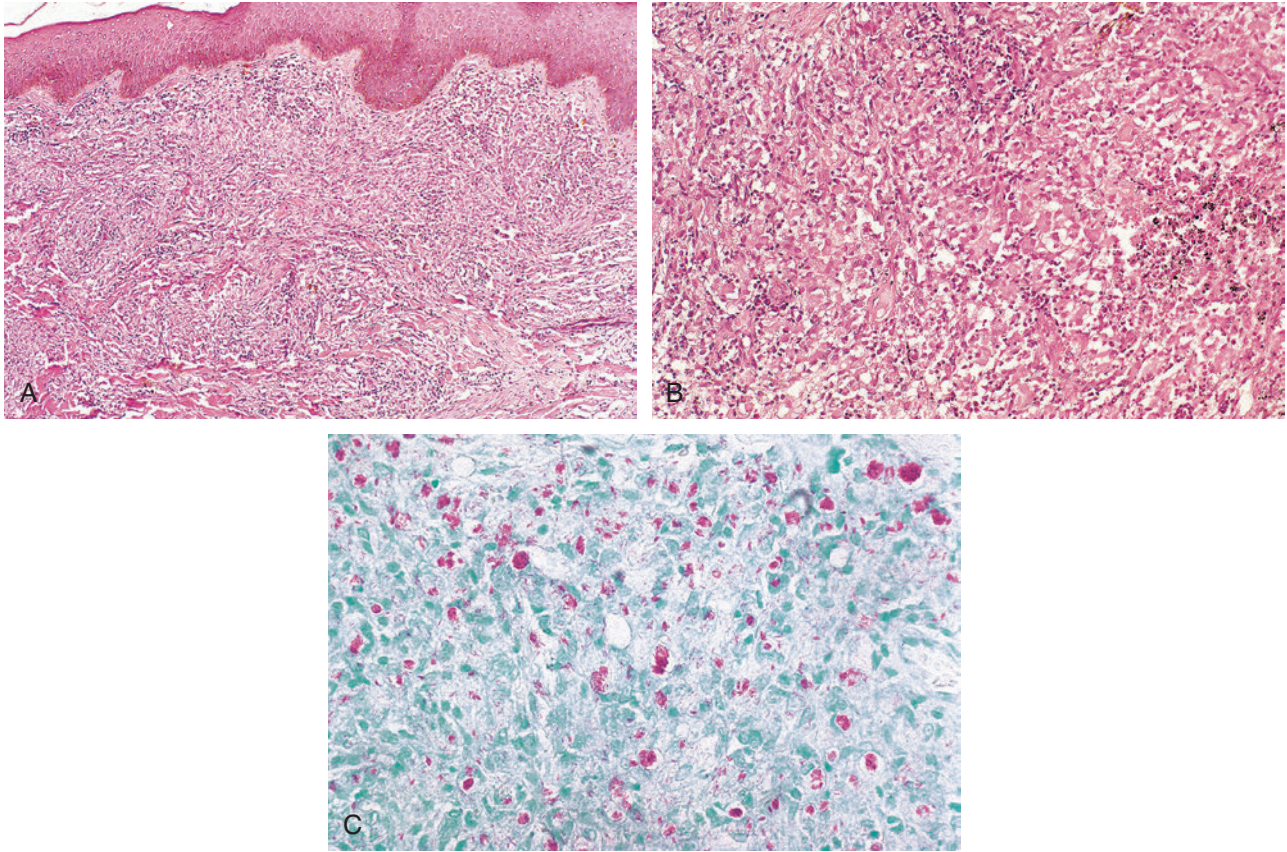


Fig. 2-52. Sinonasal leprosy (Hansen disease), lepromatous leprosy.

A, Diffuse submucosal inflammatory cell proliferation; due to decrease in the host's cell-mediated immunity there is no granulomatous inflammation as would be expected in tuberculoid leprosy. **B,** At higher magnification numerous vacuolated histiocytes (so-called lepra cells) are present. **C,** Abundant *M. lepra* microorganisms are present within the vacuolated histiocytes (lepra cells) by special stain (Fite [modified acid-fast bacilli] stain).

- Has low infectivity and exposure rarely results in infection
- Is believed to require cool host body temperature for survival
- Affects cooler peripheral areas of the body including digits, ears, nose, nasal cavity
- Sinonasal tract (mucosal) involvement is fairly common in patients with this infection and may be important in the transmission of the disease:
 - Nasal secretions contain high numbers of infectious bacilli.
 - Initial site of infection may be the nasal or oropharyngeal mucosa.
 - Oral lesions are not uncommon.
 - Less common sites of involvement of the upper aerodigestive tract include the larynx.
- Patients with sinonasal tract involvement may present with mucopurulent rhinosinusitis, nose-bleeds, and anosmia:
 - Early lesions may appear plaque-like.
 - Late lesions may be ulcerative and nodular and may result in collapse of the bridge of the nose.
- Due to involvement of peripheral nerves, pain and muscular atrophy, as well as sensory loss, frequently occur:
 - Sensory loss begins in the extremities and spreads to the rest of the body.
- Host genetic factors are thought to influence susceptibility to infection as well as disease progression:
 - Variants of genes in the NOD2-mediated signaling pathway (which regulates the innate immune response) are associated with susceptibility to infection with *M. leprae*.
- Two main clinical presentations occur based on the immune reaction to the microorganism:
 - Tuberculoid leprosy (TL):
 - Also referred to as paucicellular leprosy
 - Develops in patients with high immune reaction

- Disease is usually localized.
- Lepromin skin test is positive:
 - Purified suspension of heat-killed microorganisms
- Microorganisms are typically absent in skin biopsy.
- Lepromatous leprosy (LL):
 - Also referred to as multibacillary leprosy
 - Develops in patients with reduced cell-mediated immune reaction
 - Disease is usually diffuse.
 - Face is a common site of involvement and may result in so-called leonine facies due to skin enlargements and facial distortion.
 - Lepromin skin test is negative.
 - Microorganisms are typically present in skin biopsy.
- Variants include borderline tuberculoid and borderline lepromatous.
- Histology:
 - Tuberculoid leprosy characterized by:
 - Well-formed granulomatous inflammation with admixture of histiocytes, multinucleated giant cells, and lymphocytes
 - Paucity of microorganisms by special stains
 - Lepromatous leprosy characterized by:
 - Absence of granulomatous inflammation
 - Presence of sheets of lymphocytes and vacuolated histiocytes (lepra cells)
 - Abundant microorganisms by special stains
- For both types the histopathologic process is typically submucosal.
- Involvement of nerves by the inflammatory reaction is a helpful diagnostic finding.
- Histochemistry:
 - Special stains for microorganisms including acid-fast bacilli, Fite stain assist in identifying the presence of organisms.
- *M. leprae* does not grow on artificial media.
- Rapid quantitative serologic test assists in the detection of *M. leprae* infection:
 - Early detection of infection followed by effective treatment is critical to reduce disease progression.
 - New leprosy serologic test (NDO-LID) detects larger proportions of leprosy infection than alternative standard diagnostics leprosy test, including detection of paucibacillary leprosy.
 - Quantifiable nature of this NDO-LID also can be used to monitor treatment efficacy.
 - NDO-LID assists in diagnosis and monitoring of leprosy and can detect a significant number of earlier-stage infections.
- Molecular biologic techniques (polymerase chain reaction) assist in detecting the presence of microorganisms.

- Treatment includes:
 - Antibiotic therapy:
 - Rifampin and dapsone for tuberculoid leprosy (6-month course)
 - Rifampin and dapsone and clofazimine for lepromatous leprosy (12-month course)
 - Reconstructive surgery

Other Mycobacterial Infections

- *M. tuberculosis*:
 - Uncommon in sinonasal tract
 - Characterized by presence of well-formed caseating granulomatous inflammation
 - Acid-fast bacilli may be seen by special stains (i.e., AFB) but may be scarce to absent.
 - Microbiologic cultures may be helpful, although mycobacteriae are slow-growers and may take weeks.
 - Molecular biologic techniques facilitate the identification of the microorganism.
 - Differential diagnosis primarily with sarcoidosis
 - Well-formed granulomas are not a feature associated with granulomatosis and polyangiitis (formerly Wegener granulomatosis); rather, scattered multinucleated giant cells are present.
 - See Section 4, Neck, for discussion of *M. tuberculosis*.
- Other mycobacterial infections rarely present in the sinonasal tract including atypical mycobacterial infection:
 - May occur in immunocompromised individuals (e.g., AIDS)
 - In immunocompromised patients, the inflammatory response may not include a granulomatous inflammatory reaction; rather, a mixed inflammatory reaction including lymphocytes and histiocytes may be present.
 - Unless there is a high index of suspicion, this diagnosis may be overlooked.
 - Special stains for acid-fast bacilli confirm the presence of microorganisms.

Syphilis

- For a more complete discussion see Section 2, Oral Cavity.
- Syphilis is a systemic venereal disease caused by *Treponema pallidum*, a member of the family Spirochaetaceae that includes *T. pertenue* (yaws) and *T. carateum* (pinta).
- Clinical stages of syphilis are primary, secondary, tertiary, and congenital, any of which can affect virtually every site in the head and neck.
- Protean clinical manifestations include involvement of the head and neck, including:
 - Tonsillar involvement
 - Skin lesions and lymphadenopathy

- Pharyngotonsillitis
- Other head and neck symptoms in the secondary stage include rhinitis, laryngitis, pharyngitis, cranial nerve deficits, sensorineural deafness, labyrinthitis, and glossitis.
- Tertiary stage typically involves the central nervous system (neurosyphilis) and aorta (cardiovascular syphilis); however, localized, non-progressive lesions may develop in mucosal otolaryngic sites termed “benign tertiary syphilis” or “gummas”; the gummatous reaction represents a pronounced immunologic reaction of the host.
- In patients with a clinical “midline destructive” condition in the nasal cavity, the differential diagnosis may include tertiary syphilis.
- Histology includes a plasma cell endarteritis:
 - Nasal mucosal plasmacellular inflammation conceivably could represent secondary syphilis.
 - Diagnosis may be overlooked if not considered.
 - Serologic testing for syphilis may prove valuable.
 - Nontreponemal (nonspecific) antibody tests
 - Treponemal (specific) antibody tests
 - These tests are most reactive in the secondary stage of disease.

PROTOZOAL NASAL INFECTIONS

Mucocutaneous Leishmaniasis (Fig. 2-53)

- Leishmaniasis is a protozoal infection caused by different species of *Leishmania*; the parasite is transmitted by the bite of an infected female phlebotomine sandfly.
- The disease is prevalent throughout the world.
- Three forms of disease:
 - Cutaneous (Oriental or tropical sore):
 - Caused by *Leishmania tropica* (in Asia and Africa) and *Leishmania mexicana* (in Central and South America)
 - Endemic in the Middle East, around the eastern Mediterranean, in North Africa, and in parts of Asia
 - Acute lesions are usually single papules that may become nodules, ulcerate, heal, and leave a scar.
 - Chronic lesions (persist for 1 to 2 years) are single or occasionally multiple, raised non-ulcerated plaques.
 - Recidivous (lupoid) form includes erythematous papules, often circinate near scars of previously healed lesions

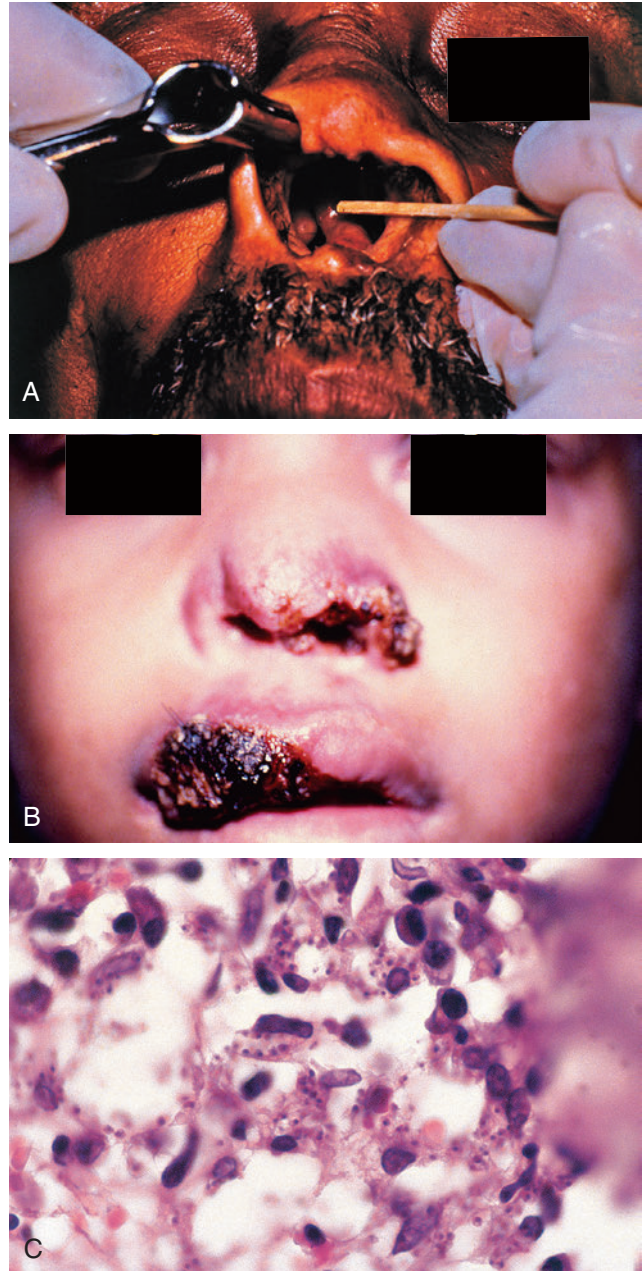


Fig. 2-53.

Mucocutaneous leishmaniasis caused by *Leishmania braziliensis* may result in (A) ulcerative and (B) destructive lesions of the sinonasal tract; this is referred to as espundia. C, The organisms of *L. braziliensis*, referred to as amastigotes, are found within histiocytes often localizing along the periphery of the cells (so-called marquee sign); the organisms are small, ovoid to round with a thin cell membrane, large nucleus, and lack a capsule, which is a differentiating feature from *Histoplasma capsulatum*.

- Disseminated form (primary diffuse cutaneous leishmaniasis) develops in anergic individuals as widespread nodules and macules without ulceration or visceral involvement:
 - Some authorities consider diffuse cutaneous leishmaniasis to represent a fourth form of disease.
- Tardive form represents the development of a lesion at the site of recent cutaneous surgery with the likely source of infection occurring over 5 decades previously.
- Mucocutaneous:
 - Caused by *Leishmania braziliensis*
 - Endemic to Central and South America, or in travelers to those areas
 - Initial lesions resemble those of the cutaneous form
 - Disseminated anergic form is rare and may occur in immunocompromised individuals (e.g., AIDS).
 - Development of destructive ulcerative lesions of mucous membranes referred to as espundia
 - Upper aerodigestive tract sites of involvement include the sinonasal tract, nasopharynx, oral cavity (tongue).
- Visceral:
 - Acute or chronic infection caused by *Leishmania donovani*
 - Synonyms include Kala-azar, dumdum fever, and black fever
 - Widely distributed but occurs predominantly in South America, Africa, the Mediterranean basin (Italy, Greece), and Asia
 - Infects multiple organs and may result in fever, hepatosplenomegaly, weight loss, anemia, and thrombocytopenia
- Leishmaniasis usually starts as a cutaneous lesion at any of a number of sites.
- Sinonasal mucocutaneous infection represents secondary spread from cutaneous infection.
- Histology of mucocutaneous infection includes:
 - Ulceration with marked lymphoplasmacytic cell infiltrate and granulation tissue
 - Pseudoepitheliomatous hyperplasia of the surface epithelium may be present.
 - In the immune competent patient, the inflammatory response may be vaguely granulomatous with some epithelioid histiocytes and scattered giant cells, as well as necrosis (necrotizing granuloma):
 - Number of microorganisms present may be sparse.
 - In diffuse anergic leishmaniasis there is absent granulomatous inflammation and presence of numerous large histiocytes with associated lymphocytes and plasma cells:
 - Numerous microorganisms are present.
- Microorganisms referred to as amastigotes are:
 - Found within histiocytes; tend to be localized at the periphery of the macrophages (so-called marquee sign)
 - Small, ovoid to round and measure 1.5 to 3 μ in diameter
 - Have a thin cell membrane, large nucleus, and a rod-shaped kinetoplast
 - Seen by hematoxylin and eosin staining
 - Nucleus and kinetoplast accentuated by Giemsa stain
 - Often require oil immersion for identification
 - Absence of a capsule assists in differentiating *Leishmania* from *Histoplasma capsulatum*
- Clinical history, especially travel to endemic area, may be necessary to suspect the possibility of this infection.
- Molecular biologic techniques (polymerase chain reaction) assist in detecting the presence of microorganisms.
- Treatment:
 - Various drugs, including antifungal ketoconazole, reported to be effective
 - The most promising drug found is an anticancer compound, miltefosine:
 - Belongs to the alkylphosphocholine group
 - Found to be 94% to 97% effective
 - Limitations include:
 - Cannot be given during pregnancy
 - Shows severe gastrointestinal side effects
 - Very costly
 - Other drugs such as paromomycin, allopurinol, and sitamaquine have been reported with variable cure rates.
 - Combination therapy is recommended, preferably coupled with specific parasite enzyme inhibitors.

VIRAL INFECTIONS

- See Section 2, Oral Cavity, for a more complete discussion on viral diseases.
- Viral infestation of the sinonasal tract is uncommon, but mucocutaneous disease with herpes simplex virus (HSV) and cytomegalovirus (CMV) may occur, especially in immunocompromised patients.
- Human papillomavirus (HPV) and Epstein-Barr virus (EBV) may be seen in association with specific sinonasal tract neoplasms:
 - HPV and Schneiderian papillomas
 - EBV and nasal type NK/T cell lymphoma
 - HPV and carcinomas:
 - See next chapter for HPV-associated sinonasal neoplasms.

SARCOIDOSIS

- See Section 4, Neck, for a complete discussion on sarcoidosis.
- Sarcoidosis of the sinonasal tract may be subclinical and not cause prominent symptoms; occasionally, sinonasal tract involvement may result in a mass-like lesion, and bone erosion may be present.
- Histology is typical for sarcoidosis, including well-formed, non-necrotizing (noncaseating) granulomas; granulomas may be small and scattered in the submucosa.
- A nasal mucosal biopsy in a patient thought clinically to have sarcoidosis may help provide support for the diagnosis.

MYOSPHERULOSIS (Fig. 2-54)

Definition: Innocuous iatrogenically induced pseudomycotic disease resulting from the interaction of red blood cells and petrolatum-based ointments.

Nomenclature: Myospherulosis was initially described in Africa, where lesions affected primarily subcutaneous tissues or muscle, resulting in the designation “myo”-spherulosis.

Clinical

- Typically, prior to the development of a nasal cavity or paranasal sinus mass patients had prior surgery for a variety of disease processes (inflammatory or neoplastic lesions) followed by packing of the area with a petrolatum-based or paraffin-based tetracycline/steroid (Terra-Cortril) ointment:
 - Similar lesions have been seen following surgery involving the ear.
 - Similar lesions reported in soft tissue areas of the extremities.
- Lesion is a chronic, fibrotic tissue reaction resulting from injected or applied medicament that acts as a foreign substance:
 - Origin of the myospherules is from red blood cells, which react with petrolatum or lanolin.

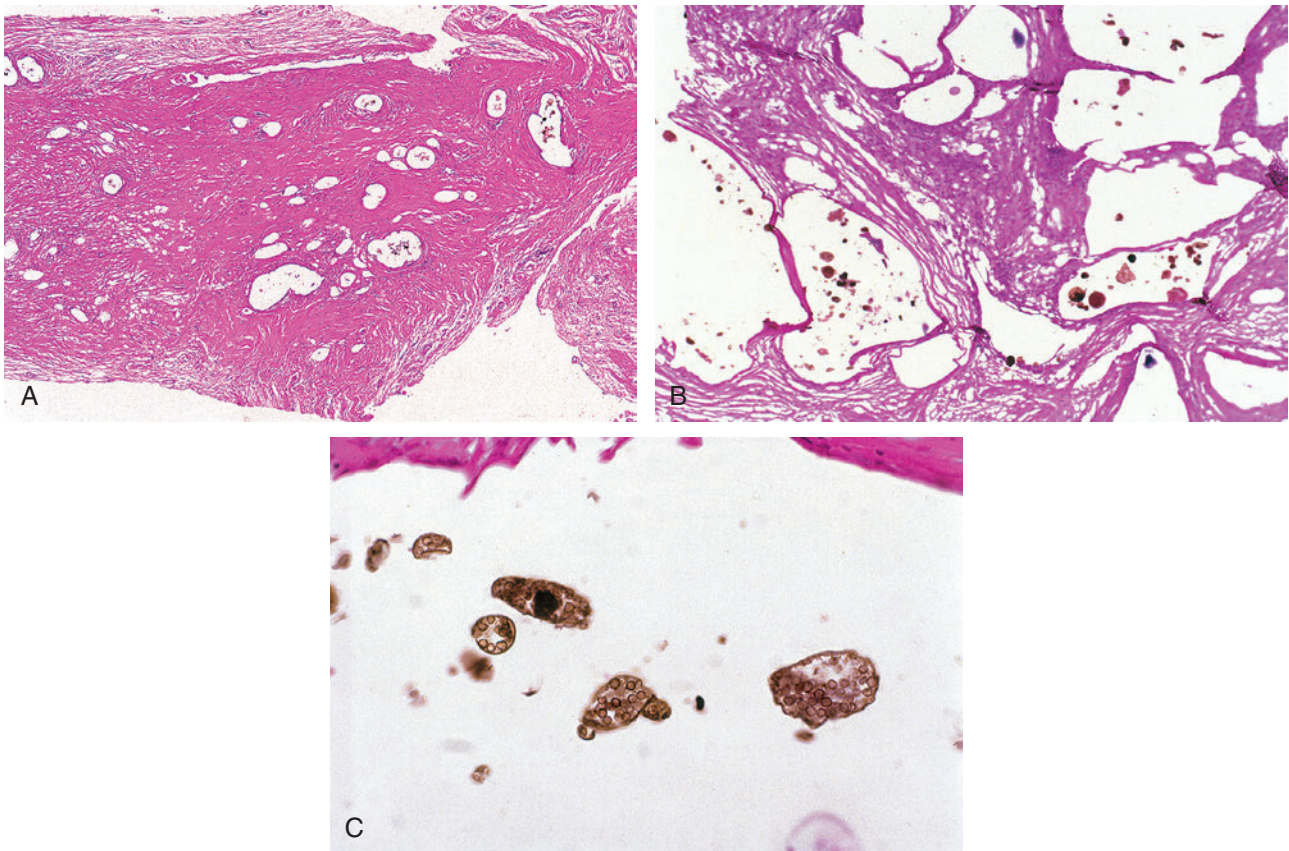


Fig. 2-54. Myospherulosis of the sinonasal tract.

A, Dense fibroconnective tissue within which are embedded multiple, irregularly shaped cystic spaces. **B,** Myospherulosis pseudocystic spaces contain round, saclike structures (“parent bodies”). **C,** The “parent bodies” are brown staining and contain numerous spherules or endobodies; stains for microorganisms are absent.

- Found in ointment used in “packing” the nasal cavity after surgery
- Emulsified fat may also induce the formation of myospherules so that fat necrosis may result in myospherulosis.
- In the nose and paranasal sinuses symptoms generally relate to a mass lesion with or without airway obstruction; local pain and tenderness, signs of malaise, and fever can occur:
 - Lesions may develop from a month to a couple of years after a sinonasal tract surgical procedure.
- Preoperative diagnosis can be suggested on CT of the paranasal sinuses by presence of macroscopic paraffin retention cysts with characteristic fat density.

Pathology

Gross

- No specific macroscopic findings other than a non-descript mass

Histology

- Pseudocysts or microcysts are embedded within fibrotic tissue, creating a “swiss-cheese” appearance.
- Pseudocysts or microcysts:
 - Measure up to 1 mm in diameter
 - Are irregular in contour
 - Contain round, saclike structures called “parent bodies”:
 - Parent bodies measure approximately 50 μ m in diameter.
 - “Parent bodies” in turn contain numerous spherules or endobodies.
 - Spherules or endobodies:
 - Measure approximately 5 μ m in diameter
 - Are variable in size and shape, with cup-shaped forms being common
 - Are usually dark brown in color
- Chronic inflammatory infiltrate composed of lymphocytes, histiocytes, giant cells, and plasma cells:
 - Inflammatory cell infiltrate can be sparse.
 - Occasional multinucleated giant cell of foreign body type may be seen.
- Histochemistry:
 - Stains for microorganisms are negative.
- Characteristic spherules may be sparse or absent; the diagnosis can be suggested even in the absence of spherules given appropriate history, anatomic location, and presence of fibrotic tissue with empty spaces.

Differential Diagnosis

- Fungal infections (rhinosporidiosis, coccidioidomycosis)

Treatment and Prognosis

- Symptomatic treatment that may include conservative surgical removal of fibrotic tissues, which is effective mode of treatment
- Prevention by the use of non-petrolatum-based antibiotic substances

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (ESHML) (Fig. 2-55)

Definition: Idiopathic histiocytic proliferative disorder generally characterized by lymph node–based disease and an indolent behavior; extranodal manifestations occur, with the upper respiratory tract being among the more common sites of involvement.

Synonyms: Rosai-Dorfman disease; Destombes-Rosai-Dorfman syndrome

- Often a nodal-based proliferation occurring as part of a generalized process involving lymph nodes
- May involve extranodal sites independent of the lymph node status
- Head and neck region represents one of the more common extranodal areas affected:
 - Within the head and neck, there is predilection for the nasal cavity and paranasal sinuses.
 - Virtually all head and neck sites may be affected in association with or independent of nodal disease.

Clinical

- Slightly more common in women than in men; occurs over a wide age range
- May be identified in virtually all extranodal head and neck sites, including:
 - Sinonasal cavity > orbit/eyelid > salivary gland > oral cavity (palate) > lower respiratory tract > nasopharynx and tonsil > middle ear and temporal bone > larynx > trachea
- Symptoms depend on the site of occurrence:
 - In the sinonasal tract symptoms predominantly relate to nasal obstruction.
 - Nonsinonasal tract–related symptoms include proptosis, ptosis, decreased visual acuity, pain, stridor, cranial nerve deficits, or a mass lesion.
- Presentation often includes multiple concurrent sites of involvement; may occur without evidence of lymph node involvement.
- In general, the diagnosis of ESHML is a pathologic diagnosis rarely, if ever, suspected by clinical evaluation.

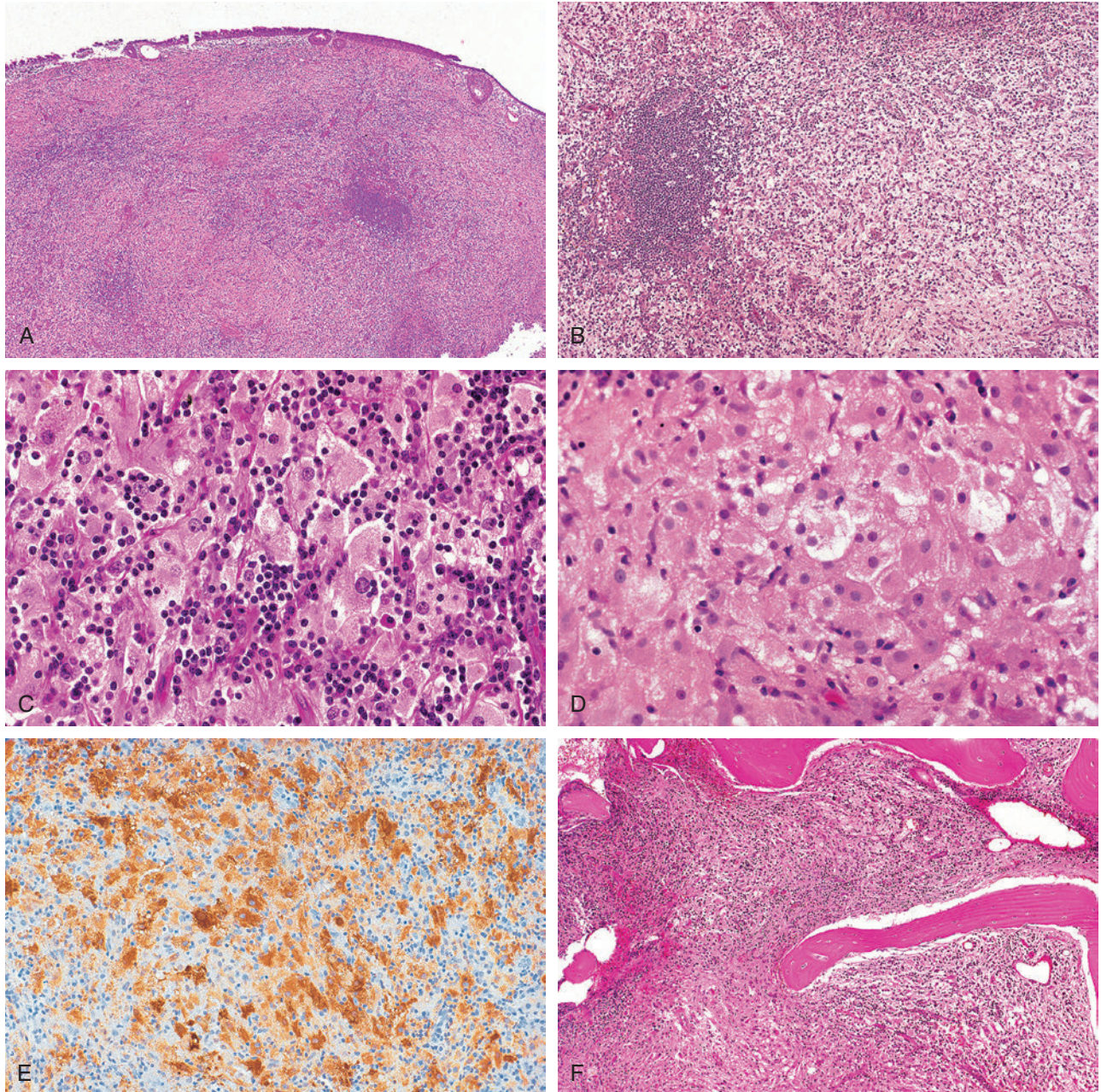


Fig. 2-55. Sinonasal tract extranodal sinus histiocytosis with massive lymphadenopathy (ESHML).

A, Submucosal diffuse inflammatory cell infiltrate with effacement of the normal submucosal structures; a benign lymphoid aggregate is present to the right of center that in conjunction with the cellular infiltrate has an architectural appearance reminiscent to that of lymph node parenchyma. **B**, Lymphoid aggregate is present at the left and is associated with a mixed cellular infiltrate composed of histiocytes admixed with lymphocytes, plasma cells, and scattered eosinophils. **C**, At higher magnification the infiltrate includes mature lymphocytes and plasma cells that somewhat obscure the histiocytic cell infiltrate; the latter demonstrates phagocytization of mononuclear cells (emperipolesis). **D**, Clusters of histiocytes predominate in this field and are composed of round nuclei with abundant clear to lightly eosinophilic cytoplasm within which an occasional mononuclear cell can be seen (emperipolesis). **E**, The histiocytes are diffusely immunoreactive for S-100 protein (but are CD1a and Langerin negative, not shown). **F**, The inflammatory cell infiltrate may extend into adjacent tissue structures, including bone.

- Hematologic and immunologic status generally intact but may be associated with polyclonal elevations in serum protein levels and raised erythrocyte sedimentation rates
- SHML has occurred in association with HIV-infected patients, Sjögren syndrome, and amyloidosis and may coexist with Langerhan cell histiocytosis.
- Although some studies implicated SHML to be an IgG4-related disease, it is not believed to belong within spectrum of IgG4-related diseases.
- Discrepancy in the literature relative to relationship to Epstein-Barr virus (EBV) and human herpes virus (HHV):
 - Some studies report elevated levels of EBV, as well as HHV6 in association with SHML.
 - Other studies report SHML cells are not infected by EBV or associated with HHV6 and HHV8.
- Cause for SHML remains obscure:
 - An infectious cause has been suggested as the cause, but an infectious agent has never been isolated.
 - Occurrence in patients with rhinoscleroma suggests a possible causative relationship with rhinoscleroma, although this has not been proven.
 - Other considerations implicated but never substantiated include immunodeficiency, autoimmune disease, or a neoplastic process.
- Immunophenotypic studies support the interpretation that the SHML cells are part of the mononuclear phagocyte and immunoregulatory effector (M-PIRE) system belonging to the macrophage/histiocytic family:
 - Stimulation of monocytes/macrophages via macrophage colony stimulating factor (M-CSF) leading to immune suppressive macrophages represents a main mechanism for the pathogenesis of SHML and provides evidence for the monocyte/macrophage but not dendritic cell differentiation of SHML histiocytes.
 - Expression of the chemokine receptors CCR6 and CCR7 in the SHML histiocytes suggests that this may be a general attribute of abnormal histiocytes and may reflect gene activation in a more mature macrophage-derived cell type.

Pathology

Cytology

- Cytologic features suggesting the diagnosis include numerous large benign histiocytes with emperipolesis.

Gross

- Mucosal thickening or polypoid, nodular, or exophytic growths with rubbery to firm consistency, pink to tan-gray color, and variation in the size

Histology

- At low magnification, the histopathologic features include the presence of fibrosis and lymphoid aggregates alternating with pale-appearing areas composed of histiocytes, lymphocytes, and plasma cells within the submucosa.
- Fibrosis may be focal or may appear as prominent fibrotic bands creating a nodular appearance to the gland.
- Lymphoid aggregates are composed of mature lymphocytes and may contain histiocytic cells imparting a mottled appearance to these aggregates; true germinal centers are not usually seen.
- In addition to the lymphoid aggregates, a polymorphous cellular infiltrate composed of mature lymphocytes, plasma cells, and histiocytes is seen:
 - Histiocytes (so-called SHML cells) appear in clusters or cell nests but may be obscured by the nonhistiocytic cell population (particularly the plasma cells).
 - Histiocytic cells are uniform with mild pleomorphism and are characterized by round to oval, vesicular to hyperchromatic nuclei, with an abundant amphophilic to eosinophilic, granular to foamy to clear cytoplasm.
 - Nuclei do not demonstrate nuclear lobation, indentation, or longitudinal grooving.
 - Histiocytes characteristically demonstrate emperipolesis; the phagocytized cells usually are lymphocytes, but plasma cells, erythrocytes, and polymorphonuclear leukocytes can also be seen engulfed within the histiocytic cell cytoplasm; emperipolesis may be less common as compared with nodal-based SHML.
 - Lymphocytes and plasma cells are nondescript.
 - Intracytoplasmic eosinophilic globules (Russell bodies) can be seen within the plasma cells.
 - Neither granulomas (well formed or otherwise) nor multinucleated giant cells are identified.
- Histochemistry:
 - Special stains for infectious organisms are negative but are required for differential diagnosis.
- Immunohistochemistry:
 - SHML cells are diffusely S100 protein positive but negative for CD1a and Langerin.
 - SHML cells may also demonstrate alpha-1-antichymotrypsin (ACT), CD68 (KP1), lysozyme, and MAC-387 immunoreactivity.
 - Plasma cells demonstrate a polyclonal pattern of proliferation as seen by the cytoplasmic positivity for both kappa and lambda light chains.
 - A subset of SHML cases reported to have features of IgG4-related disease suggest an overlap between certain aspects of the two diseases.

Differential Diagnosis

- Infectious (granulomatous) diseases:
 - Rhinoscleroma
 - May include the presence of emperipolesis
- Leprosy
- Langerhan cell histiocytosis:
 - Langerhan cells are immunoreactive for S100 protein, CD1a, and Langerin.
- Fibroinflammatory lesions
- Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
- Hematolymphoid malignancy:
 - Heterogeneous cell population typical for SHML as well as the presence of emperipolesis, CD68 and S100 protein reactivity should allow for differentiation from a hematolymphoid malignancy.
 - Although rare, emperipolesis can be seen in association with B-cell lymphomas.
 - SHML on rare occasions has been identified in lymph nodes affected by malignant lymphomas, including non-Hodgkin lymphomas, multiple myeloma, and Hodgkin disease, mixed cellularity type.
 - Transformation of SHML to a high-grade lymphoma has also been reported.

Treatment and Prognosis

- Considered an indolent, self-limiting disease; severe morbidity and mortality have been attributed to complications of SHML.
- There is no ideal treatment for involvement of the head and neck.
- Treatment protocols should mirror the clinical manifestations such that a range of therapeutic modalities may be used:
 - In cases of airway compromise, treatment should be directed at alleviating the obstruction, which would require surgical intervention.
 - For those patients with extensive or progressive disease, more radical surgical intervention may be required.
 - Surgical eradication of disease may prove difficult in cases with craniofacial bones and/or cranial cavity involvement.
 - Radiotherapy and chemotherapy have been used, but the efficacy of these agents has not been proven.
 - Patients with progressive disease course and/or compromise of vital structures and functions may be treated with combination chemotherapy including etoposide or 6-mercaptopurine plus low dose methotrexate potentially with favorable outcomes.
- Extension of disease to vital structures, particularly to the cranial cavity, may result in the death of the patient; however, mortality related to SHML is a rare occurrence.

- Unfavorable prognostic factors include disseminated nodal disease, involvement of multiple extranodal organ systems, and deficiencies in hematologic and/or immunologic status.

GRANULOMATOSIS WITH POLYANGIITIS (GPA)

(Figs. 2-56 through 2-59)

Definition: GPA is a non-neoplastic, idiopathic aseptic necrotizing disease with predilection for the upper/lower respiratory tract and the genitourinary system characterized by the presence of vasculitis and destructive properties.

This classic definition calls for involvement of the head and neck region, the lung, and the kidney. The majority of GPA patients do not exhibit this classic clinical triad simultaneously at the time of initial presentation. Therefore it is possible that, in a given patient, the initial biopsy material may originate from lesions of the upper aerodigestive tract (UADT) in the absence of a clinical suspicion for GPA.

Synonym: Wegener granulomatosis

Clinical

- GPA may be systemic or localized; the extent of disease is reflected in the clinical manifestations such that limited or localized disease may be asymptomatic, whereas in systemic involvement the patient is always sick.
- Disease may progress from localized to systemic involvement or may remain limited or even regress with treatment.
- ELK classification of GPA includes: E = ear, nose, and throat involvement; L = lung involvement; K = kidney involvement:
 - Patients with E or EL disease are considered to have the limited form of GPA.
 - Patients with ELK disease correspond to systemic GPA.
 - The incidence of limited GPA varies from 29% to 58%.

Localized Upper Aerodigestive Tract (UADT) GPA

- Localized UADT GPA tends to affect men more than women except in laryngeal GPA, which is seen predominantly in women.
- GPA occurs over a wide age range with the average age of occurrence in the fourth and fifth decades of life.
- In the UADT, the most common site of occurrence is the sinonasal region with the nasal cavity > maxillary > ethmoid > frontal > sphenoid.
 - Other sites of involvement include nasopharynx, larynx (subglottis), oral cavity, ear (external and

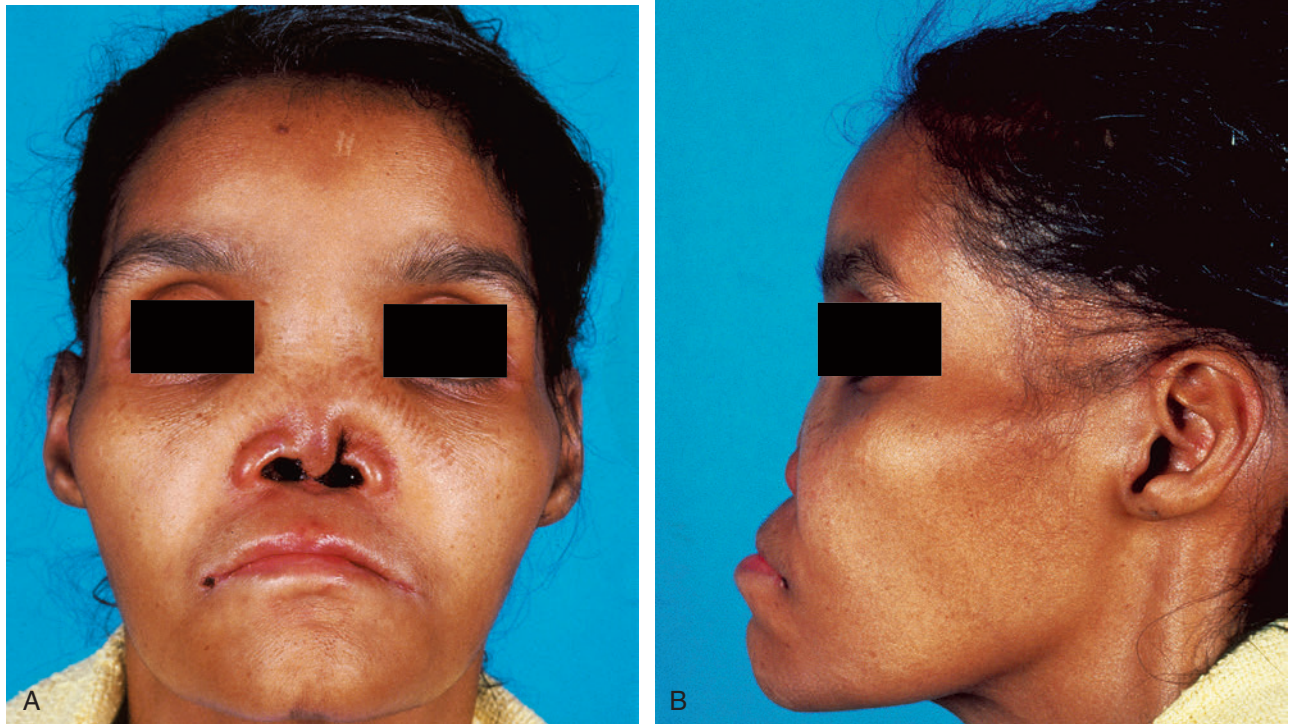


Fig. 2-56. Granulomatosis and polyangiitis.

Severe nasal deformity is seen including nasal septal destruction.

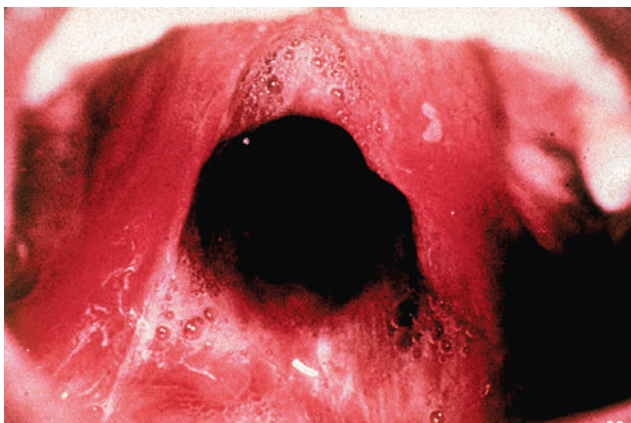


Fig. 2-57. Granulomatosis and polyangiitis.

The lesion began in the nasal cavity with erosion through the floor of the nasal cavity resulting in complete erosion through the palate.

- middle ear including the mastoid), and salivary glands.
- Symptoms vary according to the site of involvement and include:
 - Sinonasal tract and nasopharynx: sinusitis with or without a purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches

- Larynx: dyspnea, hoarseness, voice changes:
 - Involvement of the larynx is seen more often in the setting of pre-existing disease elsewhere, and so presentation with laryngeal GPA is a rare event.
 - Between an estimated 8% and 25% of patients with GPA will develop disease referable to the larynx.
 - Laryngeal involvement most often involves the subglottic region.
- Oral: ulcerative lesion, gingivitis
- Ear: hearing loss, pain
- Radiographic features of sinonasal GPA include:
 - Sinus opacification, bone destruction, ossification of the sinus walls, and soft tissue destruction
- Laboratory studies:
 - Useful laboratory studies include elevated erythrocyte sedimentation rate and, in renal disease, elevated serum creatinine and abnormal urinary sediment.
 - An important laboratory finding in GPA is an elevated antineutrophil cytoplasmic antibody (ANCA):
 - Reported specificity for the diagnosis of GPA from 85% to 98% of cases
 - ANCA reactivity is seen in the form of cytoplasmic (c-ANCA) versus perinuclear (p-ANCA) staining.

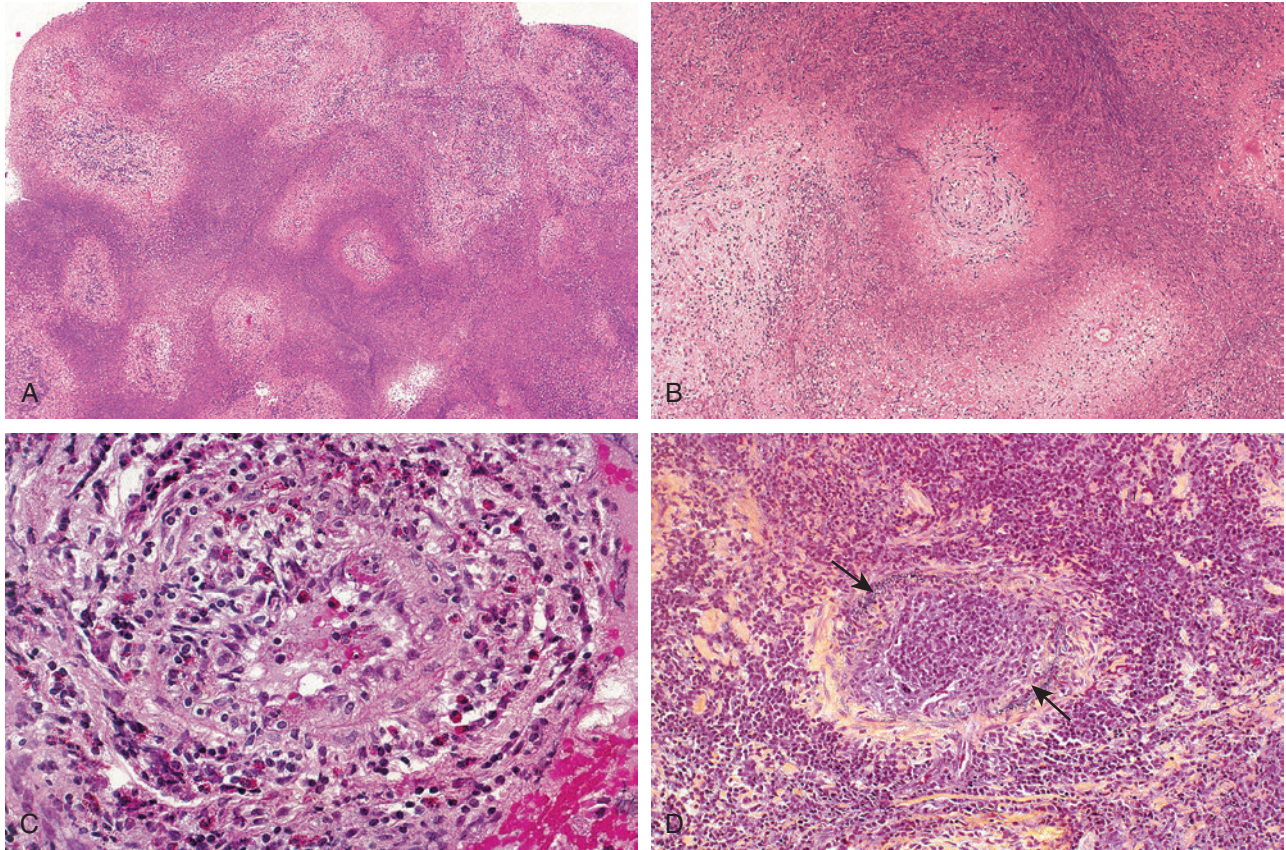


Fig. 2-58. Granulomatosis and polyangiitis.

A and B, At low magnification the changes include the presence of multifocal necrobiosis (“geographic or ischemic-type” necrosis) with a basophilic smudgy appearance; scattered areas of inflammation and thrombotic-like changes of vascular spaces are present. **C,** Vasculitis, a potentially difficult finding on histology, is seen here with the inflammatory infiltrate concentrically surrounding a blood vessel (angiocentric) and invading through the wall (angioinvasion) with occlusive changes of the endothelial lined lumen. **D,** Elastic stain, which may be of assistance in identifying vasculitis, shows the disruption of the black-staining external elastic membrane by the angiocentric and angioinvasive inflammatory cell infiltrate. The latter in both **C** and **D** is a mixed (benign) infiltrate including variable numbers of mature lymphocytes, plasma cells, and eosinophils.

- GPA is characteristically associated with cytoplasmic (c-ANCA) and only infrequently with perinuclear (p-ANCA).
- c-ANCA is of greater specificity than p-ANCA.
- Sensitivity of the test varies with the extent of disease:
 - Patients with limited GPA have a 50% to 67% c-ANCA positivity.
 - Patients with systemic GPA have a 60% to 100% positivity.
 - Negative test does not rule out GPA.
- Elevated in other vasculitides and in inflammatory bowel disease and hepatobiliary diseases
- ANCA titers are not elevated in infections or in lymphomas.
- ANCA titers follow the disease course; titers will revert to normal levels with remission and

will be elevated with recurrent or persistent disease.

- Decline in C-ANCA titer may lag behind clinical evidence of remission by up to 6 to 8 weeks.
- Proteinase 3 (PR-3):
 - PR-3 is a neutral serine proteinase present in azurophil granules of human polymorphonuclear leukocytes and monocyte lysosomal granules.
 - PR-3 serves as the major target antigen of anti-neutrophil cytoplasmic antibodies with a cytoplasmic staining pattern (c-ANCA) in GPA.
 - ANCA with specificity for PR3 are characteristic for patients with GPA.
 - Patients with GPA demonstrate a significantly higher percentage of mPR3+ neutrophils than

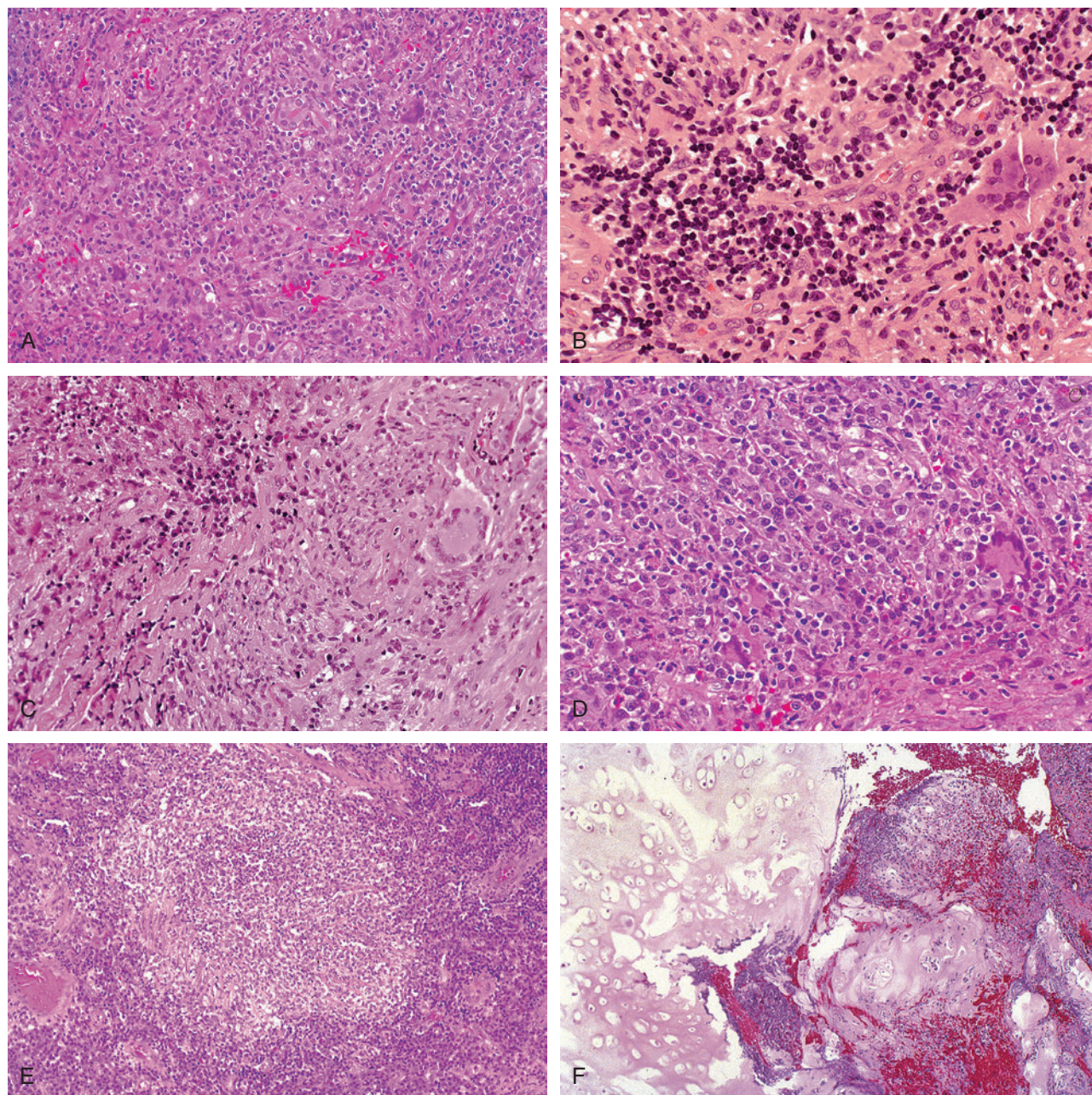


Fig. 2-59. Granulomatosis and polyangiitis.

A through **D**, The inflammatory cellular components are polymorphous, composed of variable admixture of mature lymphocytes, plasma cells, histiocytes, eosinophils, and neutrophils without evidence of atypical or overtly malignant cells. In all the illustrations are isolated multinucleated giant cells that represent the granulomatous component of the disease ("poor man's" granuloma), because well-formed granulomas are not typically identified in granulomatosis and polyangiitis despite its designation as a granulomatous process. **E**, Neutrophilic microabscess formation is another feature that can be seen whether associated with necrobiosis (*left of center*) or unrelated to necrosis (not shown). **F**, The inflammation extends into and through elastic cartilage, a contributing component to the clinical findings of saddle nose deformity and/or septal destruction. Finding vasculitis, necrosis, and granulomatous inflammation in a single case occurs in less than 20% of cases, and detailed clinical correlation including serum ANCA and PR3 levels is often required to support the histopathologic findings to confirm the diagnosis of granulomatosis and polyangiitis.

healthy controls and patients with other inflammatory diseases.

- Detection of ANCA directed against proteinase 3 (PR3-ANCA) is highly specific for GPA.
- ANCA positivity is found only in about 50% of the patients with localized GPA, whereas PR3-ANCA positivity is seen in 95% of the patients with generalized GPA.
- Pathogenesis of vascular injury in GPA is ascribed to antineutrophil cytoplasmic antibodies directed mainly against PR-3.
- Interaction of ANCA with neutrophilic ANCA antigens is necessary for the development of ANCA-associated diseases; ANCA bind to membrane-expressed PR-3 and induce full-blown activation in primed neutrophils.
- In patients with GPA, high expression of PR3 on the surface of nonprimed neutrophils is associated with an increased incidence and rate of relapse.
- ANCA-associated vasculitis (AAV) includes GPA, microscopic polyangiitis (MPA), allergic granulomatous angiitis (AGA), and eosinophilic GPA (Churg-Strauss disease):
 - Major target antigens of AAV are PR3 and myeloperoxidase (MPO).
 - PR3-ANCA is the marker for GPA.
 - MPO-ANCA is related to MPA and AGA.
 - ANCA appears to induce vasculitis by directly activating neutrophils.
 - No immunoglobulins or complement components are detected in vasculitis lesions; as such, AAV is called pauci-immune vasculitis.
 - ANCA directed against proteinase 3 (PR3) preferentially associated with GPA
 - Anti-myeloperoxidase (MPO) ANCA are associated mainly with MPA and eosinophilic GPA.
- Genome-wide analysis of patients with ANCA-associated vasculitides confirmed genetic contribution to the pathogenesis of these conditions:
 - Significant association of PR3-ANCA and human leukocyte antigen-DP and the genes encoding α 1-antitrypsin and PR3
 - MPO-ANCA were significantly associated with human leukocyte antigen-DQ.
- Despite decades of intensive investigation, the cause of GPA remains unknown:
 - Although speculative, an infectious cause (e.g., bacterial) either as the cause or as a co-factor in the disease is suggested on the basis of:
 - Reported beneficial effects of trimethoprim-sulfamethoxazole therapy on the initial course of the disease
 - Histologic features of the disease are similar to what might be found in infectious diseases.

Pathology

Gross

- Sinonasal area: diffuse ulcerative and crusted lesions with tissue destruction; in advanced cases, septal perforation may be seen resulting in a “saddle nose” deformity.
- Laryngeal area: subglottic stenosis with associated ulcerative lesions
- Oral cavity: ulcerative, destructive lesions often seen along the palate and alveolar region

Histology

- Histologic features of GPA include the classic triad of: (1) vasculitis, (2) granulomatous inflammation (which may involve vessel walls as well as the supporting tissues), and (3) tissue necrosis:
 - In practice, however, it has become apparent that finding all of three of these “characteristic” features in a single or even a series of biopsies is actually very uncommon.
 - Accordingly, the pathologist faces the twin risks of underdiagnosing GPA when all of the classic histologic components are lacking and of overdiagnosing GPA when excessive reliance is placed upon the presence of minimal histologic changes that fall far short of the classic findings expected.
 - Presence of all three defining criteria in the same head and neck region biopsy is decidedly unusual, seen in only 16% of biopsies from patients with proven GPA.
 - As a consequence, the diagnostic pathologist must be prepared to advance the *possibility* of GPA (among other differential diagnostic considerations) even when the full-blown range of classic histologic changes is not present in the biopsy.
 - Clearly, requiring the presence of all classic features of GPA in a single biopsy before the possibility of GPA is advanced results in “nondiagnostic” interpretations being rendered for the majority of head and neck biopsies from patients with the disease.
- Vasculitis involving small to medium-sized arteries consists of a polymorphous inflammatory infiltrate composed of lymphocytes and histiocytes and less often eosinophils and polymorphonuclear leukocytes:
 - Vasculitis may be difficult to identify histologically and is often absent.
 - Inflammatory infiltrate is angiocentric (surrounding vessels) and angioinvasive (invading through the vessel wall) and may result in thrombosis of the involved blood vessel.

- Vasculitis is not limited to GPA and can be seen in infectious diseases (e.g., mucormycosis, aspergillosis) as well as in NK/T cell lymphoma.
- Necrosis is “ischemic” or “geographic”-type (multifocal necrobiosis) with a basophilic smudgy appearance:
 - Necrotic foci should be within the stromal connective tissues and not along the surface or edge of the tissue specimen, which may represent nonspecific ulceration seen in a wide variety of lesions.
- Granulomatous inflammations are not well-formed granulomas but include the presence of scattered isolated or less common clustered multinucleated giant cells:
 - Well-formed granulomas uncommonly occur and when present should raise concern for an infectious cause.
- Parenchymal inflammatory infiltrate is composed of predominantly lymphocytes, histiocytes, and plasma cells; eosinophils, although generally uncommon, may be numerous on occasion.
- Microabscesses with or without granuloma formation may be identified.
- Bacterial superinfection of the diseased mucosa, particularly *Staphylococcus aureus*, may complicate the clinical picture.
- Histochemistry:
 - Elastic stains may assist in the identification of vasculitis.
 - Because GPA is a diagnosis of exclusion, staining for microorganisms should be performed but is invariably negative.
- Immunohistochemistry:
 - Immunoreactivity for both B-cell (CD20) and T-cell (CD3) markers indicative of a benign (polyclonal) cellular population
 - Immunohistochemical staining for EBV and/or in situ hybridization for Epstein Barr encoded RNA (EBER) is negative.
- IgG4 immunostaining:
 - Increased IgG4+ cells can be seen in sinonasal (or orbital/periorbital) biopsies of GPA.
 - This finding could pose a pitfall in the diagnosis of IgG4-related disease.
 - GPA in other organs and controls does not show increased IgG4+ cells.
 - Biologic or clinical importance of increased IgG4+ cells in GPA involving head and neck region remains uncertain relative to potential pathogenic relationship between IgG4-related disease and GPA in those cases.
- Diagnosis of GPA is often one of exclusion:
 - Because the histologic findings are often meager, a “negative” biopsy may be of little or no help in excluding GPA.

- Histomorphologic diagnosis may be limited based on the tissue sampling; therefore the clinician must obtain multiple biopsies, especially in areas from the ulcer bed as well as in areas of more viable-appearing tissue.
- In any given biopsy if the histologic features do not support a diagnosis of GPA, but the clinical index of suspicion for GPA is high, additional biopsies may be indicated.
- If the patient has been treated with steroids prior to biopsy, this can suppress the histologic features and make the histologic diagnosis even more difficult and problematic.

Differential Diagnosis

- Infectious diseases:
 - Fungal, mycobacterial, parasitic
- Nonspecific sinusitis/rhinitis
- Collagen vascular disease
- Cocaine use/abuse:
 - Cocaine is a potent vasoconstrictor and with chronic use may result in clinical signs and symptoms as well as mucosal lesions similar to those of GPA.
 - Chronic intranasal inhalation may result in rhinorrhea, nasal obstruction, rhinosinusitis, ulceration, crusting, epistaxis, anosmia, septal perforation, saddle nose deformity, osteocartilaginous necrosis, and/or pain.
 - Not associated with elevated levels of ANCA or PR3
 - Histologic findings may include surface ulceration and crusting with associated acute and chronic inflammation as well as a foreign body (multinucleated) giant cell reaction:
 - Giant cells may engulf and/or surround polarizable material, the latter often used to “cut” or dilute the cocaine.
 - Bacterial and fungal tissue invasion may be identified.
 - Not associated with vasculitis
- Churg-Strauss syndrome (Table 2-2 and Fig. 2-60)
 - Also referred to as allergic granulomatosis and vasculitis, and eosinophilic GPA
 - Characterized by asthma, systemic vasculitis, tissue and peripheral eosinophilia, and nasal manifestations
 - Findings that assist in differentiating from GPA include:
 - Clinical manifestations of peripheral (serum and tissue eosinophilia) may include:
 - Signs and symptoms of eosinophilic pneumonia, eosinophilic gastroenteritis
 - Other nasal manifestations include:
 - Rhinorrhea, rhinosinusitis, nasal polyps, obstruction

TABLE 2-2 Clinicopathologic Comparison: Granulomatosis and Polyangiitis (GPA), Allergic Granulomatosis and Vasculitis,* and Sinonasal Malignant Lymphomas

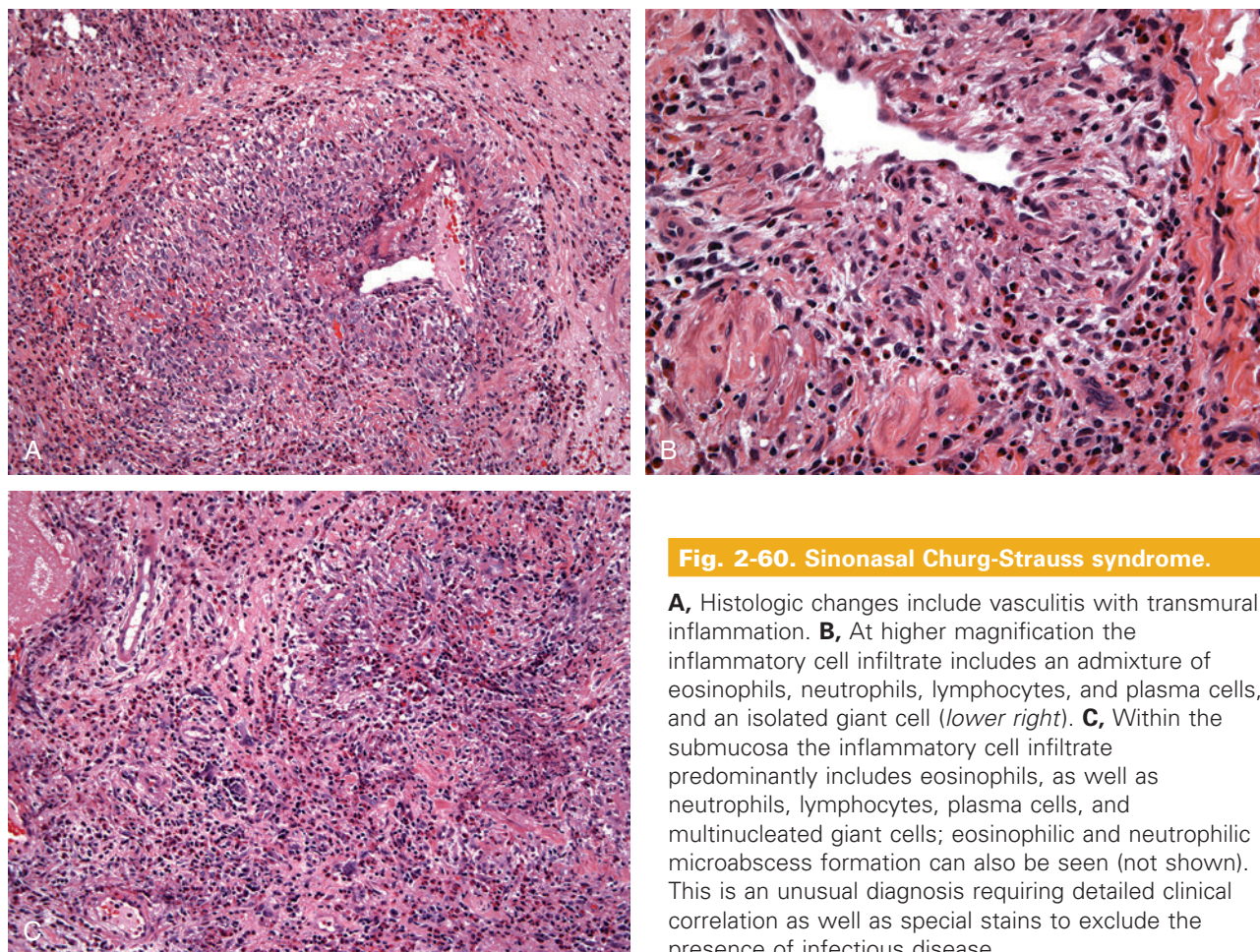
	GPA	Allergic Granulomatosis and Vasculitis	Extranodal NK/T-Cell Lymphoma, Nasal Type	DLCBL
Gender/age	M > F; fourth-fifth decades; laryngeal GPA affects F > M	M > F; wide age range (third-sixth decades)	M > F; sixth decade; most common in Asians; occurs in Western population but with less frequency	M > F; seventh decade
Location	Localized UADT GPA most common in nasal cavity > paranasal sinuses; other sites may include nasopharynx, larynx (subglottis), oral cavity, trachea, ear, salivary glands	Multisystem disease including pulmonary, nasal, renal, cutaneous, cardiac and nervous system involvement	Generally limited to the sinonasal region; extra-sinonasal involvement occurs and represents a higher stage tumor	Nasal cavity and one or more paranasal sinuses
Symptoms	SNT: sinusitis, with or without purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches Larynx: dyspnea, hoarseness; voice changes Oral: ulcerative lesion Ear: hearing loss, pain	Asthma, allergic rhinitis, evidence of serum and tissue eosinophilia (e.g., eosinophilic pneumonia, eosinophilic gastroenteritis, other), evidence of vasculitis	Destructive process of midfacial region: nasal septal perforation, obstruction, palate destruction, orbital swelling	Nonhealing ulcer, epistaxis, facial swelling, pain, cranial nerve manifestations
Systemic involvement	ELK Classification: E: ear, nose, throat; L: lung; K: kidney; E, EL = limited form GPA; ELK = systemic GPA	Typically patients multisystem involvement although limited forms of disease exist	Majority are localized (stage IE/II/E); May progress to disseminated/systemic involvement	Majority are localized (stage IE/II/E); May progress to disseminated/systemic involvement
Serology	ANCA and PR3 positive: • Increased in primary disease and recurrent disease • (c-ANCA more specific than p-ANCA)	ANCA and PR3 levels may or may not be present; peripheral eosinophilia; may be associated with anti-myeloperoxidase (MPO) ANCA	ANCA and PR3 negative; no specific serologic marker(s)	ANCA and PR3 negative; no specific serologic marker(s)
Histology	Polymorphous (benign) cellular infiltrate; vasculitis; ischemic-type necrosis; isolated multinucleated giant cells (not well-formed granulomas); negative cultures and stains for organisms	Polymorphous (benign) cellular infiltrate, predominantly eosinophils; vasculitis that may be a granulomatous vasculitis (multinucleated giant cells in the wall of involved blood vessels); eosinophilic microabscesses; negative cultures and stains for organisms	Overtly malignant cellular infiltrate but in early phases malignant cells may not be overtly identifiable; angiocentricity and angioinvasion; ischemic-type necrosis; no giant cells or granulomas; negative cultures and stains for organisms	Diffuse dyscohesive cellular proliferation of medium to large cells with large round to oval vesicular (noncleaved) nuclei, prominent nucleoli, increased mitotic activity and necrosis
IHC	LCA, B- and T-cell markers, kappa and lambda light chains	LCA, B- and T-cell markers	CD3 cytoplasmic, CD2, CD56 positive; T-cell markers (CD3, others) positive; cytotoxic granule markers (granzyme B, TIA-1, perforin) positive	LCA and B-cell markers (CD20, CD79) positive; p63 may positive (focal to diffuse)
EBV	Negative	Negative	Strong association	No to weak association

TABLE 2-2 Clinicopathologic Comparison: Granulomatosis and Polyangiitis (GPA), Allergic Granulomatosis and Vasculitis,* and Sinonasal Malignant Lymphomas—cont'd

	GPA	Allergic Granulomatosis and Vasculitis	Extranodal NK/T-Cell Lymphoma, Nasal Type	DLCBL
Treatment	Cyclophosphamide and prednisone	Systemic corticosteroids	Radiotherapy for localized disease; chemotherapy for disseminated disease	Radiotherapy and/or chemotherapy
Prognosis	Limited disease associated with a good to excellent prognosis and occasional spontaneous remissions; mortality related to complications of renal and pulmonary involvement	62% 5-year survival; increased morbidity and mortality due to cardiac involvement resulting in CHF or MI	5-year survival for Stage I is approximately 50%; local recurrence/relapse and systemic failure common	Dependent on stage; 5-year survival rates vary in the literature from 29% to 80%

ANCA, Antineutrophil cytoplasmic antibodies; CHF, congestive heart failure; DLCBL, diffuse large cell B-cell lymphoma; EBV, Epstein-Barr virus; F, female; GPA, granulomatosis and polyangiitis (formerly referred to as Wegener granulomatosis); IHC, immunohistochemistry; M, male; MI, myocardial infarction; NK, natural killer; PR3, proteinase 3; SNT, sinonasal tract; UADT, upper aerodigestive tract.

*Also known as Churg-Strauss syndrome as well as eosinophilic granulomatosis and polyangiitis.

**Fig. 2-60. Sinonasal Churg-Strauss syndrome.**

A, Histologic changes include vasculitis with transmural inflammation. **B**, At higher magnification the inflammatory cell infiltrate includes an admixture of eosinophils, neutrophils, lymphocytes, and plasma cells, and an isolated giant cell (*lower right*). **C**, Within the submucosa the inflammatory cell infiltrate predominantly includes eosinophils, as well as neutrophils, lymphocytes, plasma cells, and multinucleated giant cells; eosinophilic and neutrophilic microabscess formation can also be seen (not shown). This is an unusual diagnosis requiring detailed clinical correlation as well as special stains to exclude the presence of infectious disease.

- Nasal crusting and septal perforation (similar to GPA) may occur.
- Nasal manifestations reported in a majority of patients with this disease
- Constitutional findings include malaise, fever, weight loss, night sweats, arthralgia(s), and myalgia(s).
- Renal involvement results in hypertension but usually not as clinically aggressive as seen in GPA.
- Pulmonary involvement rarely results in cavitation.
- Cutaneous (maculopapular eruptions, nodules, and purpura), cardiac (pericarditis, myocardial infarction), and nervous system involvement (neuropathy, cerebral hemorrhage, infarction)
- Limited form of disease exists, lacking full clinical and pathologic features, and without systemic involvement and with limited sites of involvement
- ANCA levels may or may not be present:
 - Because elevated ANCA levels have been reported in Churg-Strauss syndrome, this finding cannot be used to differentiate Churg-Strauss syndrome from GPA.
 - May be associated with anti-myeloperoxidase (MPO) ANCA
- Additional laboratory findings may include increased serum IgE, anemia (normochromic, normocytic), and elevated erythrocyte sedimentation rate.
- Serum IgG4 levels are markedly elevated in active Churg-Strauss syndrome and correlate with the number of organ manifestations and disease activity.
- Histologic findings include:
 - Vasculitis of small to medium-sized blood vessels with transmural inflammatory cell infiltrate (angioinvasion); vasculitis is present in the majority of cases (70%).
 - Infiltrate predominantly includes eosinophils, but lymphocytes and neutrophils may be present in small numbers; tissue eosinophilia is found in approximately 57% of cases.
 - Granulomatous vasculitis may be seen and is characterized by the presence of multinucleated giant cells found within the vessel wall; the latter may or may not be associated with fibrinoid necrosis; granulomas are found in approximately 38% of cases.
 - Eosinophilic microabscesses (not related to blood vessels) may be present.
 - Likelihood of finding vasculitis, granulomas, and tissue eosinophilia in a single biopsy is small (less than 15% of cases).
- Systemic corticosteroids are the preferred treatment.
- In patients resistant to standard therapy, rituximab may be used and has been shown to be effective and safe.
- 5-year survival rate of 62%
- Relapses are frequent, especially in patients with anti-myeloperoxidase antibodies and baseline eosinophilia $<3000/\text{mm}^3$.
- Death results from cardiac involvement with congestive heart failure or myocardial infarction.
- IgG4-related disease:
 - See Section 6, Salivary Glands, for more detailed discussion.
 - Increased IgG4+ cells not uncommonly present sinonasal (or orbital/periorbital) GPA, which could pose a diagnostic pitfall
 - GPA in other organs and controls does not show increased IgG4+ cells.
 - Biologic or clinical importance of increased IgG4+ cells in GPA cases involving head and neck region is uncertain but raises potential pathogenic relationship between IgG4-related diseases and GPA.
- Nasal-type NK/T cell lymphoma ([Table 2-2](#)):
 - Cytologic characteristics of the lymphoid infiltrate often permit distinction between GPA and NK/T cell lymphoma.
 - Lymphoid infiltrates in GPA lack an appreciable degree of cytologic atypia; atypia is characteristic of the tumor cells of malignant lymphoma.
 - In view of the fact that some degree of subjectivity may enter into the recognition of lymphoid atypia by light microscopic features alone, immunohistochemical, in situ hybridization, and/or molecular biologic studies may be helpful in a diagnosis of nasal-type NK/T cell lymphoma (see next chapter).

Treatment and Prognosis

- Once the diagnosis and extent of disease is determined, most patients with GPA receive a combination of cyclophosphamide and prednisone:
 - 75% complete remission rate may be achieved with this treatment regimen, although patients may experience one or more relapses from 3 months to 16 years after complete remission.
 - Patients with GPA who experience remission are not necessarily cured of disease and are at risk for recurrences throughout their life.
- Rituximab can be used in patients with refractory or relapsing disease.
- Patients with limited disease are treated with antibiotics (trimethoprim-sulfamethoxazole).
- Steroid therapy may alter the histomorphology, with reduction or elimination of the vasculitic component.

- GPA surgical intervention may be required in treating patients with progression of disease in the upper aerodigestive tract:
 - Frequent surgical intervention may be required.
 - Endoscopic surgical technique offers safe and successful approach for treatment of subglottic stenosis due to GPA.
 - Patients with fulminating disease, especially with renal failure, are treated with high doses of prednisone:
 - This treatment is maintained until the disease is under control as evidenced by improved ESR, serum creatinine, or ANCA titer, at which time cyclophosphamide therapy is begun.
 - Prednisone is continued until the cyclophosphamide can take effect, which occurs approximately 2 to 3 weeks after initiation of therapy.
 - Limited GPA responds well to cyclophosphamide and/or steroid therapy and has a good prognosis.
 - Mortality rates of up to 28% have been reported:
 - Major source of morbidity and mortality is renal or pulmonary insufficiency and/or complications of therapy (e.g., sepsis, drug-induced malignancies).
 - Occasionally, spontaneous remissions may be seen with milder forms of disease when only one or a few organs are involved (but not the kidneys).
- Although uncommon, changes of NS can occur in seromucous glands of sinonasal tract similar to that seen in relationship to oral cavity minor salivary glands (a more frequent site of occurrence).
 - Similar to NS of other locations, sinonasal NS can easily be misinterpreted as carcinoma:
 - Usually the metaplasia is a small focus and seldom is it as extensive as has sometimes been found in the lesions of the palate.
 - Histologically, the findings are similar to those found in more common locations.

EOSINOPHILIC ANGIOCENTRIC FIBROSIS (EAF) (Fig. 2-61)

Definition: Rare chronic sclerosing and fibroinflammatory disorder of the upper aerodigestive tract.

Clinical

- Uncommon lesion
- Postulated to represent the mucosal variant of granuloma faciale owing to:
 - Histologic similarities of early nasal mucosal lesions to those seen in granuloma faciale
 - Concurrent occurrence of EAF and granuloma faciale in approximately 25% of EAF cases
- Much more common in women than in men; occurs in adults over wide age range.
- Sites of involvement include the nasal cavity, larynx (subglottis), orbit, lacrimal gland, and oral cavity (gums):
 - In the nasal cavity affects the septum > lateral wall

NECROTIZING SIALOMETAPLASIA (NS)

- See Section 6, Salivary Glands, for a more complete discussion.

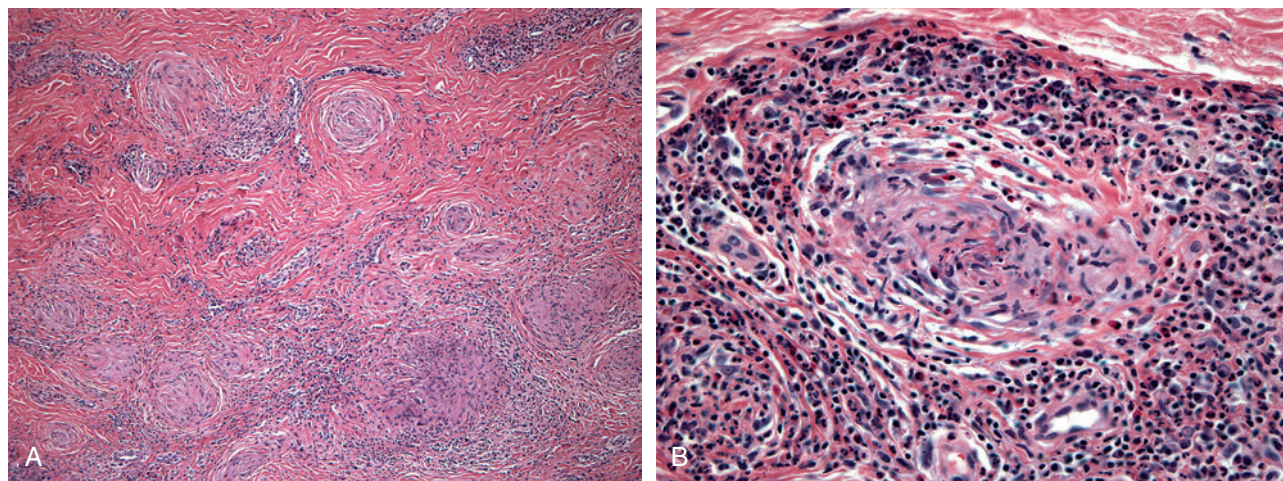


Fig. 2-61. Eosinophilic angiocentric fibrosis.

A and B, The histologic features include an eosinophilic perivascular infiltrate that surrounds and extends into capillaries and venules (eosinophilic angiitis); plasma cells and mature lymphocytes may also be present. In contrast to granulomatosis with polyangiitis, vascular thrombosis and “ischemic” type necrosis are not identified.

- Often unilateral but may be bilateral
- May rarely extend to paranasal sinuses (usually maxillary sinus) or orbit
- Clinical presentation is that of progressive airway obstruction over several years; some patients have associated allergies, including allergic rhinitis, chronic urticaria, sensitivity to penicillin.
- Laboratory findings are nonspecific:
 - ANCA levels are not elevated.
 - No abnormalities reported in erythrocyte sedimentation rate or urinalysis.
- No known cause
- Recent evidence supports including EAF in the spectrum of IgG4-related diseases as evidenced by the presence in patients with EAF of:
 - Serum IgG4 concentration of 1490 mg/dl (normal, 8 to 140 mg/dl)
 - IgG4-positive plasma cells ranging from 43 to 118 per high-power field
 - IgG4:IgG from 0.68 to 0.97

Pathology

- Histologic features described include an early and late phase, both of which can be seen in any given biopsy.
- In early lesions there is an eosinophilic perivascular infiltrate in the lamina propria:
 - Eosinophils surround and extend into capillaries and venules (eosinophilic angiitis).
 - Plasma cells and mature lymphocytes may also be present.
 - Thrombosis and “ischemic” type necrosis are not identified.
- In late lesions, the most characteristic feature is the presence of dense fibrosis with a layered “onion-skin-type” perivascular fibrosis (angiocentric fibrosis):
 - The fibrosis is hypocellular, but areas of mixed inflammatory cells remain, including eosinophils.
- Cytologic atypia is not present.
- No microorganisms, granulomatous inflammation, or giant cells are seen.

- Histochemistry:
 - Special stains for microorganisms are negative.
- Immunohistochemistry:
 - Plasma cells are polyclonal.
 - Lymphocytes are predominantly T-cells.

Differential Diagnosis

- Infectious disease
- Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
- Churg-Strauss syndrome
- Fibromatosis
- Subglottic stenosis for cases involving the larynx
- Nasal-type NK/T cell lymphoma

Treatment and Prognosis

- Surgery may be required in the patients with airway obstruction to create a patent airway by excising the area of stenosis.
- Corticosteroids and antihistamines do not appear to be effective modes of treatment.
- Disease progression stabilizes over time but typically not prior to the development of airway obstruction.

IGG4-RELATED DISEASES

- Relatively recently described group of diseases with characteristic morphology that may be systemic with multiorgan involvement or localized to specific anatomic sites
- May occur in the sinonasal tract independent of involvement of more common nonhead and non-neck sites of occurrence (i.e., pancreas) and/or more common head and neck sites of occurrence (i.e., submandibular gland)
- See Section 6, Salivary Glands, for a more complete discussion.

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Embryology, Anatomy, and Histology of the Oral Cavity

EMBRYOLOGY OF THE ORAL CAVITY

- Primitive mouth or stomodeum develops partly from the surface ectoderm and partly from the endoderm of the cranial end of the foregut (the future site of the pharynx):
 - Initially, the oropharyngeal membrane separates these structures, but at the end of the fourth week of gestation the oropharyngeal membrane disappears, allowing for direct communication of the mouth with the pharynx.
- Most of the epithelium of the oral cavity (lips, gums, palate) are of ectodermal origin.
- Epithelium of tongue varies in its development:
 - Anterior two thirds of oral tongue is of ectodermal origin, developing from the tuberculum impar (median tongue bud or swelling), and is of first branchial arch derivation.
 - Posterior or pharyngeal portion of the tongue is of endodermal origin, developing from the hypobranchial eminence, and is of third branchial arch derivation.
- Muscles of mastication (temporalis, masseter, and medial and lateral pterygoids) are derived from the first branchial arch (mandibular arch).
- Mandible is formed from the mandibular prominence of the first branchial arch.
- Maxilla, zygomatic bone, and squamous part of the temporal bone derive from the maxillary prominence of the first branchial arch.
- Nerves:
 - Trigeminal nerve (V) (maxillary and mandibular branches) arises from the first branchial arch.
 - Facial nerve (VII) arises from the second branchial arch.
 - Glossopharyngeal nerve (IX) arises from the third branchial arch.
 - Vagus nerve (X) arises from the fourth branchial arch.

CONTENTS OF THE ORAL CAVITY

- Structures within the anatomic confines of the oral cavity (Fig. 4-1) include:

- Lips:
 - Mucosal lip begins at the junction of the vermilion border with the skin and includes only the vermilion surface or that portion of the lip that comes in contact with the opposing lip.
 - Vermilion border represents the junction between the skin and the oral mucosa.
- Oral vestibule:
 - Slit-like space between the lips or cheeks on one side and teeth on the other side
 - When teeth occlude the vestibule is a closed space that only communicates with the oral cavity proper in retromolar region behind the last molar tooth on each side.
 - Mucosa that covers the alveolus of the jaw is reflected onto the lips and cheeks; a trough or sulcus is formed called the fornix vestibuli.
 - In midline there are upper and lower labial frena or frenula.
 - Upper frenula attached well below alveolar crest
- Buccal mucosa (cheeks):
 - Includes all the membrane lining of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa of the alveolar ridge (upper and lower) and pterygomandibular raphe
- Floor of mouth:
 - Semilunar or horseshoe-shaped area situated beneath the movable tongue between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones
 - Extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone
 - A fold of tissue, lingual frenulum, extends from the inferior surface of tongue near the base of the tongue.
 - Submandibular ducts open into the mouth at the sublingual papilla (caruncle), which is a large positioned protuberance at the base of the tongue.
- Retromolar trigone:
 - Attached mucosa overlying the ascending ramus of the mandible from the level of the

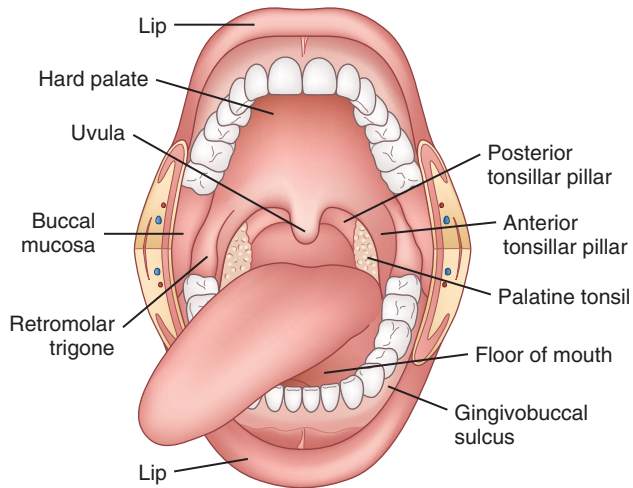


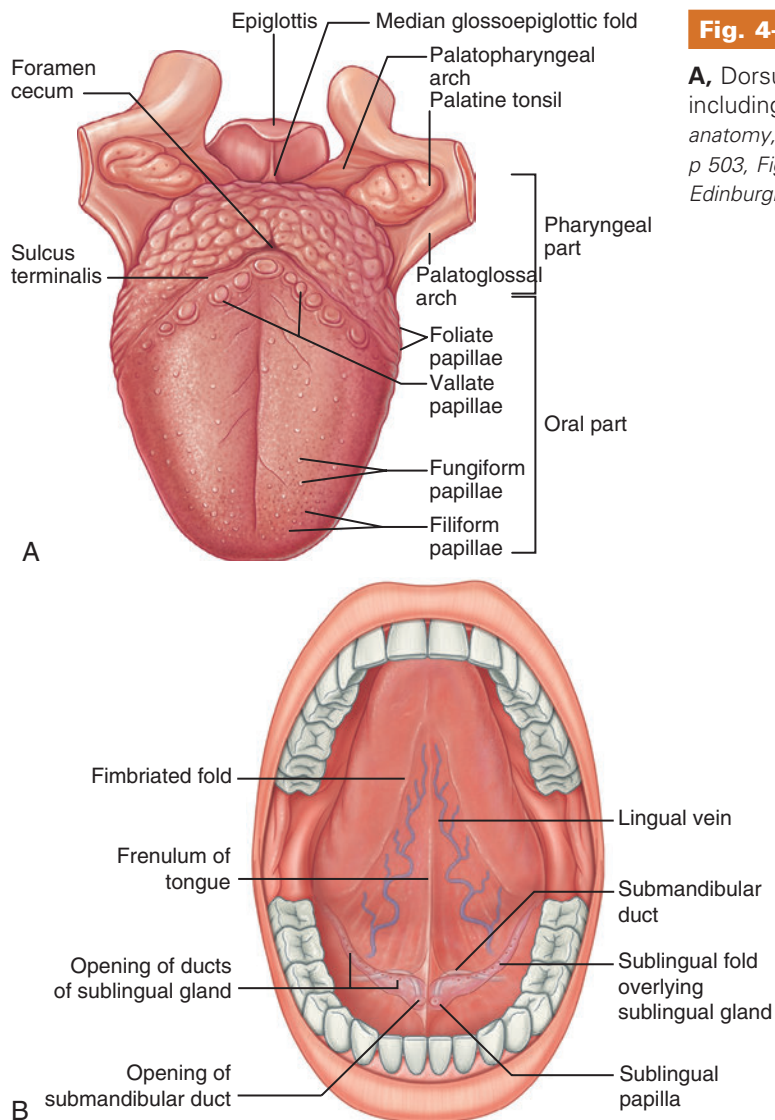
Fig. 4-1. Contents of the oral cavity.

(From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 27-1, p 1618.)

posterior surface of the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla

- Tongue (Fig. 4-2):
 - Highly muscular organ of deglutition, taste, and speech
 - Attached by muscles to hyoid bone, mandible, styloid process, soft palate, and pharyngeal wall
 - Has root, apex, curved dorsum, and inferior (ventral) surface
 - Dorsal tongue:
 - Represents the superior surface related to hard and soft palates
 - Located in floor of the oral cavity
 - Generally convex in all directions at rest
 - Divided by V-shaped sulcus terminalis into anterior (oral or presulcal) part, which faces upward, and posterior (pharyngeal or post-sulcal) part, which faces posterior
 - Oral (presulcal) tongue:
 - Anterior two thirds of tongue lying in floor of oral cavity
 - Freely mobile portion
 - Extending anteriorly from the line of circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth
 - Covered by numerous papillae, some of which bear taste buds
 - Pharyngeal (postsulcal) part:
 - Posterior one third of tongue representing its base lying posterior to palatoglossal arches

- Forms anterior wall of oropharynx
- Mucosa reflects laterally onto palatine tonsils and pharyngeal wall and posteriorly onto the epiglottis by glossoepiglottic folds surrounding two depressions or valleculae
- Devoid of papillae
- Underlying lymphoid nodules embedded in submucosa collectively referred to as lingual tonsil
- In situations in which the thyroid does not migrate during development, it remains in postsulcal part of the tongue (lingual thyroid, see Section 8)
- Ventral surface of tongue:
 - Represents the undersurface (nonvillous ventral surface)
 - Visible when the tip of the tongue is turned upward
- Palatine bone:
 - Posteriorly placed in nasal cavity between maxillae and pterygoid processes of the sphenoid bones
 - Contribute to:
 - Floor and lateral walls of the nose
 - Floor of the orbit
 - Hard palate
 - Pterygopalatine and pterygoid fossae
 - Inferior orbital fissure
 - Each palatine bone has:
 - Two plates (horizontal and perpendicular) arranged as L-shaped
 - Three processes: pyramidal, orbital, and sphenoidal
- Hard palate:
 - Semilunar area between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones
 - Extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone
- Soft palate:
 - See Section 3, Pharynx.
- Gingivae (gums):
 - Lining mucosa of the (inner) cheeks
- Gnathic (jaw) bones:
 - Include maxilla and mandible
- Maxilla:
 - Largest of facial bones (other than the mandible) that jointly form the whole of the upper jaw
 - Each maxillary bone forms the greater part of the floor and lateral wall of the nasal cavity, floor of orbit, contributes to the infratemporal and pterygopalatine fossae and bounds inferior orbital and pterygomaxillary fissures

**Fig. 4-2. The tongue.**

A, Dorsum of the tongue. **B**, Ventral aspect of the tongue including the floor of mouth. (**A**, From *Standring S: Gray's anatomy, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, p 503, Figure 30.5*. **B**, From *Standring S: Gray's anatomy, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, Figure 30.4, p 502*.)

- Each maxilla has a body; four processes including:
 - Zygomatic
 - Frontal
 - Alveolar
 - Palatine
- Mandible:
 - Largest and strongest bone of the face wholly forming the lower jaw
 - Composed of:
 - Horizontally curved body that is convex forward
 - Two broad rami that ascend posteriorly
 - Body of mandible supports mandibular teeth within alveolar process
 - Rami bear coronoid and condylar processes:
 - Each condyle articulate with adjacent temporal bone at the temporomandibular joint
- Synovial joint between the articular fossa (referred to as glenoid or mandibular fossa), temporal bone above and mandibular condyle
- Articular surface lined by fibrocartilage rather than hyaline cartilage
- Alveolar bone
 - Part of maxilla or mandible that supports and protects the teeth
 - Arbitrary boundary at level of root apices of the teeth separates alveolar processes from the body of the mandible and/or maxilla.
 - Alveolar ridges (lower and upper):
 - Bony structures supporting teeth and periodontal tissue arise from floor of mouth and descend from hard palate
 - Lower alveolar ridge:
 - Mucosa overlying the alveolar process of the maxilla that extends from the line of

attachment of the mucosa in the upper gingival buccal gutter to the junction of the hard palate

- ◻ Posterior margin is the upper end of the pterygopalatine arch.
- Lower alveolar ridge:
 - Mucosa overlying the alveolar process of the mandible that extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth
 - Posteriorly, it extends to the ascending ramus of the mandible.
- Teeth (Fig. 4-3):
 - Composed of tubular dentin capped by thin shell of very hard but brittle enamel in tooth crown
 - Tooth root surrounded by cementum
 - Periodontal membrane attaches to cementum on one side and alveolar bone on the other side.
 - Tooth numbering:
 - Total of 32 teeth
 - American Dental Association system includes numbering of each tooth by one number from 1 to 32, starting from right maxillary third molar moving clockwise
- Periodontal ligament
 - Functions to support the teeth, generate force of tooth eruption, and provide sensory information about tooth position and forces to facilitate reflex jaw activity
 - Dense fibrous connective tissue 0.2 mm wide containing cells associated with development and maintenance of alveolar bone (osteoblasts and osteoclasts) and cementum (cementoblasts and odontoclasts)
 - Contains network of epithelial cells (epithelial cell rests of Malassez), which are embryologic remnants of an epithelial root sheath
 - No evident function but may give rise to dental cysts

ANATOMIC BORDERS OF THE ORAL CAVITY

- Anterior: vermillion border of the lips
- Posterior: line drawn from the junction of the hard and soft palate to the circumvallate papillae of the tongue
- Superior: hard palate until its junction with the soft palate
- Inferior: anterior two thirds of the tongue to the line of the circumvallate papillae
- Lateral: buccal mucosa of the cheeks

Histology (Figs. 4-4 and 4-5)

- Histology of epithelial surfaces of oral cavity mucosa is detailed in Table 4-1
- Tongue:
 - Dorsal tongue:
 - Anterior two thirds (specialized oral mucosa):
 - Keratinized squamous epithelium covered with numerous small mucosal projections forming papillae with slender rete ridges
 - According to shape papillae may appear filiform, fungiform, foliate, or circumvallate
 - Majority are filiform papillae appearing as conical projections of keratinized epithelium
 - Fungiform papillae appear as rounded elevations of nonkeratinized epithelium mainly on lingual margin but also irregularly on dorsal surface
 - Foliate papillae located posteriorly along sides of tongue appearing as leaf-like mucosal ridges covered by nonkeratinized epithelium
 - Circumvallate papillae present at junction of anterior two thirds and posterior one third of tongue representing the largest papillae arranged in a V-shape located immediately anterior to sulcus terminalis covered by nonkeratinized epithelium
 - Taste buds
 - Pale, oval bodies within the papillae epithelium
 - Numerous within circumvallate papillae
 - Less numerous in fungiform and foliate papillae as well as elsewhere along dorsal and lateral aspects of tongue
 - Intraepithelial localization appearing as lighter staining structures oriented at a right angle to the surface composed of spindle cells with elongated nuclei
 - Composed of three cell types:
 - ◻ Gustatory or taste cells
 - ◻ Supporting or sustentacular cells
 - ◻ Basal cells
 - Immunoreactive for cytokeratins (CAM5.2, CK18)
 - Ventral tongue:
 - Stratified nonkeratinized squamous epithelium with short, blunt rete ridges
 - Submucosa merges with connective tissue intersecting with ventral muscle bundles
 - Papillae seen on dorsal tongue are absent on ventral tongue surface
- Minor salivary glands: (see Section 7, Salivary Glands, for histologic illustrations)
 - Seen throughout the oral cavity
 - Appear as scattered unencapsulated small lobules within the oral cavity mucosa and submucosa

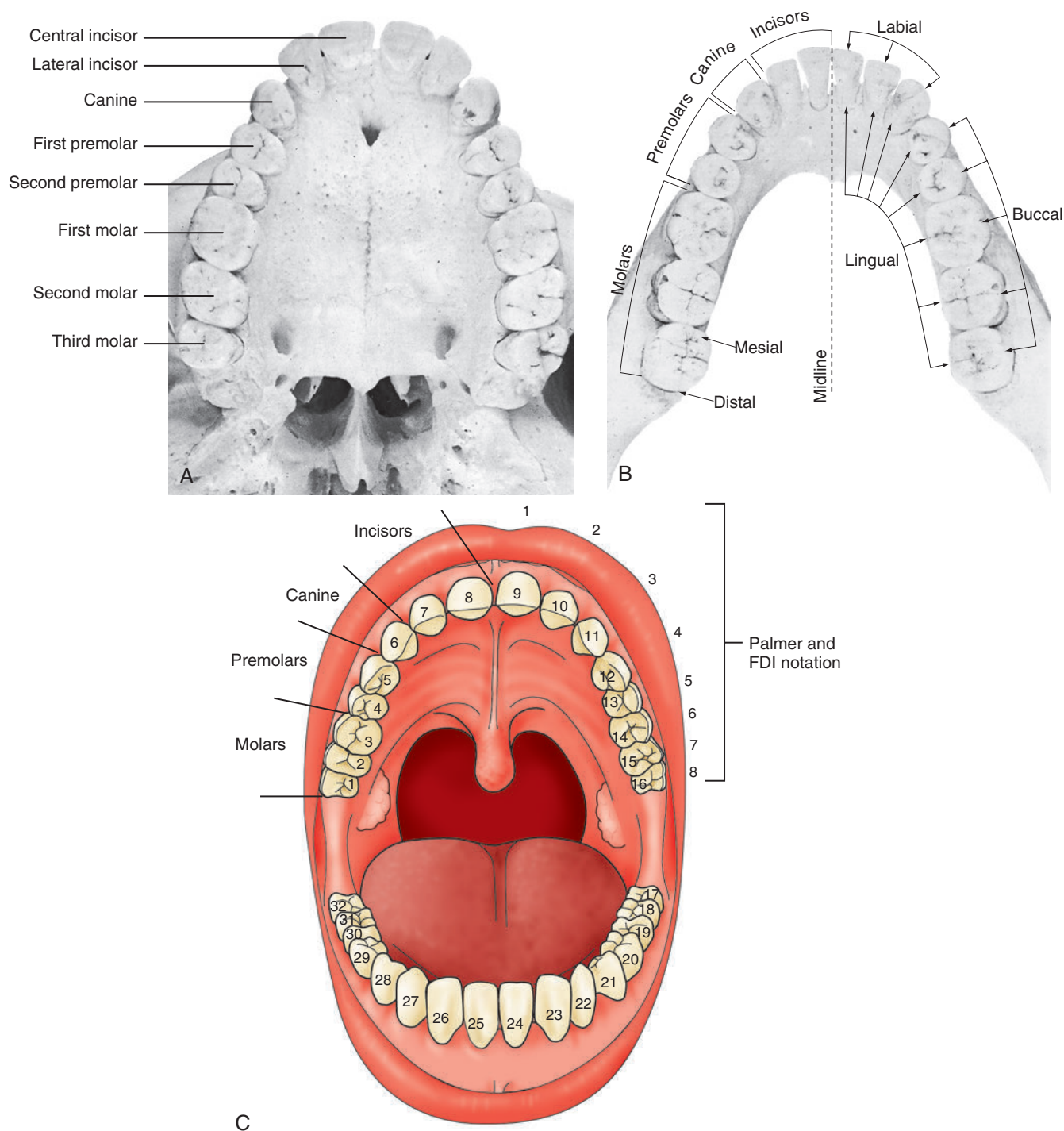


Fig. 4-3. Teeth.

A, Upper dental arch. **B**, Lower dental arch. **C**, Tooth numbering system. (**A**, From Standring S: *Gray's anatomy*, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, Figure 30.14A, p 509. **B**, From Standring S: *Gray's anatomy*, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, Figure 30.14B, p 509. **C**, From Woo SB: *Oral pathology*, Philadelphia, 2012, Elsevier, Figure 1-12, p 6.)

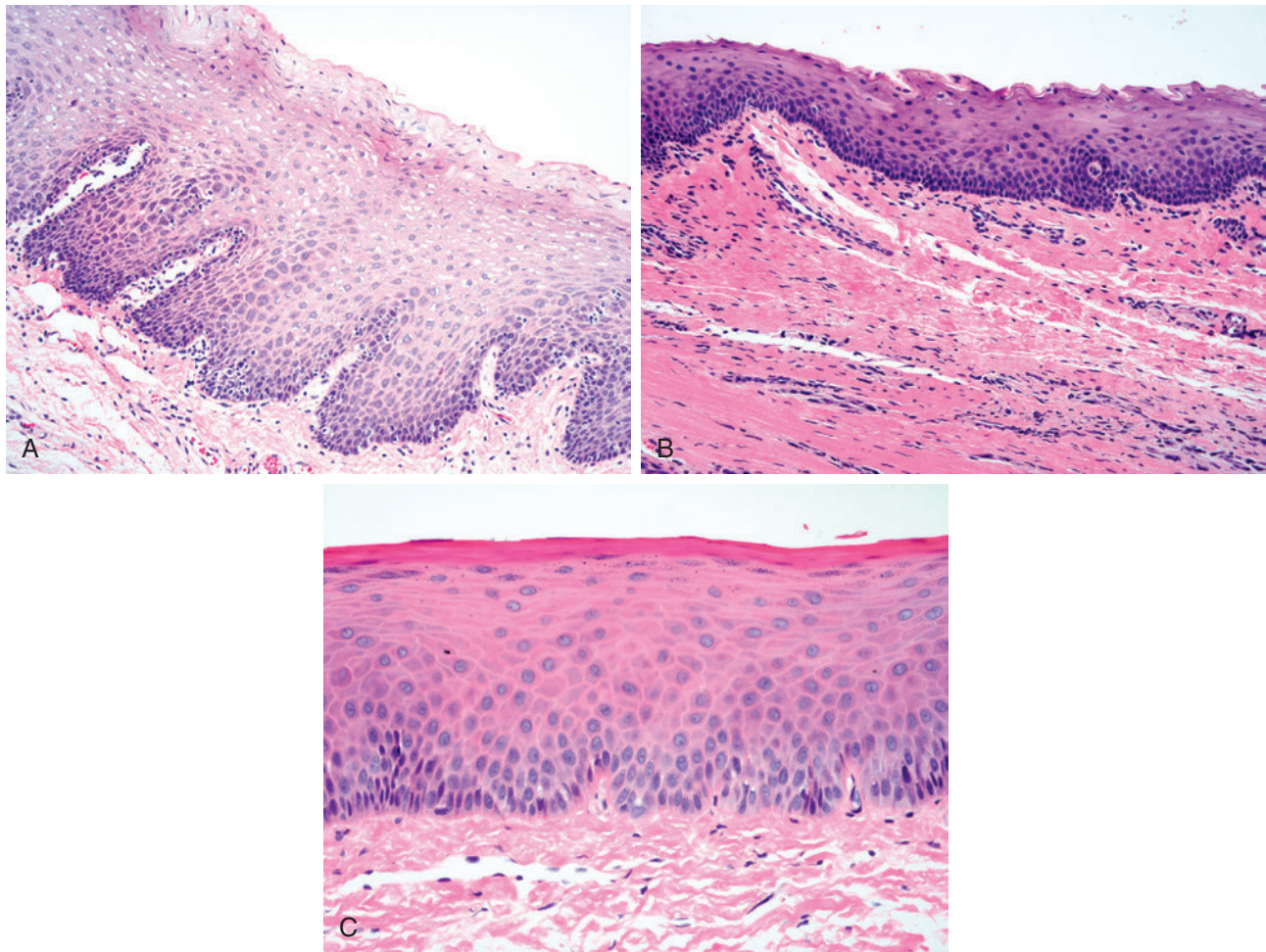


Fig. 4-4. Histology of oral mucosa.

A, Normal buccal mucosa composed of nonkeratinized stratified squamous epithelium including cells with vacuolated appearing cytoplasm due to the presence of glycogen and broad rete ridges. **B**, Normal floor of mouth composed of thin stratified squamous epithelium with poorly formed rete ridges. **C**, Normal hard palate mucosa composed of a thin layer of orthokeratinized epithelium with thin granular cell layer. In this location submucosal mucous glands are identified in a dense lamina propria (not shown).

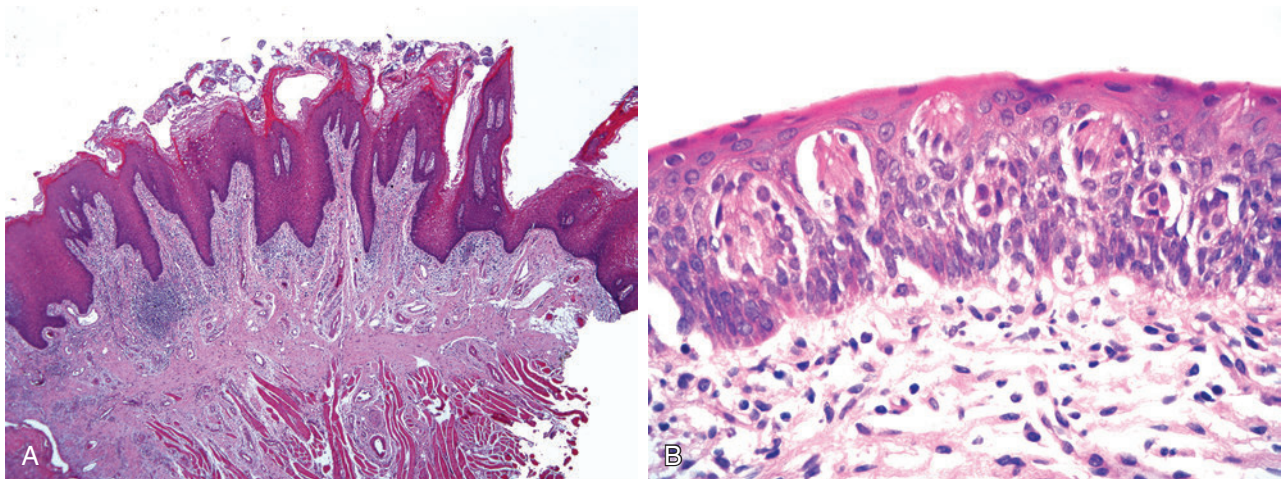


Fig. 4-5. Histology of oral mucosa.

A, Dorsal aspect of the tongue, in particular the anterior portion, is characterized by the presence of numerous mucosal projections forming papillae; these papillae are absent on the ventral surface. **B**, Taste buds located along the dorsal and lateral aspects of the tongue appear as pale, oval bodies within the papillae epithelium.

TABLE 4-1 Oral Mucosa: Histologic Features

Site	Histology
Buccal and labial mucosa (contiguous structures)	Thick, nonkeratinizing, stratified squamous epithelium with broad, tapered rete ridges
Dorsal tongue	Moderate to thick keratinized squamous epithelium with parakeratosis
Floor of mouth and ventral tongue (contiguous structures and histology similar to soft palate)	Thin, nonkeratinizing, stratified squamous epithelium with short or poorly formed rete ridges Serous minor salivary glands identified in anterior ventral tongue (glands of Blandin and Nuhn) and posterior ventral tongue (von Ebner glands)
Gingiva, attached (histology similar to hard palate)	Thin layer of orthokeratin with thin granular layer of nonkeratinizing stratified squamous epithelium with poorly formed rete ridges; rete ridges tend to be more tapered and slender as compared with hard palate May contain odontogenic epithelial rests (rests of Serres)
Gingiva, nonattached	Nonkeratinized epithelium
Hard palate (histology similar to attached gingiva)	Thin layer of orthokeratin with thin granular layer of nonkeratinizing stratified squamous epithelium with poorly formed rete ridges; dense lamina propria; submucosal minor salivary glands present
Soft palate	Thin nonkeratinizing stratified squamous epithelium with short or poorly formed rete ridges

- Intramuscular location seen in association with the tongue and lips
- Minor salivary glands in the tongue are located:
 - In anterior ventral portion (referred to as Blandin or Nuhn glands) composed of mixed serous and mucous types
 - In region of the circumvallate papillae on the posterior and lateral portion (referred to as von Ebner glands) composed of pure serous type
 - In remainder of the oral cavity the glands are mixed seromucous with mucous glands predominating and in area of hard palate are pure mucous glands
 - Minor salivary glands are present in the retro-molar mandibular ridge but the anterior hard palate and gingiva are typically devoid of minor salivary glands.
- Nonepithelial intraepithelial cells:
 - Nonepithelial cells present in oral mucosa include:
 - Melanocytes:
 - Located in basal layer
 - Most common in gingiva but also present in lips, palate, buccal mucosa
 - Immunoreactivity includes S100 protein and melanocytic markers
 - Langerhans (dendritic) cells:
 - Mostly located in suprabasal layers
 - Play role in immune response
 - Dendritic nature cannot be recognized by routine staining
 - Immunoreactivity includes S100 protein, CD1a
 - Dendritic processes best seen following S100 protein staining
 - Merkel cells:
 - Located in basal layer individually or in clusters
 - Represent neuroendocrine cells
 - Not recognized by routine staining
 - Immunoreactivity for neuroendocrine markers (e.g., synaptophysin, chromogranin), S100 protein, neuron-specific enolase, cytokeratins (AE1/AE3, CAM5.2, CK20)
 - Lymphocytes
- Juxtaoral organ of Chievitz (Fig. 4-6):
 - Well-delineated normal microscopic structure of uncertain function normally situated at the angle of the mandible, bilaterally, near the buccotemporal space:
 - Recent evidence supports possible neurosecretory or neuroreceptor function
 - Multilobulated round to elongated nests of squamoid epithelial cells embedded in a fibrous stroma rich in small peripheral nerves:
 - More central cells are nonkeratinizing with identifiable intercellular bridges composed of uniform, bland-appearing nuclei, eosinophilic to clear cytoplasm and inconspicuous nucleoli.
 - More peripheral cells are basaloid appearing with nuclear palisading
 - Occasionally duct-like lumens may be identified
 - Delineated/prominent basement membrane is present around the squamoid cell nests.
 - Absence of keratinization and/or keratohyaline granules
 - Melanin pigment may be identified.

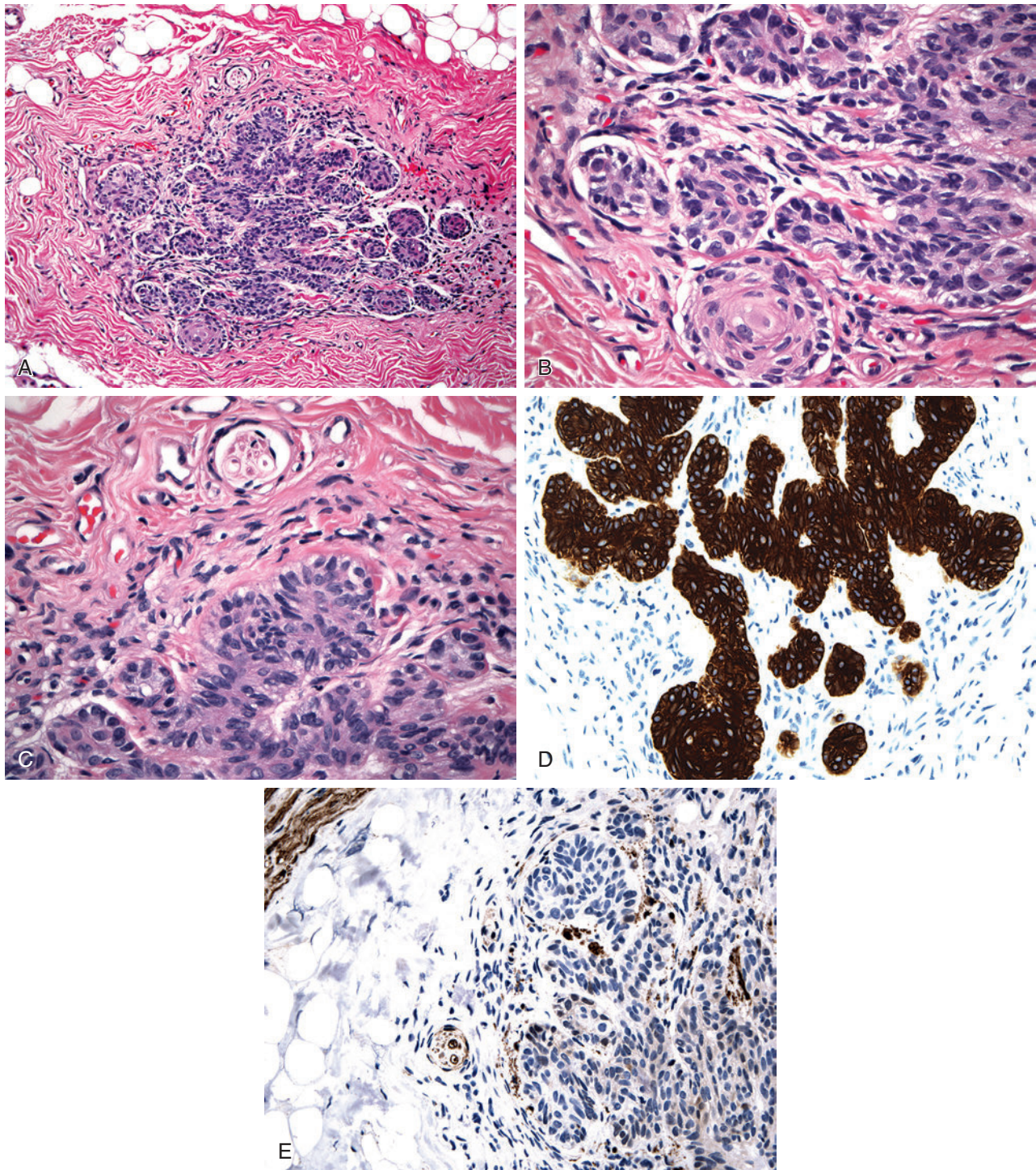


Fig. 4-6. Juxtaoral organ of Chievitz.

A, Multilobulated round nests of squamoid epithelial cells within a fibroconnective tissue stroma. **B**, Nonkeratinizing cells composed of uniform, bland-appearing nuclei, eosinophilic to clear cytoplasm, and inconspicuous nucleoli. **C**, The cell nests lie in close proximity to small peripheral nerves; immunoreactivity is present for **(D)** cytokeratin and **(E)** focally for S100 protein; the latter also delineates the small peripheral nerve. Usually, this normal structure is an incidental finding at frozen section or in permanent sections but its presence, squamoid cells, and normal intimate association with small peripheral nerves (branches of the buccal nerve) may result in diagnostic confusion with an invasive neurotropic squamous cell carcinoma (see Figure 7-10 for frozen section appearance of the juxtaoral organ of Chievitz).

- Immunoreactivity may be present for cytokeratin and S100 protein.
- Usually an incidental finding at frozen section (see section on intraoperative consultation at end of this section) or in permanent sections in tissue excised for other reasons:
 - Given histology that includes squamoid cells and normal intimate association with small peripheral nerves (branches of the buccal nerve), diagnostic confusion may arise with an invasive squamous cell carcinoma with neurotropism.

INNERVATION

- Innervation of the oral cavity structures are from cranial nerves V and VII:
 - Fifth nerve branches to the oral cavity include the maxillary nerve (entirely sensory) and the mandibular nerve (sensory and motor); each of these nerves is further divided into various nerve groups that innervate specific oral cavity structures (for more details the reader is referred to specific anatomy text).
 - Cranial nerve VII:
 - Motor root supplies the muscles of the face.
 - Sensory root supplies the taste fibers via the chorda tympani for the presulcal area of the tongue and via the palatine and greater petrosal nerves the soft palate.
- Innervation of the tongue:
 - Motor innervation to the intrinsic muscles of the tongue are supplied by the hypoglossal (XII) nerve.
 - Sensory nerves include:
 - Lingual branch of the mandibular nerve for ordinary sensibility to the anterior tongue
 - Chorda tympani branch of the facial nerve (VII) for taste to the anterior tongue (excluding the circumvallate papillae)
 - Lingual branch of the glossopharyngeal (IX) nerve for taste and general sensibility to the mucous membranes at the base and lateral aspects of the tongue and to the circumvallate papillae
 - Superior laryngeal nerve to the vallecular area (in front of the epiglottis)

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE

- Arteries and veins:
 - Arterial supply to the oral cavity structures comes via branches of the internal carotid artery (facial

artery and its branches) and the external carotid artery (lingual and maxillary arteries and their branches).

- Venous drainage from the oral cavity structures flows to the internal jugular vein via the facial vein and pterygoid plexus and to the external jugular vein via numerous smaller veins, including the facial vein and the maxillary vein.
- Lymphatics:
 - Lips:
 - Upper lip: preauricular, infraparotid, submandibular, and submental lymph nodes:
 - Relative absence of anastomotic channels results in ipsilateral drainage.
 - Lower lip, medial portion: submental lymph nodes
 - Lower lip, lateral portion: submandibular lymph nodes

NOTE: Due to numerous anastomotic lymphatic vessels near the midline of the lower lip, lymphatic drainage occurs bilaterally.

- Buccal mucosa:
 - Lymph nodes in the submental and submandibular triangles of the neck
- Alveolar ridges:
 - Buccal aspect: submental and submandibular lymph nodes
- Retromolar trigone:
 - Upper deep cervical lymph nodes
- Floor of mouth:
 - Anterior part to inferior lymph nodes of the upper deep cervical group via the submental lymph nodes
 - All other parts to submandibular and upper deep cervical lymph nodes
- Tongue:
 - Lymphatics arise from an extensive submucosal plexus with ultimate drainage to the deep cervical lymph nodes.
- Hard palate:
 - Upper deep cervical and retropharyngeal lymph nodes
- Gingiva:
 - Upper gums and lower posterior part: submandibular lymph nodes
 - Lower anterior part: submental lymph nodes

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Non-Neoplastic Lesions of the Oral Cavity

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE ORAL CAVITY (Box 5-1)

BOX 5-1 Classification of Non-Neoplastic Lesions of the Oral Cavity

Developmental Cystic Anomalies

Nonodontogenic Cysts

- Nasopalatine duct cyst
- Median palatal cyst
- Nasolabial cyst
- Surgically ciliated cyst
- Others

Nonodontogenic, Nondevelopmental Cysts

- Mucocoeles (mucus extravasation phenomenon; mucus retention cyst, ranula)
- Oral lymphoepithelial cyst
- Simple bone cyst

Odontogenic Developmental Cysts

- Dentigerous cyst
- Eruption cyst
- Lateral periodontal cyst
- Botryoid odontogenic cyst
- Glandular odontogenic cyst
- Gingival cyst
- Primordial cyst

Odontogenic Nondevelopmental Cysts

- Radicular or periapical cyst
- Residual cyst
- Buccal bifurcation cyst
- Paradental cyst

Hamartomas and Choristomas

- Fordyce granules
- Others (e.g., osseous, cartilaginous, glial, and gastrointestinal)
- Ectopias (e.g., lingual thyroid, others)

Infectious and Related Diseases or Lesions

- Fungal
- Viral
- Bacterial
- Mycobacterial
- Protozoal
- Others

Reactive, Inflammatory, and Tumor-like Lesions

- Epithelial reactive lesions (e.g., verrucae, focal epithelial hyperplasia, pseudoepitheliomatous hyperplasia, necrotizing sialometaplasia, others)
- Mesenchymal lesions (e.g., irritation fibromas, oral submucous fibrosis, gingival fibromatosis, others)
- Non-neoplastic osseous lesions (e.g., giant cell granuloma, aneurysmal bone cyst, others)
- Autoimmune, allergic, systemic, cutaneous-type lesions (e.g., granulomatosis with polyangiitis, recurrent aphthous stomatitis, oral lichen planus, others)

CYSTIC (NON-NEOPLASTIC) LESIONS OF THE ORAL CAVITY

- Cystic lesions of the oral cavity represent a diverse group of lesions listed in Box 5-2.
- Cysts of these anatomic sites include nonodontogenic and odontogenic cysts:
 - Both categories include developmental and non-developmental cysts.
- Developmental cysts form for no clinically apparent reason.
 - Nasolabial cyst
 - Surgically ciliated cyst
- The reader is referred to other texts for a discussion of these lesions.

NONODONTOGENIC DEVELOPMENTAL CYSTS

- Oral cavity developmental cysts include:
 - Nasopalatine duct cyst
 - Median palatal cyst

NONODONTOGENIC NONDEVELOPMENTAL CYSTS

- Oral cavity nondevelopmental cysts include:
 - Mucocoele:
 - Mucus extravasation phenomenon, mucus retention cyst, ranula
 - Lymphoepithelial cyst
 - Simple bone cyst

BOX 5-2 Selective Oral Cavity Autoimmune, Systemic, Cutaneous-Type Diseases

- Aphthous stomatitis
- Behçet disease
- Crohn disease
- Dermatitis herpetiformis
- Erythema multiforme
- Granulomatosis with polyangiitis
- Lichen planus
- Pemphigus
- Pemphigoid
- Systemic lupus erythematosus
- Others

- Salivary gland mucocele is a general term used to describe minor salivary gland lesions resulting from obstruction secondary to a mucous plug or intraluminal sialolith, resulting in a mucus retention cyst, or due to trauma resulting in mucus extravasation phenomenon.
- For a more detailed discussion on mucus extravasation phenomenon, mucus retention cyst, and ranulas see Section 6, Salivary Glands.

Oral Lymphoepithelial Cyst (Fig. 5-1)

Definition: Squamous epithelial-lined cystic cavity with an associated benign lymphoid infiltrate in the cyst wall analogous to lymphoepithelial cysts that occur in various anatomic locations, such as salivary gland lymphoepithelial cyst, cervical lymphoepithelial cyst, and pancreatic lymphoepithelial cyst.

Synonym: Benign lymphoepithelial cyst

Clinical

- More common in men than in women; occur over a wide age range with a mean age of occurrence in the fourth decade
- Most common on the floor of the mouth; may also be found on the ventral tongue, posterolateral tongue, soft palate, palatine pillar, and buccal vestibule
- Clinical presentation is that of an asymptomatic swelling
- Cause:
 - No known cause(s)
 - Association with EBV or HIV has not been established.

Pathology**Gross**

- Usually a submucosal, freely mobile nodular mass with a slightly yellow color; overlying mucosa is normal or slightly telangiectatic
- Diameter of the lesions may range from 0.1 to 1.0 cm

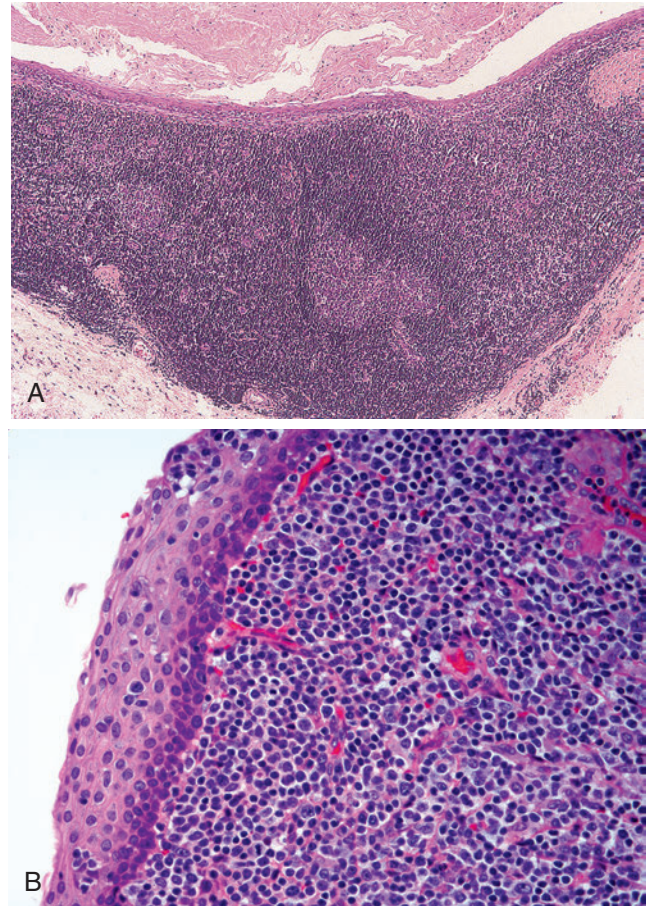


Fig. 5-1. Oral lymphoepithelial cyst.

A and B, Unilocular cyst filled with keratin debris lined by stratified squamous epithelium and characterized by the presence of lymphocytic infiltrate with lymphoid follicles in the cyst wall.

Histology

- Characteristically composed of a well-circumscribed, benign, unilocular epithelial-lined cyst:
 - Cyst lumen is lined by stratified or simple squamous epithelium with transition between the two cell types.
 - Cyst does not form complex loculations.
- Cyst wall is characterized by the presence of benign lymphoid follicular hyperplasia:
 - Lymphoid follicles are usually easily identified and may bulge into the luminal surface.
 - Germinal center formation may or may not be present.
 - Focal exocytosis of the lymphocytes into the epithelial lining may be present.
- Lumen may be filled with keratin, mucoid material sparsely interspersed with polymorphonuclear leukocytes and histiocytes, or empty:
 - Occasionally, bacterial colonization may be seen in the cystic space.

- Lumen may be dilated or collapsed.
- Connection to the surface may be found in some cases.

Differential Diagnosis

- Salivary duct cyst
- Squamous cell carcinoma:
 - Rarely oral lymphoepithelial cyst may coexist with squamous cell carcinoma.
- Malignant lymphoma

Treatment and Prognosis

- Complete surgical excision is curative.

ODONTOGENIC CYSTS

Definition: Cysts derived from the various components of the dental apparatus.

- Include developmental and nondevelopmental cysts
- Odontogenic developmental cysts include:
 - Dentigerous cyst:
 - Eruption cyst
 - Lateral periodontal cyst:
 - Botryoid cyst
 - Glandular odontogenic cyst
 - Gingival cyst
 - Primordial cyst
- Odontogenic nondevelopmental cysts include:
 - Radicular or periapical cyst
 - Residual cyst
 - Buccal bifurcation cyst
 - Paradental cyst

- Complete coverage of odontogenic cysts is beyond the scope of this text; the reader is referred to other texts that cover the full clinicopathologic spectrum of odontogenic cystic lesions.
- The following discussion is limited to a few of the more common odontogenic cysts that the surgical pathologist may be confronted with in daily practice.
- Odontogenic keratocyst is, according to the World Health Organization 2005 Working Group, now considered as a bona fide neoplasm and is discussed in Chapter 6 under Odontogenic Neoplasms.

ODONTOGENIC DEVELOPMENTAL CYSTS

Dentigerous Cyst (Figs. 5-2 and 5-3)

Definition: Nonkeratinizing cyst that develops in association with the crown of an unerupted or impacted tooth.

Synonym: Follicular cyst

Clinical

- Most common developmental odontogenic cyst representing up to approximately 20% to 25% of all odontogenic cysts
- More common in men than in women; most frequent in the second through fourth decades of life
- Always associated with the crown of an impacted or unerupted tooth:
 - Permanent teeth are affected.
 - Rarely affect primary teeth

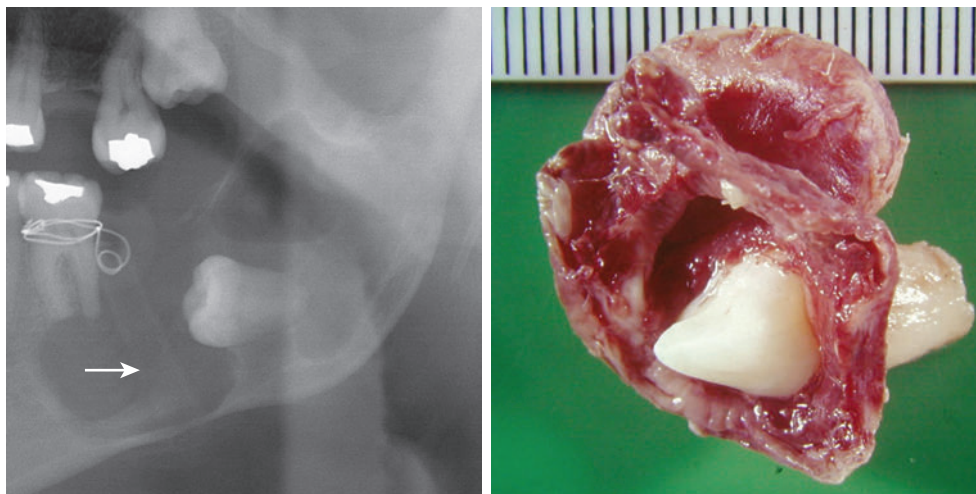


Fig. 5-2. Dentigerous cyst.

Left panel: An unerupted tooth is associated with the cyst (arrow). Right panel: Gross specimen. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 4-238, p 375.)

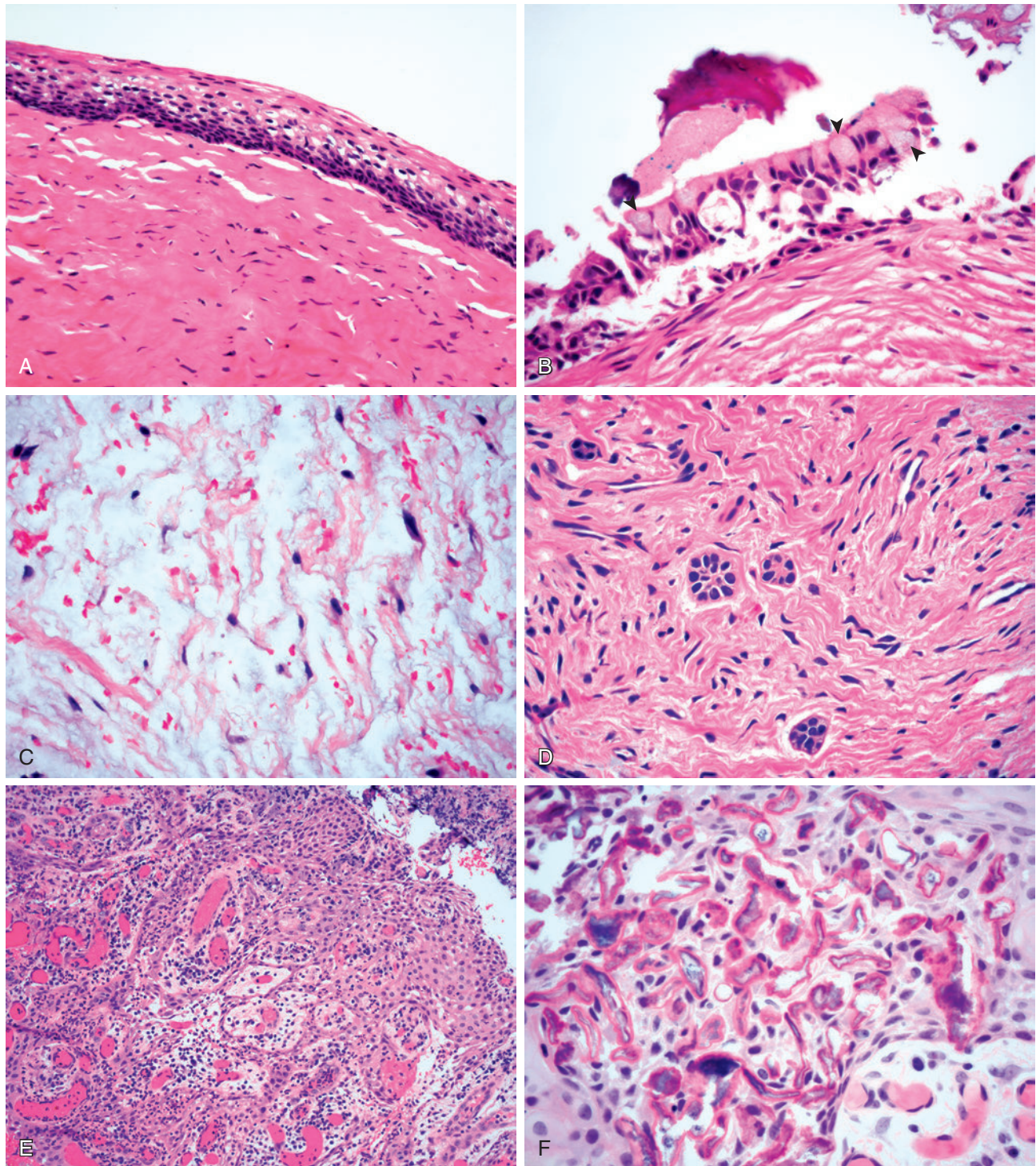


Fig. 5-3. Dentigerous cyst.

A, Cyst lining composed of thin layer of cuboidal-appearing epithelium with eosinophilic cytoplasm. **B**, Mucous cells (*arrowheads*) can be seen in the cyst lining epithelium. **C**, Fibromyxomatous stroma in dentigerous cyst may be misinterpreted as odontogenic myxoma. **D**, Epithelial odontogenic rests in the cyst wall. **E**, In inflamed cysts the epithelial component may become thicker (hyperplastic) and have a more squamous appearance. **F**, Rushton body formation appearing as hyalinized, eosinophilic, angulated, linear, or curved foci within epithelium can be seen; these formations are not unique to dentigerous cyst and can be seen in other odontogenic lesions (e.g., radicular cyst, odontogenic keratocyst).

- Most commonly affects:
 - Mandibular third molar
 - Maxillary canines and molars
 - Mandibular second molars
- Usually asymptomatic; symptoms related to continuous expansion of the cyst, including displacement of teeth, facial asymmetry:
 - With progression and expansion including bone, pain, numbness, and paresthesia may develop due to pressure on nerves
 - Superimposed infection may result in associated pain.
 - Draining sinus tract may develop with progression (cyst expansion).
- Typically solitary, but may be multifocal:
 - Multiple cysts may occur sporadically or part of mucopolysaccharidoses.
 - Bilateral nonsyndromic cysts may occur.
- Radiology:
 - Well-defined, unilocular radiolucency around crown of impacted tooth:
 - Similar imaging findings found in association with enlarged dental follicle
 - Three radiologic variations identified:
 - Central:
 - Symmetric envelopment by crown of tooth
 - Lateral (paradental):
 - Asymmetric development by the follicle with identification to one side of crown
 - Circumferential:
 - Entire tooth is encircled by radiolucency.
 - Presence of a multilocular lesion more likely represents an odontogenic keratocyst or odontogenic tumor (ameloblastoma, other).
- Cause:
 - Caused by accumulation of fluid (and subsequently glycosaminoglycans from capsular ground substance) between the layers of the reduced enamel epithelium or between the epithelium and the crown of the tooth, causing separation of the follicle from the crown

Pathology

Gross

- Unilocular, smooth-walled cyst

Histology

- In noninflamed cyst, the cyst lining resembles reduced enamel epithelium composed of two to three layers of nonkeratinizing stratified squamous epithelium
- Cyst wall composed of thin fibroconnective tissue:
 - Nests and cords of odontogenic epithelium may be present.
 - Dystrophic calcifications may be present.
 - Connective tissue may be fibrous or fibromyxomatous.

- Under normal situations is devoid of an inflammatory cell component
- If inflamed:
 - Epithelial component may become thicker (hyperplastic), may be squamous in appearance, and/or may show downward expansion of the rete ridges.
 - Cyst wall may show the presence of a mixed chronic inflammatory cell infiltrate, cholesterol clefts/granulomas, and/or a foreign body giant cell reaction.
 - Rushton body formation can be seen:
 - Hyalinized, eosinophilic, angulated, linear, or curved foci within epithelium
 - Not specific for dentigerous cyst as can be seen in other developmental and inflamed cysts, including:
 - Radicular cysts and odontogenic keratocyst
 - Of unknown origin
- In general are devoid of keratinization but rarely may show limited foci of surface keratinization:
 - Occasionally may be orthokeratinized but lacks characteristic features of odontogenic keratocyst
 - In the presence of more extensive surface keratinization may represent an odontogenic keratocyst (see below)
 - Other findings that may be identified in the epithelial component include mucous (goblet) cells and ciliated cells.
- Special stains:
 - Noncontributory to diagnosis

Differential Diagnosis

- Enlarged dental follicle ([Fig. 5-4](#)):
 - Dental follicles are characterized by presence of reduced enamel epithelium, a copious myxoid-appearing stroma with scattered identifiable epithelial (odontogenic cell) nests; the latter may be limited in extent.
- Dental papilla ([Fig. 5-5](#)):
 - Composed of primitive myxoid connective tissue lined by odontoblasts:
 - Histologically identical to odontogenic myxoma
 - Clinical and radiologic correlation reveals that a developing tooth was removed rather than an odontogenic cyst/neoplasm.
- Radicular or periapical cyst (see below)
- Calcifying odontogenic cyst
- Ameloblastoma, unicystic
- Odontogenic adenomatoid tumor
- Squamous odontogenic tumor

Treatment and Prognosis

- Therapy varies depending on the cyst size:
 - Small cyst can be treated by enucleation and removal of the involved tooth.

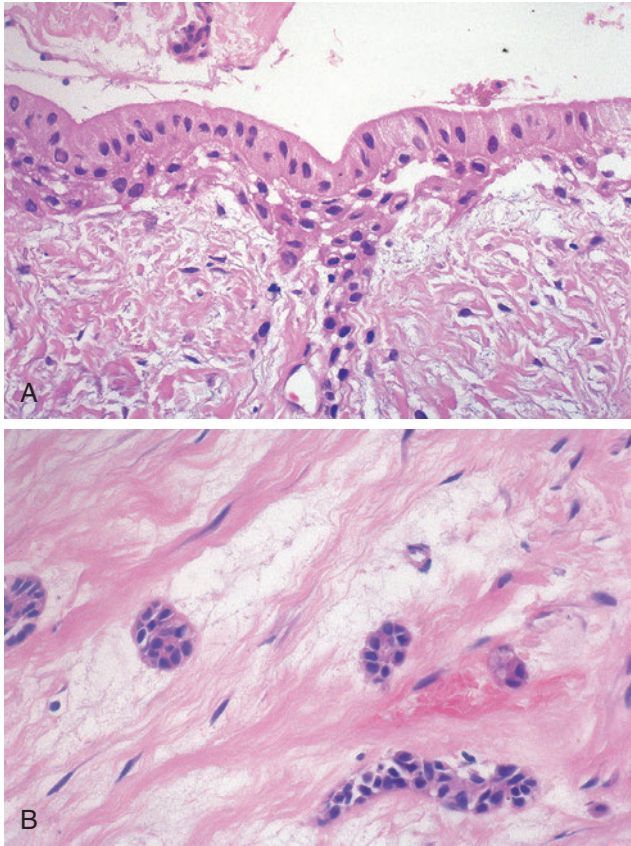


Fig. 5-4. Dental follicle.

Dental follicle composed of **(A)** reduced enamel epithelium and **(B)** nests of odontogenic epithelium within the stroma. These findings may suggest a diagnosis of dentigerous cyst.

- Larger cyst can be managed by marsupialization.
- Recurrence is uncommon and generally relates to incomplete excision.
- May give rise to various odontogenic tumors, including:
 - Ameloblastoma
 - Odontogenic adenomatoid tumor
 - Intraosseous carcinoma including:
 - Squamous cell carcinoma
 - Mucoepidermoid carcinoma

Eruption Cyst

Definition: Soft tissue variant of dentigerous cyst:

- Represents a dilation of the normal follicular space
- Develops secondary to accumulation of blood or fluid between the tooth crown and an erupting or permanent tooth and the overlying mucosa

Synonym: Eruption hematoma

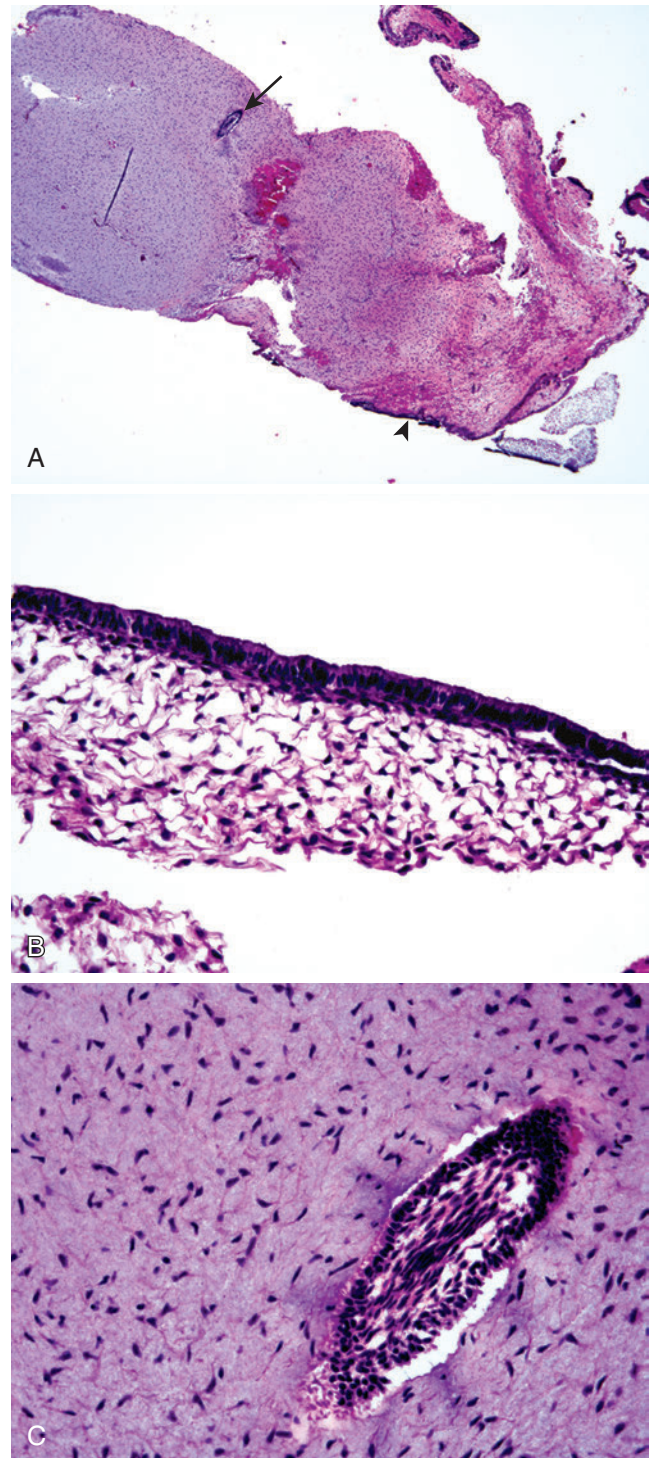


Fig. 5-5. Dental papilla.

A, Rounded fragment of primitive myxoid tissue (*left*) including odontogenic cell nest (*arrow*) and lined by odontoblasts (*arrowhead*). **B**, Higher magnification of the columnar odontoblastic cell lining and **(C)** odontogenic cell nest within the myxoid connective tissue. These histologic features are identical to those seen in odontogenic myxoma. Clinical and radiologic correlation reveals that a developing tooth was removed rather than an odontogenic cyst/neoplasm.

Clinical

- Occurs almost exclusively in infants and young children
- More common in girls than in boys
- Present as a bluish-appearing firm to fluctuant swelling of the alveolar ridge overlying an erupted tooth
- Usually asymptomatic but if inflamed may be painful and tender
- Unilateral or bilateral cyst:
 - Most common locations include central incisor and primary first molar region.
- Radiology:
 - Associated tooth lies immediately below a soft tissue swelling

Pathology

- Lined by nonkeratinized stratified squamous epithelium with a chronic inflammatory cell infiltrate in the cyst wall
- Cyst epithelial lining may be absent; in such instances the designation eruption hematoma can be used.

Treatment and Prognosis

- Usually resolves spontaneously with eruption of the associated tooth
- Surgical intervention (exposure of tooth with removal of portion of enclosed mucosa) may be required in the presence of infection or resulting delay in the eruption of the involved tooth.

Glandular Odontogenic Cyst (GOC)

(Fig. 5-6)

Definition: Nonkeratinizing cyst in tooth-bearing areas of the jaws lined by cuboidal to columnar epithelial cells and crypt-like and microcystic spaces often lined by mucous cells.

Synonyms: Sialo-odontogenic cyst; mucus-producing cyst; mucoepidermoid odontogenic cyst

Clinical

- More common in males than females; wide age range but most common in fifth through decades
- Most often involves the mandible, in particular anterior portions:
 - Canine region most common for maxillary lesions
- Symptoms include jaw swelling or expansion with or without pain:
 - May be associated with:
 - Tooth displacement or root resorption
 - Impacted tooth
 - Perforation and thinning of cortical plates

- Radiology:
 - Unilocular or multilocular radiolucency with well-defined sclerotic borders

Pathology**Histology**

- Features include:
 - Surface eosinophilic cuboidal cells (“hobnail cells”) present on surface of cyst lining and resemble cuboidal cells of the reduced enamel epithelium that lines dental follicles and dentigerous cysts
 - Intraepithelial microcysts or duct-like spaces lined by a single layer of cuboidal to columnar cells similar to surface cells:
 - Microcysts may be lined by mucous goblet cells.
 - Microcysts may contain mucous pools and eosinophilic material or may appear to be empty.
 - In areas, microcysts may open onto surface of lining epithelium.
 - Apocrine snouting of hobnail cells:
 - Hobnail cells demonstrate “pinching off” of surface similar to decapitation secretion seen in cells that line apocrine gland ducts.
 - Clear or vacuolated cells may be present in the basal and/or parabasal layers.
 - Cells contain glycogen
 - Variable thickness of cyst lining
 - Papillary projections or “tufting” into cyst lumen
 - Papillary projections sometimes are formed by several microcysts opening onto surface of the cyst lining but may also be formed independent of microcyst.
 - Mucous goblet cells may be present singly or in small clusters on the surface or within cyst lining; may also line microcysts.
 - Epithelial spheres or plaque-like thickenings
 - Plaque-like thickenings may have swirled appearance histologically similar to that seen in association with lateral odontogenic cyst and botryoid odontogenic cyst.
 - True cilia on surface of eosinophilic cuboidal cells distinct from apocrine snouting
 - Multiple compartments or cystic spaces similar to those seen in botryoid odontogenic cysts
- Immunohistochemistry:
 - Positive for cytokeratins (CK5/6, CK7)
 - Variable reactivity for calponin
 - Negative for S100 protein and smooth muscle actin
- Cytogenetics and molecular genetics:
 - Absence of *MECT1-MAML2* translocation:
 - Translocation present in salivary gland mucoepidermoid carcinoma and central mucoepidermoid carcinoma

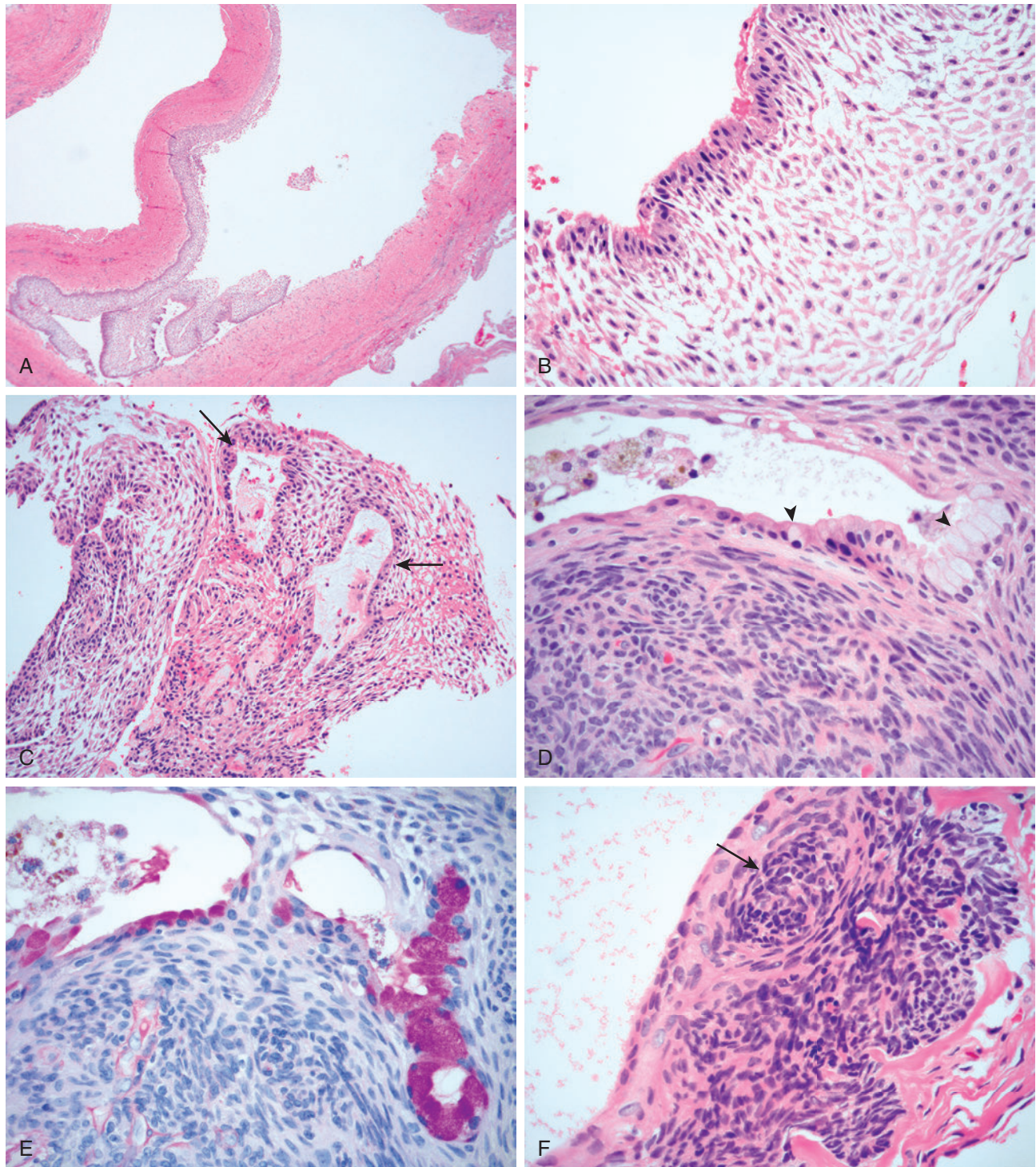


Fig. 5-6. Glandular odontogenic cyst.

A, Low magnification shows a cystic lesion with variably thickness of the lining epithelium. **B**, Cells with eosinophilic-appearing cytoplasm line the cyst surface resembling the cells of the reduced enamel epithelium that line dental follicles and dentigerous cysts. **C**, Intraepithelial microcysts or duct-like spaces (*arrows*) are lined by a layer of cuboidal to columnar cells appearing epithelium similar to surface epithelial cells. **D**, Mucous (goblet) cells are present singly or in small clusters (*arrowheads*). **E**, Mucous (goblet) cells show intracytoplasmic mucin-positive material. **F**, Epithelial spheres or plaque-like thickenings have swirled or whorled appearance (*arrow*); similar epithelial swirls can be seen in with lateral odontogenic cyst and botryoid odontogenic cyst.

Differential Diagnosis

- Central mucoepidermoid carcinoma (CMEC) (Fig. 5-7):

Definition: Malignant epithelial salivary gland neoplasm originating in the jaws, an area normally devoid of salivary gland tissue, and composed of a variable admixture of epidermoid and mucus-secreting cells.

- Predilect to mandible; less often affect maxilla:
 - In mandible, third molar region is most common site
 - In maxilla, molar region is most common site
- May be asymptomatic and identified incidentally in radiologic evaluation as a radiolucent lesion

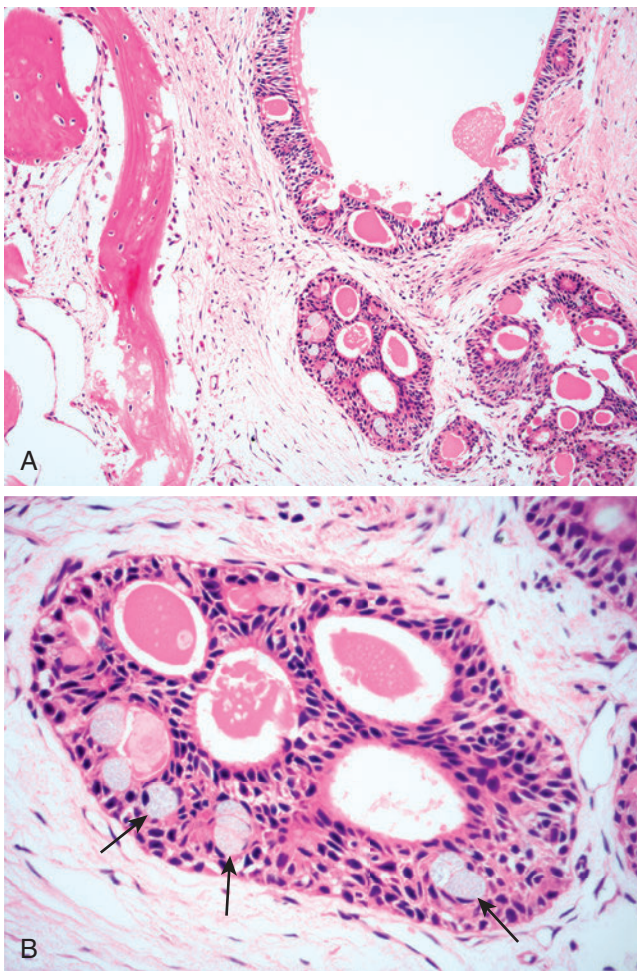


Fig. 5-7. Central mucoepidermoid carcinoma.

The presence of infiltrative epithelial nests composed of more proliferative (thicker) epithelium, including an admixture of mucocytes (arrows), epidermoid cells, and intermediate cells are findings that assist in the differential diagnosis with glandular odontogenic cyst.

- Symptomatic cases may include swelling, pain, facial asymmetry, or trismus.
- More than 50% associated with an unerupted tooth or a cyst
- Proposed origin includes:
 - Ectopic salivary gland tissue (not favored)
 - Development from odontogenic cyst, which is the favored origin given:
 - Metaplastic cells seen in odontogenic lesions
 - Half of central MECs occur in association with a cyst or an unerupted tooth.
 - Other neoplasms develop from odontogenic cyst.
- Histologic findings (i.e., cellular components) similar to salivary gland tumors:
 - Tend to be histologically low grade
 - Histology similar to glandular odontogenic cyst and histologic differentiation may be problematic resting on:
 - Extent of the cellular proliferation:
 - More proliferative (i.e., thicker) cellularity in CMEC composed of admixture of mucocytes, epidermoid cells, and intermediate cells
 - GOC has thinner epithelium with little tendency to be as proliferative as MEC.
 - Presence of invasive growth:
 - Invasive growth associated with CMEC but not GOC
- Cytogenetics and molecular genetics:
 - *MECT1-MAML2* translocation identified in salivary gland MECs also reported in CMEC
 - Possible relationship of GOC and CMEC proposed, perhaps even GOC representing a precursor lesion to CMEC:
 - Absence of *MECT1-MAML2* translocation in GOC discredits it from being a precursor lesion to GOC.
- Staging system includes:
 - Stage I: tumors within intact cortical bone without clinical expansion
 - Stage II: tumors within intact cortical bone with clinical expansion
 - Stage III: tumors with perforation of cortical bone
- Surgical resection is preferred treatment for CMEC and may include conservative versus aggressive surgical intervention:
 - Conservative surgery includes curettage, enucleation, or marsupialization:
 - Recurrence rates of up to 40%
 - Aggressive surgery includes segmental resection:
 - Recurrence rates of approximately 13%
- Metastatic disease occurs in less than 10% of cases.

Treatment and Prognosis

- Marginal resection is recommended:
 - Enucleation or curettage not advocated owing to associated high recurrence rates (>50%)
- Long-term follow-up recommended

ODONTOGENIC NONDEVELOPMENTAL CYSTS

Radicular or Periapical Cyst (Figs. 5-8 through 5-9)

Definition: Inflammatory odontogenic epithelial-lined cyst arising from epithelial odontogenic rests (rests of Malassez) in the periodontal ligament secondary to inflammation following necrosis of the dental pulp:

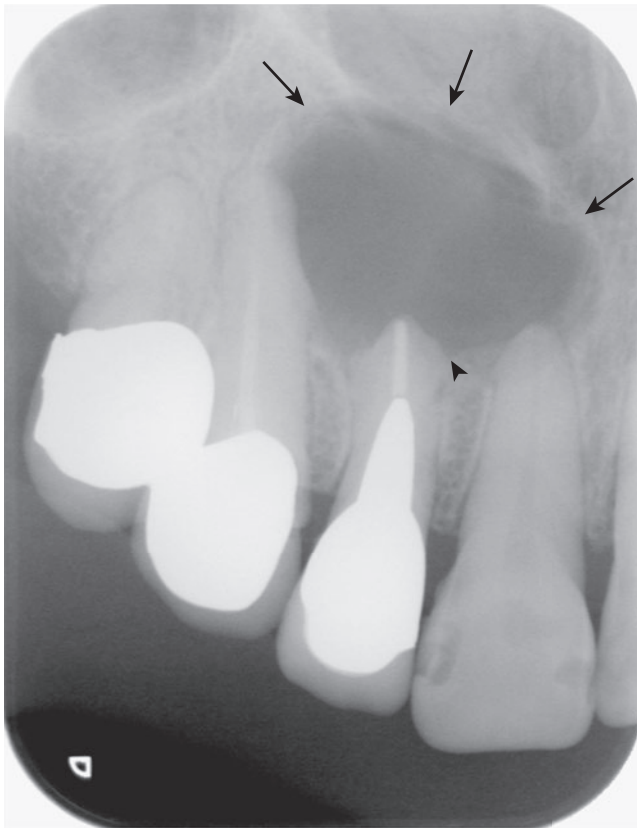


Fig. 5-8. Radicular cyst: imaging findings.

Radicular cyst in the maxilla of right lateral incisor tooth. Periapical image shows a well-defined unilocular radiolucency (arrows), around the apex of the upper right lateral incisor tooth. Note the continuity between the cystic lesion and the periodontal ligament space of the affected tooth (arrowhead). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-8, p 1476.)

- In many instances, true epithelial-lined cysts do not develop and tissue represents inflamed connective tissue referred to as periapical granuloma:
 - Not true granuloma
 - Also referred to as chronic apical periodontitis
 - Represents a mass of granulation tissue at the apex of a nonvital tooth resulting from escape of inflammatory cells and bacterial products from a necrotic pulp usually caused by dental caries
 - Periapical granulomas may develop after resolution of a periapical abscess.

Synonyms: Apical cyst, apical periodontal cyst, dental cyst

Clinical

- Most common cyst of the jaws
- No gender predilection; may occur at any age but most commonly occurs in the third to sixth decades of life
- May affect any tooth but is most commonly identified in association with the anterior maxilla:
 - Invariably associated with nonvital tooth:
 - Associated with teeth that have extensive caries or history of trauma (physical, chemical) resulting in pulpal necrosis
 - Rarely seen in primary dentition
 - Usually associated with apical foramen of nonvital tooth, hence the designation periapical cyst
 - May occur in association with any portion of the tooth, hence the term radicular cyst, which is the preferred terminology
- Most cases are asymptomatic unless there is exacerbation by an acute inflammatory reaction.
- Symptoms associated with the affected tooth include pain during mastication and sensitivity to percussion.
- Multiple cysts may develop in the same patient; no association with any syndromes
- Radiographic features include:
 - Presence of a well-circumscribed, unilocular radiolucency of variable size surrounding the apex of the involved tooth

Pathology

Histology

- Cyst is lined by nonkeratinizing stratified squamous epithelium.
 - In presence of inflammation, the epithelial lining of the cyst may be hyperplastic with acanthosis and spongiosis.
 - A variable number of mucocytes (goblet cells, mucous cell metaplasia) may be identified but are not as common as seen in dentigerous cysts.
 - Intraepithelial linear or arch-shaped calcifications known as Rushton bodies occasionally can be identified:

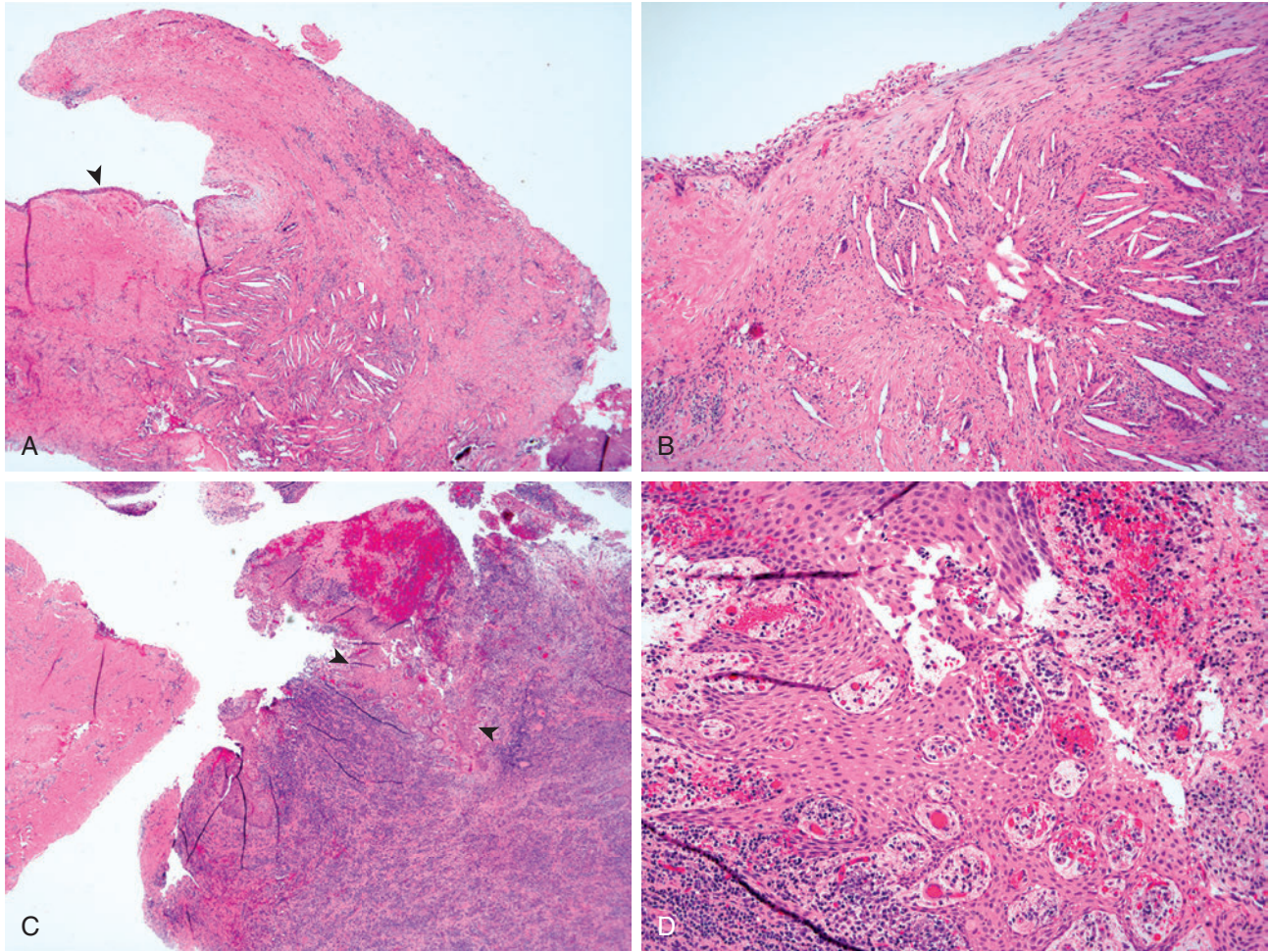


Fig. 5-9. Radicular cyst.

A, Noninflamed epithelial lined cyst (*arrowhead*) with mural cholesterol granuloma formation. **B**, Higher magnification of the noninflamed epithelial-lined cyst composed of a nonkeratinizing, nonproliferative (hyperplastic)-appearing squamous epithelium (*top*). **C**, Inflamed epithelial lined cyst (*arrowheads*) showing proliferative (hyperplastic) epithelial changes. **D**, Higher magnification shows the proliferative (hyperplastic) appearing squamous epithelium.

- Hyalinized, eosinophilic, angulated, linear, or curved foci within epithelium
- Not specific for radicular cyst as can be seen in dentigerous and other cysts
- Of unknown origin
- Cyst wall consists of dense fibroconnective tissue with an admixed acute and chronic inflammatory cell infiltrate.
- Additional histologic findings that can be found include:
 - Mineralization/dystrophic calcification
 - Cholesterol clefts with multinucleated giant cells (cholesterol granulomas)
 - Hemorrhage (recent and remote in the form of hemosiderin deposition)
 - Hyaline bodies can be found in the cyst wall appearing as small circumscribed pools of eosinophilic material that may be surrounded by an inflammatory cell infiltrate, including neutrophils, lymphocytes, plasma cells, and multinucleated giant cells
- Cyst lumen is filled with fluid and cellular debris.
- Cysts that approximate a paranasal sinus may be lined in part or in total by pseudostratified respiratory epithelium.
- Periapical granuloma:
 - Composed of granulation tissue with associated mixed acute and chronic inflammation surrounded by fibrous connective tissue
 - Among the chronic inflammatory cells seen are mature plasma cells with intracytoplasmic eosinophilic globules representing immunoglobulins (Russell bodies) and foamy (lipid-laden) histiocytes.
 - Scattered epithelial nests (rests of Malassez) may be identified within the granulation tissue.

- Cholesterol granulomas, fresh hemorrhage, and hemosiderin deposition may be present.
- Scattered small foci of neutrophilic accumulation (abscess) may be found but do not reach a level diagnostic for a periapical abscess.
- Periapical abscess represents the accumulation of neutrophils at the apex of a nonvital tooth.

Differential Diagnosis

- Variety of odontogenic and nonodontogenic cysts
- Periapical scar:
 - Area in bone in which a defect is created by periapical inflammatory lesions that is filled in with dense collagenous tissue
 - Features seen in association with a periapical scar that are similar to those of periapical cysts and granulomas include involvement of a nonvital tooth, asymptomatic presentation, and presence of a sharply delineated radiolucency.
 - Histologically, periapical scars consist of collagenous stroma with sparse inflammatory cells.
 - Diagnosis of a periapical scar is suspected in the presence of a history of previous periapical lesion, and radiographic imaging showing evidence of root canal filling.

Treatment and Prognosis

- Treatment includes curettage after extraction of the involved tooth or conservative nonsurgical endodontic therapy with or without extraction of the root apex.
- Recurrence is rare; however, incomplete excision may result in a residual cyst:
 - Designation used for periapical cysts that remain in the jaws after extraction of associated tooth
 - Histologically, may represent area of chronic inflammation or show features of periapical granuloma
- Potential complications may include development of abscess formation, which in turn may progress into an osteomyelitis.
- No known progression to an ameloblastoma

HETEROTOPIAS (CHORISTOMAS) OF THE ORAL CAVITY

Fordyce Granules (Fig. 5-10)

Definition: Collections of sebaceous glands in the oral cavity:

- Because sebaceous glands are not a normal histologic component of the oral cavity mucosa these collections of sebaceous glands are heterotopic.

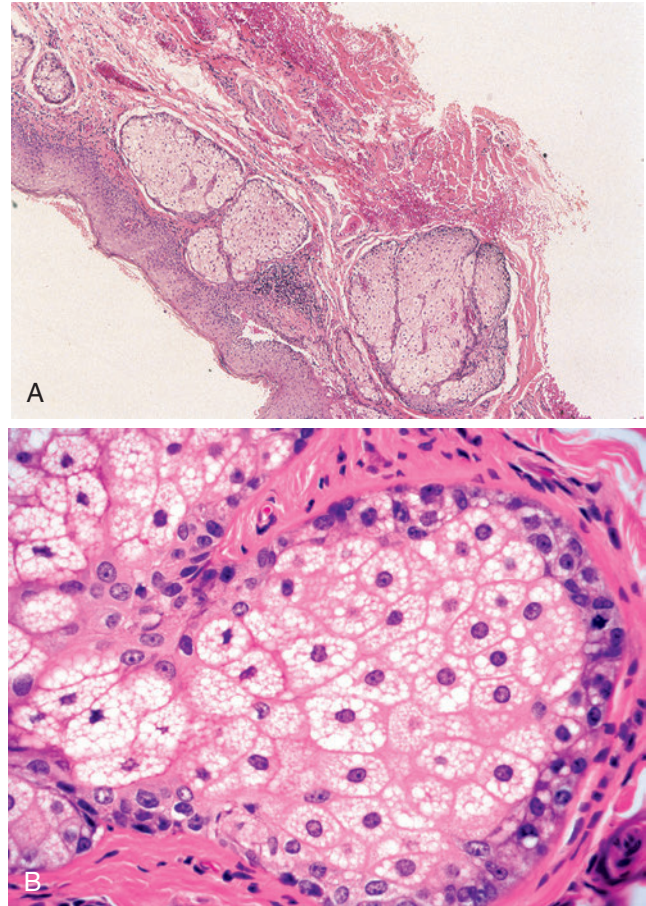


Fig. 5-10.

A, Oral cavity biopsy in which there were incidentally identified submucosal lobules of unremarkable sebaceous glands (Fordyce granules) with intact overlying stratified squamous epithelium. **B,** Higher magnification showing typical sebaceous cells characterized by multivacuolated cytoplasm and scalloped centrally located nuclei.

Synonyms: Fordyce disease; Fordyce condition; ectopic sebaceous glands; sebaceous hyperplasia

Clinical

- Presence of sebaceous glands within the oral cavity affect from 70% to 95% of the adult population but seldom do these collections coalesce to form a mass lesion.
- No gender predilection; occurs primarily in adults and only rarely identified in children:
 - Paucity in children probably related to the fact that sebaceous glands and hair follicles do not attain maximal development until puberty
- Although any mucosal site of the oral cavity may be affected, most commonly occur on the buccal mucosa, upper and lower lips (inner surface),

retromolar region, tongue, gingival, palate, and tonsillar areas:

- Most commonly seen in a bilateral symmetric distribution on the buccal mucosa opposite the molar teeth
- Other than the oral cavity, head and neck sebaceous gland ectopia may be seen in the parotid gland, larynx, middle ear, and sinonasal region.
- Usually asymptomatic; sometimes create surface roughness
- Appear as raised, yellow- or white-appearing spots or papules with a symmetric distribution measuring 1 to 3 mm in greatest dimension:
 - Uncommonly, coalesce to form large plaques
 - May appear cauliflower-like

Pathology

Gross

- Clinical appearance of Fordyce granules is often diagnostic; these lesions are usually not biopsied.

Histology

- Most often the histologic diagnosis of Fordyce granules is an incidental finding in biopsies of the oral mucosa for other reasons.
- Histologic appearance includes presence of typical sebaceous glands composed of cells with abundant foamy-appearing cytoplasm:
 - Sebaceous glands are present in one or more lobules and are found within the submucosa immediately beneath an intact squamous epithelium.
 - Intact squamous epithelium may be raised owing to the sebaceous gland proliferation.
- In contrast to cutaneous sebaceous glands, those of Fordyce granules are not associated with hair follicles.
- Adjacent stroma is unremarkable except for the possible presence of an inflammatory cell reaction.
- Immunohistochemistry:
 - EMA and cytokeratin positive

Differential Diagnosis

- Coalescence of sebaceous glands into a larger mass may engender the diagnosis of sebaceous gland hyperplasia or sebaceous adenoma:
 - Differentiation of heterotopia versus hyperplasia versus neoplasia is academic because the treatment would essentially be similar.
 - Some authorities advocate that in the setting of a clinically distinct lesion requiring a biopsy for diagnosis and composed of no fewer than 15 normal sebaceous lobules should be diagnosed as sebaceous gland hyperplasia.
- Salivary gland neoplasms with sebaceous cells

Treatment and Prognosis

- No treatment is required.
- Antibiotic therapy may be required for those lesions that become inflamed or infected.
- Very rarely a sebaceous adenoma may develop from these structures.
- Intraoral sebaceous carcinoma presumably originating from Fordyce granules is a rare occurrence (Fig. 5-11):
 - Associated with infiltrative growth
 - May identify presence of pagetoid spread of sebaceous cells within the surface epithelium

Other Oral Choristomas (Fig. 5-12)

- Other choristomas of the oral cavity include the following tissue types:
 - Glial (central nervous system), gastrointestinal, osseous, cartilaginous, or hair follicles
- Uncommon lesions
- More common in women than in men; occur over a wide age from newborns to the eighth decade
- Most common site of occurrence is the tongue
- Present as painless swellings in the oral cavity:
 - Duration of lesions ranges from months to years
 - Appear as nodular, firm mass with normal overlying mucosa
- Glial (central nervous system) heterotopia:
 - Lack connection to the central nervous system.
 - May be composed of astrocytes, oligodendrocytes, ependymal tissue, choroid plexus
 - Immunoreactive for GFAP and S100 protein
- Oral heterotopic gastrointestinal tissue or cyst:
 - Predilection for males; most cases seen by 2 years of age
 - Asymptomatic swelling in floor of mouth
 - Cyst lined by gastric (cardiac, fundic, or pyloric) or intestinal epithelium (e.g., colonic, pancreatic)
 - Stratified squamous or respiratory epithelium may be present.
 - Cyst wall may contain smooth muscle and/or gastric glands.
- For all choristomatous lesions, simple surgical excision is curative.

Ectopic Thyroid Tissue

Definition: Presence of thyroid tissue in abnormal locations.

- Most common in neck in association with the hyoid bone representing thyroglossal duct cyst; for detailed discussion see Section 8.
- Excluding and in comparison to thyroid tissue seen in association with thyroglossal duct cysts, the

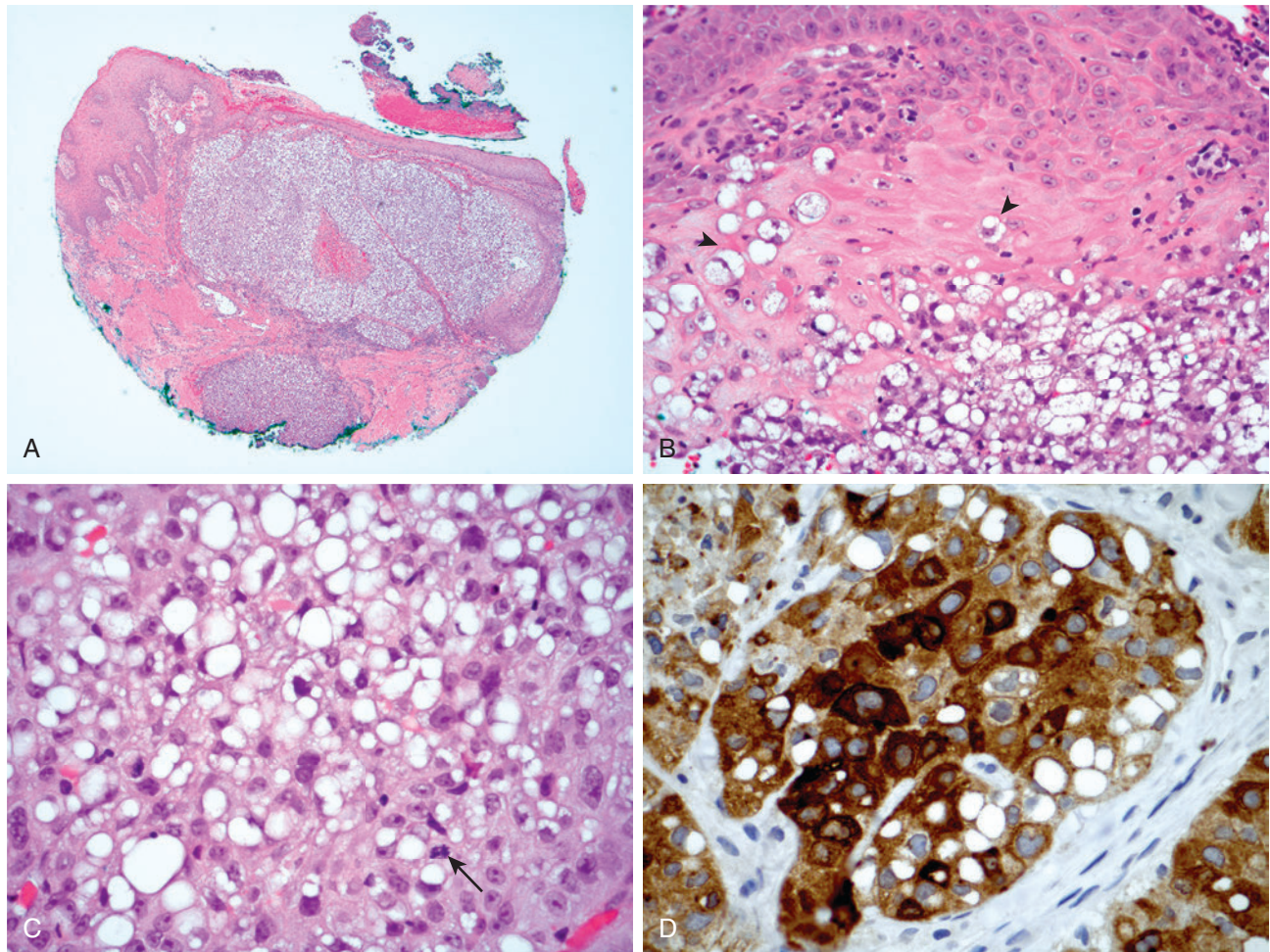


Fig. 5-11. Sebaceous carcinoma of the oral cavity.

Intraoral sebaceous carcinoma presumably arising from Fordyce granules. **A**, Lobulated neoplastic proliferation lying contiguous to the surface epithelium. **B**, Lesional cells infiltrate into surface epithelium (pagetoid spread; *arrowheads*). **C**, Lesional (sebaceous) cells characterized by irregular appearing nuclei pleomorphism and abundant vacuolated cytoplasm with distinct scalloping of the nuclei; scattered mitotic figures are seen (*arrow*). **D**, Lesional cells are immunoreactive for epithelial membrane antigen.

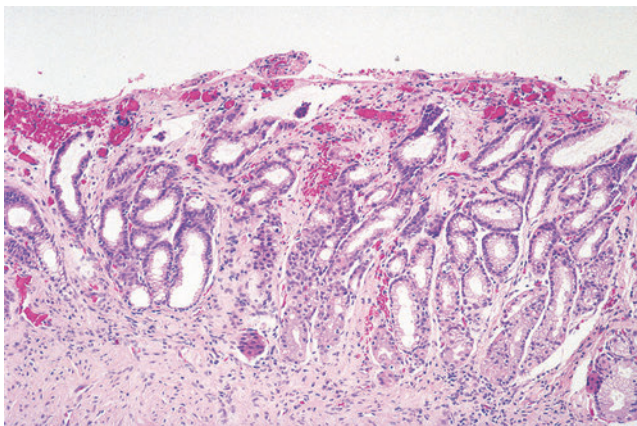


Fig. 5-12. Oral heterotopic gastrointestinal tissue.

Oral cavity cyst in which heterotopic gastrointestinal tissue was identified.

presence of ectopic thyroid tissue in other sites is rare and is seen almost exclusively in suprahyoid locations.

- Most common ectopic focus for thyroid tissue is the base of the tongue, where it is referred to as lingual thyroid; however, ectopic thyroid may be seen in any location from the tongue to the supra-sternal notch.

Lingual Thyroid

Definition: Developmental anomaly in which there is abnormal descent of the thyroid gland with localization to the base of tongue.

- For a more complete discussion, including illustrations, see Section 8, Thyroid Gland.

INFECTIOUS DISEASES OF THE ORAL CAVITY

- Infectious diseases of the oral cavity occur in immune-competent and immunocompromised individuals and include a variety of infectious agents, including:
 - Fungal
 - Viral
 - Bacterial and mycobacterial
 - Others

FUNGAL DISEASES

Oral Candidiasis (Fig. 5-13)

Definition: Infection with yeastlike fungal microorganisms *Candida albicans* with diverse clinical presentations and influenced by host immune status.

Synonyms: Moniliasis; candidosis



Fig. 5-13. Oral candidiasis.

A, Oral candidiasis (thrush) in an immunocompromised patient appearing as “cheesy” or creamy-appearing plaques coating the tongue. **B,** Periodic acid Schiff staining highlighting *Candida* spores and hyphae.

Clinical Features

- One of the more common fungal infection in humans and the most common oral fungal infection
- Clinical forms of candidiasis are varied and include:
 - Pseudomembranous candidiasis (also known as thrush):
 - Most common
 - Erythematous candidiasis
 - Chronic hyperplastic candidiasis (also referred to as candidal leukoplakia)
 - Mucocutaneous candidiasis
- Often occurs in setting of immunocompromised and/or debilitated patient:
 - This patient population makes up the largest percentage of patients with oral candidiasis.
- Oral candidiasis also occurs in immune-competent (healthy) patients.
- Staining (10% KOH) and culture (Sabouraud dextrose agar) are methods most commonly used for diagnosing primary candidiasis.

Pseudomembranous Candidiasis or Thrush

- Characterized by presence of white plaques that adhere to the mucosa and give appearance of cottage cheese
- Common sites of occurrence include the buccal mucosa, dorsal tongue, and palate.
- Patients may experience a burning sensation and/or have a foul taste in their mouths.
- Plaques may be removed with exposing an underlying erythematous-appearing mucosa.

Erythematous Candidiasis

- Includes varying clinical presentations
- Early or acute atrophic candidiasis typically follows a course of broad-spectrum antibiotics:
 - Includes diffuse loss of the filiform papillae of the dorsal tongue appearing as patchy, denuded foci; patients complain of a burning sensation.
- Chronic erythematous candidiasis includes:
 - Median rhomboid glossitis (also referred to as central papillary atrophy of the tongue), which was initially considered to be a developmental defect of the tongue
 - Lesions typically asymptomatic, resulting in filiform papillae of the posterior tongue appearing as well-demarcated, erythematous zones seen in the midline, posterior dorsal tongue
 - When these lesions are associated with candidiasis of other oral mucosal sites, it is termed chronic multifocal candidiasis.

- Other sites of involvement may include:
 - Junction of the hard and soft palate
 - Angles of the mouth (angular cheilitis or perlèche)

Chronic Hyperplastic Candidiasis

- Represents mucosal white patch that cannot be rubbed off and is the result of candida infection
- Also referred to as candidal leukoplakia (see later section under inflammatory lesions epithelial lesions):
 - Controversial entity in that a cause and effect (candidal infection producing a leukoplakic lesion) is not universally accepted, and some authorities feel that this process may represent candidal infestation occurring as a secondary process on a preexisting leukoplakic lesion
 - Clinical appearance is that of nondescript leukoplakia typically involving the (anterior) buccal mucosa.
 - Some lesions have admixed red-white lesion referred to as erythroleukoplakia; the latter, in contrast to a purely leukoplakic lesion, is more apt to harbor an underlying significant dysplasia and/or carcinoma.

Mucocutaneous Candidiasis

- Rare acquired or inherited (autosomal recessive) immunologic disorder in which the extent of candida infection is predicated on the extent of the immunologic disorder
- Immunologic dysfunction generally manifests in the first few years of life.
- Intraoral candidal infection manifests as thick, white plaques that do not rub off.

Pathology

Histology

- There are several members of the *Candida* genus, but most common cause of upper aerodigestive tract mucosal candidiasis is *C. albicans*:
 - Dimorphic fungus that includes a yeast form and a hyphal form:
 - Hyphal form is considered responsible for tissue invasion and a diagnosis of candidiasis is based on finding hyphae or pseudohyphae.
 - Hyphae vary in length, are branched, and may be apparent by hematoxylin and eosin staining.
- Histochemistry:
 - Microorganisms may be difficult to identify by conventional staining and in suspected cases special stains, including periodic acid Schiff or Gomori methenamine silver, may be required for definitive identification.
- Microorganisms are typically found in the thickened parakeratin layer and in the superficial spinous layer.

- In conjunction with the fungal infestation there usually is an associated neutrophilic infiltrate that may or may not coalesce to form microabscesses; the neutrophilic cell infiltrate is not a pathognomonic finding, but its presence in the superficial areas should prompt consideration for an infectious cause, specifically fungal infection.
- In addition to the fungal infection and acute inflammatory cell reaction additional findings may include:
 - Hyperkeratosis, parakeratosis, orthokeratosis, irregular epithelial hyperplasia with elongated rete ridges, and a submucosal nonspecific chronic inflammatory cell reaction
 - Reactive basal zone epithelial atypia may be present.
- Less commonly, fungi are present within deeper epithelial layers; the latter is more common in patients with a significant immunocompromised condition.

Differential Diagnosis

- In general, a diagnosis of oral mucosal candidiasis is established on clinical grounds:
 - Biopsy of a given lesion may be required for those lesions that are unresponsive to antifungal therapy or in the setting of chronic hyperplastic candidiasis.
 - Differential diagnosis in the setting of chronic hyperplastic candidiasis may include exclusion of a significant epithelial dysplasia (i.e., moderate or severe dysplasia) and/or squamous cell carcinoma.

Treatment

- Antifungal therapy is preferred treatment:
 - Mainstay for treatment is use of polyenes, such as nystatin and amphotericin B, and azoles including miconazole, fluconazole, and itraconazole:
 - May be used prophylactically during cancer therapy
- Oropharyngeal candidiasis remains a problem in HIV-infected population despite the availability of antiretroviral therapy (ART).
- Topical therapies may provide effective management in noncompromised hosts.

Other Fungi

- Other fungal infections include histoplasmosis, cryptococcosis, mucormycosis, blastomycosis, and aspergillosis.
- More often these fungi infect nonoral mucosal sites or the skin.
- Mucosal infestation may be associated with (florid) pseudoepitheliomatous hyperplasia of the surface epithelium.
- See Section 1, Sinonasal Tract, for a more complete discussion.

VIRAL DISEASES OF THE ORAL CAVITY

- Numerous viral diseases may potentially infect sites in the oral cavity, including:
 - Herpesvirus family characterized by:
 - Double-stranded DNA core surrounded by capsid proteins and ensheathed in an envelope
 - Herpesvirus pathogens include:
 - Herpes simplex viruses (HSV)
 - Varicella-zoster virus (VZV)
 - Cytomegalovirus (CMV)
 - Epstein-Barr virus (EBV)
 - Kaposi sarcoma-associated herpesvirus (KSHV)
 - Human papillomavirus
- Viral infection of the mucosa of the upper aerodigestive tract often occurs in setting of immunocompromised and/or debilitated patient (e.g., organ recipient, immunosuppressive oncologic therapy in cancer patient):
 - Makes up the largest percentage of patients with oral viral diseases
 - Coinfections may occur, including:
 - HSV and CMV
 - EBV and CMV
 - In the above settings *Candida* infestation may also be identified.

Herpes Simplex Virus (HSV)

(Figs. 5-14 and 5-15)

- DNA virus that is trophic to epithelium (epitheliotropic) and nerve ganglia
- Two distinct subtypes of HSV are identified:
 - HSV type 1, referred to as the “oral” type
 - HSV type 2, referred to as the “genital” type
 - Virus type is not necessarily a reliable indicator of anatomic site affected, especially with changing sexual habits.
- Owing to its tendency to infect cells of ectodermal origin (skin or mucous membranes) HSV is a frequent cause of mucocutaneous disease.
- Primary herpetic gingivostomatitis:
 - Acute onset of painful coalescent ulcers on any mucosal surface
 - Frequent on labial mucosa, tongue, and gingiva
 - May be associated with viral prodrome, malaise, and fever
- In healthy patients recrudescence infection includes herpes labialis (fever blisters or cold sores)
- In immune-compromised patients, recrudescence infection may include ulcers anywhere on oral mucosa and appear aphthous-like.

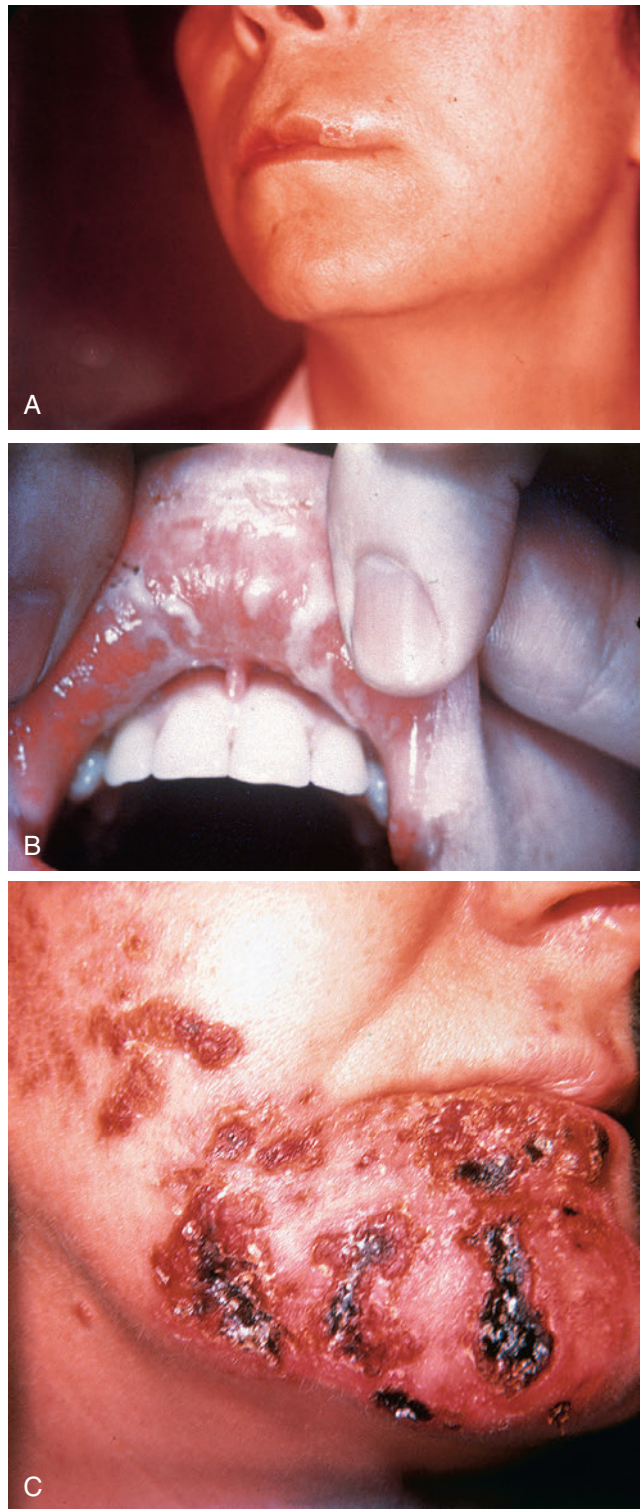


Fig. 5-14. Herpesvirus infection.

Mucocutaneous involvement by herpes simplex virus includes (A) external lip; (B) labial mucous membrane (herpetic stomatitis); (C) herpes zoster infection or dermatomal zoster (shingles).

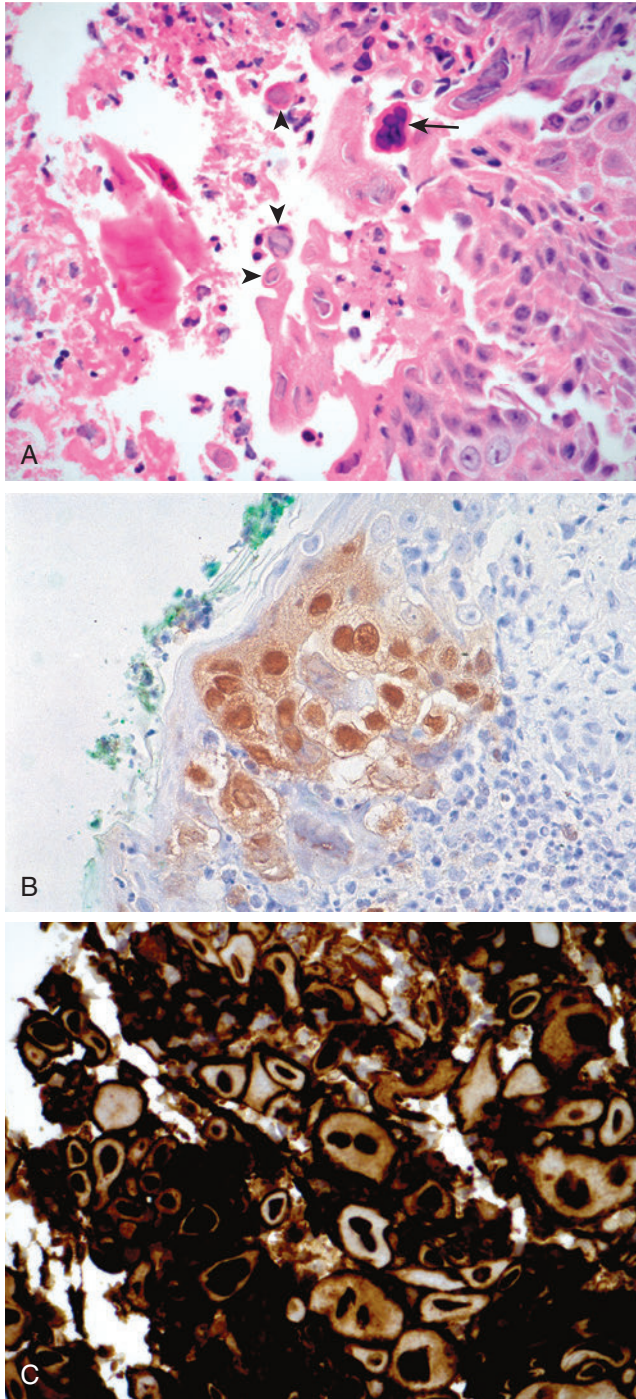


Fig. 5-15. Herpes simplex virus infection.

A, Histologic findings in herpes simplex virus (HSV) include the presence of intranuclear eosinophilic inclusions (Cowdry cells; *arrowheads*) within degenerating (squamous) epithelial cells imparting a ground glass appearance and multinucleated giant cell (*arrow*) characterized by presence of syncytial cells with intranuclear inclusions and tendency of nuclei to mold to one another. **B**, HSV immunoreactivity (nuclear) and in situ hybridization (nuclear) staining confirm the diagnosis.

Pathology

Gross

- Single or multiple, oval, tan-white, ulcerated lesions with a hyperemic rim with or without an associated exudate

Histology

- Ulceration with associated acute and chronic inflammation:
 - Intraepithelial vesicle formation marked by acantholysis and balloon degeneration of epithelial cells
 - Intranuclear eosinophilic inclusions (Cowdry cells) may be identified within the degenerating epithelial cells, imparting ground glass appearance
 - Multinucleated giant cells may be numerous, identified along edge of the ulcer, and characterized by:
 - Syncytial cells with intranuclear inclusions
 - Tendency of nuclei to mold to one another
- Special stains:
 - Immunoreactivity for HSV-1 and/or HSV-2 (nuclear staining)
 - In situ hybridization positive in infected cells (nuclear staining)

Differential Diagnosis

- Herpes zoster infection:
 - Part of varicella zoster virus, the agent for chickenpox and herpes zoster infections
 - May occur as varicella (chickenpox) or as dermatomal zoster (shingles):
 - Zoster may represent an early marker for the immunosuppression associated with HIV infection but is not specific for HIV infection.
 - Can localize to any dermatome, is neurotropic, and can cause unremitting pain
 - Infection may appear as vesicular lesions that bleed easily and may be covered with a black crust or as shallow tonsillar ulcers covered with a gray exudates; histologic findings may overlap with those of HSV, so immunostains and in situ hybridization are required for accurate diagnosis.
 - Head and neck manifestations include involvement of the eighth nerve or geniculate ganglion (Ramsay Hunt syndrome), producing severe ear pain, hearing loss, vertigo, and facial nerve paralysis.
 - Intranuclear inclusions indistinguishable from those seen in herpes simplex are identified.
- Cytomegalovirus

Treatment

- Antiviral chemotherapy including acyclovir, ganciclovir, and foscarnet

Cytomegalovirus (CMV)

(Fig. 5-16)

- In general, CMV infection involving the head and neck is not common, when it occurs in the head and neck usually occurs in immunocompromised and/or debilitated patient or organ transplant recipients:
 - Most common opportunistic pathogen recognized at autopsy in AIDS patients
- Appears as an ulcerative mucocutaneous lesion

Pathology

Gross

- Single or multiple, oval, tan-white, ulcerated lesions with a hyperemic rim with or without an associated exudate

Histology

- Mucosal ulceration, necrosis, and cytomegaly, the latter including:
 - Epithelial and/or mesenchymal (e.g., endothelial) cells with enlarged nuclei and prominent red nucleoli (“owl-eye”) and dark pink intracytoplasmic granules
- Special stains:
 - Immunoreactivity for CMV (nuclear and/or cytoplasmic)

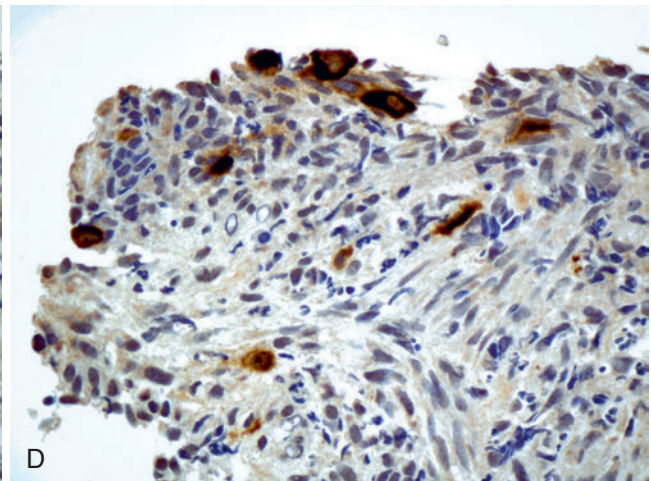
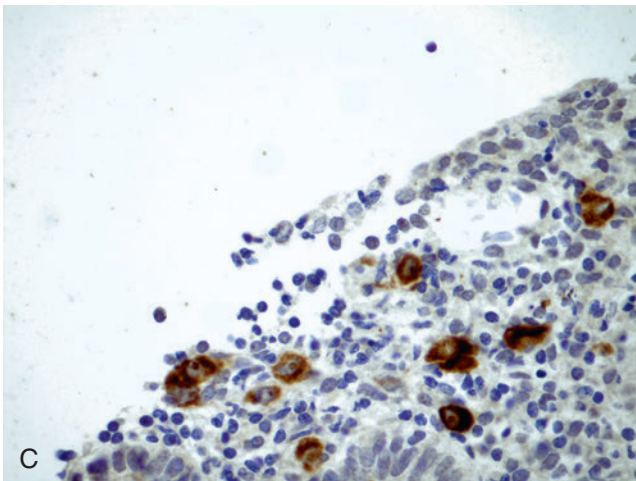
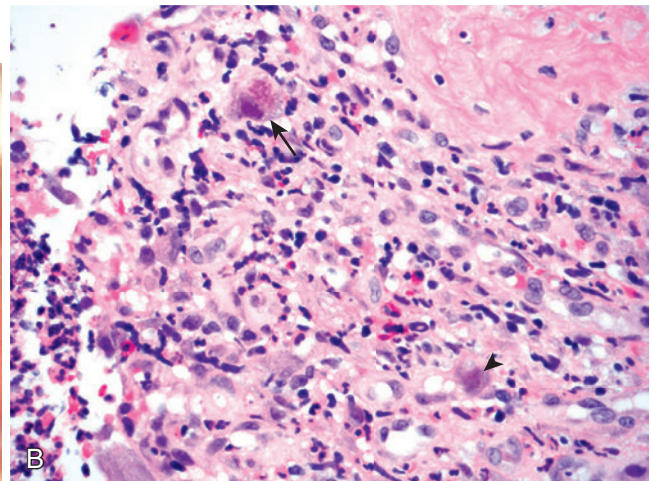


Fig. 5-16. Oral mucosal cytomegalovirus infection.

A, Cytomegalovirus (CMV) lesions on palate characterized by multiple, discrete, oval mucosal lesions. **B**, Histologic findings include cytomegaly with enlarged nuclei and prominent red nucleoli (*arrowhead*) and dark pink intracytoplasmic granules (*arrow*). **C**, CMV immunoreactivity and (**D**) in situ hybridization staining (nuclear and/or cytoplasmic) confirms the diagnosis. Infected cells may include epithelial and/or mesenchymal (e.g., endothelial) cells.

- In situ hybridization positive in infected cells (nuclear and/or cytoplasmic)

Treatment and Prognosis

- Antiviral therapy with ganciclovir and valganciclovir

Epstein-Barr Virus (EBV)

- Epstein-Barr virus (EBV) is an enveloped icosahedral herpesvirus with double-stranded linear DNA.
- EBV is strongly tropic for B-lymphocytes and also tropic for T-lymphocytes.
- Oral manifestations of EBV infection include oral hairy leukoplakia; see later in this section.
- For more complete discussion on EBV-related diseases, see Section 3, Pharynx.

Kaposi Sarcoma–Associated Herpesvirus (KSHV)

- Large, enveloped, double-stranded DNA virus
- Represents eighth human herpesvirus, hence the designation as human herpesvirus-8 (HHV-8):
 - HHV-8 is presumed causative agent of Kaposi sarcoma (KS)
- HHV-8 infects endothelial cells as well as peripheral blood monocytes and B lymphocytes in patients with KS.
- Latency-associated nuclear antigen (LANA-1) is KSHV latent protein:
 - LANA expressed during latent HHV-8 infection:
 - Expression (nuclear staining) by immunohistochemical staining found in all cases of KS
 - Expression not reported in non-KS neoplasms except for primary effusion lymphoma and Castleman disease
- For more complete discussion of Kaposi sarcoma and HHV-8, see later in this section.

Human Papillomavirus (HPV)

- HPV represents a large group of small, double-stranded circular DNA viruses.
- HPV is strongly epitheliotropic.
- HPV is a sexually transmitted disease.
- Non-neoplastic oral diseases associated with HPV include (but are not limited to):
 - Verrucae (verruca vulgaris [wart], condyloma acuminatum)

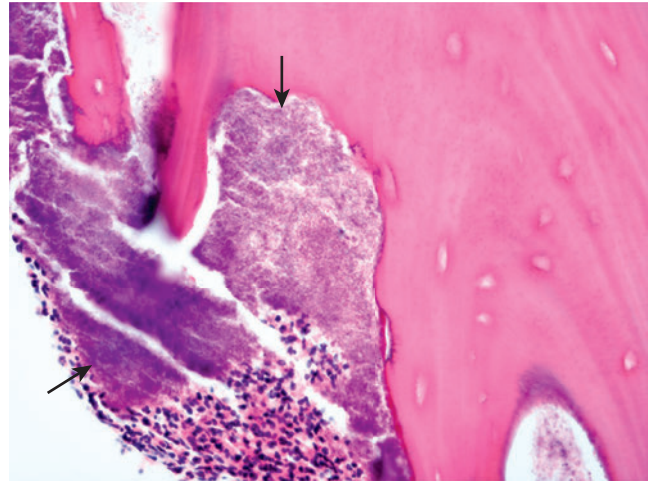


Fig. 5-17. Actinomycotic infestation of bone.

Actinomycotic infestation of the mandible in a patient with a history of squamous cell carcinoma and postoperative radiotherapy. The microorganisms appear light blue (arrow) with associated neutrophilic infiltrate involving necrotic bone.

- Heck disease (also known as focal epithelial hyperplasia); see later in this section
- HPV is also associated with oral epithelial neoplasms, including squamous papilloma.
- For a more complete discussion see Section 3, Pharynx, and Section 4, Neck.

BACTERIAL DISEASES

Bacteria and Spirochetes

- Oral bacterial diseases may include gonorrhea and syphilis:
 - May occur in immunocompromised or in immune-competent (healthy) individuals
- For detailed discussion see Section 3, Pharynx.
- Actinomycotic colonies may infect bone, especially secondary to invasive squamous cell carcinoma (Fig. 5-17).
 - For more complete discussion of actinomycosis see Section 4, Neck.

Mycobacterial Infections

- See Section 4, Neck, for detailed discussion including illustrations.

REACTIVE, INFLAMMATORY, AND TUMOR-LIKE LESIONS OF THE ORAL CAVITY

ORAL HPV-ASSOCIATED EPITHELIAL LESIONS

- HPV is epitheliotropic, infecting stratified squamous cutaneous and mucosal epithelial cells.
- Benign HPV-associated oral epithelial lesions include:
 - Oral verruca vulgaris (common wart)
 - Oral condyloma acuminatum
 - Focal epithelial hyperplasia (Heck disease)
 - Oral squamous papilloma
- May share similar clinical presentations and histologic features

Verruca Vulgaris (VV) of the Oral Mucosa (Fig. 5-18)

Definition: Benign squamous epithelial proliferation related to human papillomavirus (HPV).

Synonym: Wart

Clinical

- More common in men than in women; occurs over a wide age range but most common in the third and fourth decades of life:
 - Can also be seen in children

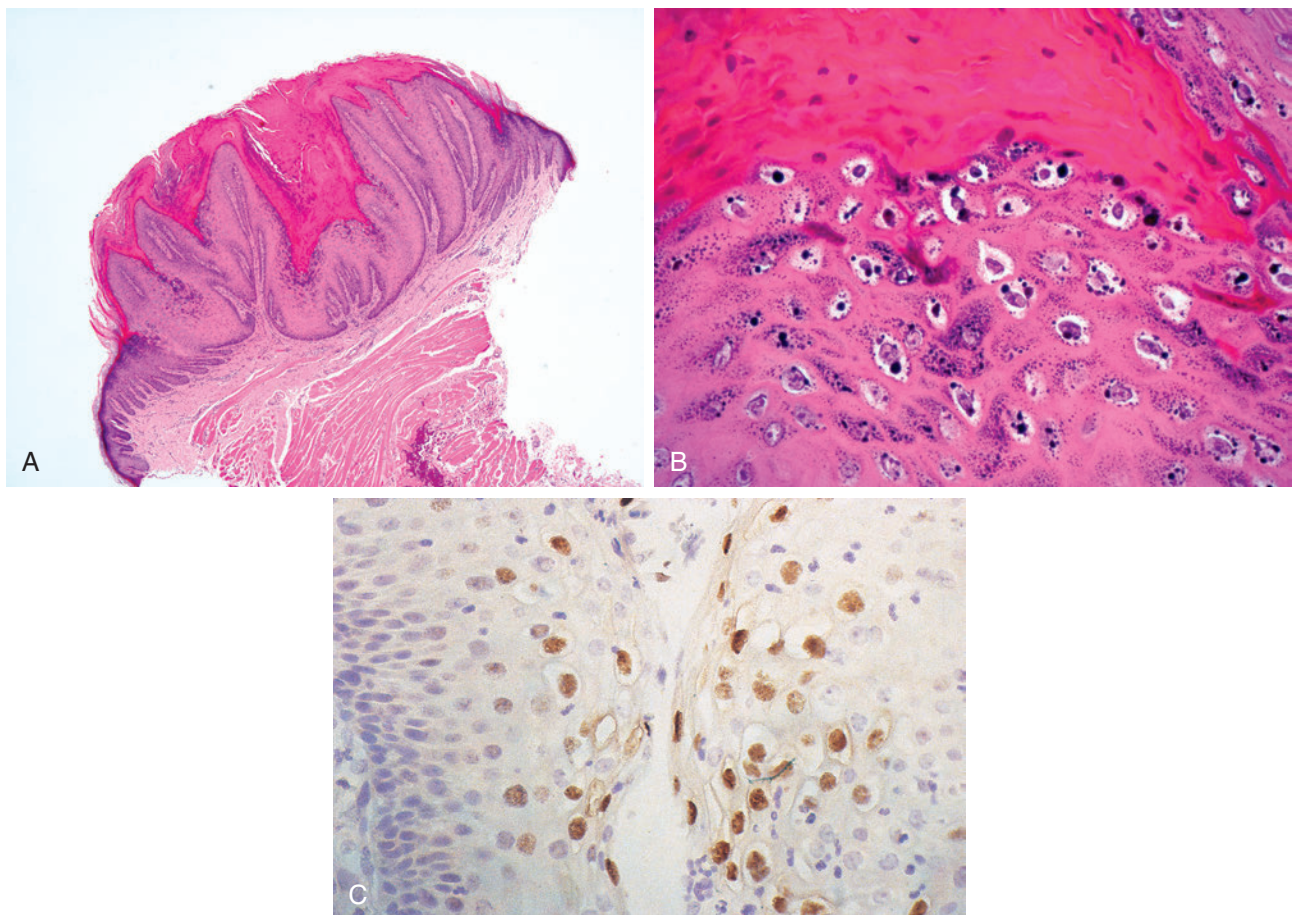


Fig. 5-18. Oral verruca vulgaris.

A, At low magnification characterized by an exophytic papillomatous epithelial proliferation with prominent hyperkeratosis, including thickened external orthokeratosis, acanthosis, and elongated rete ridges; characteristically rete ridges along the periphery show angulation toward the center of the lesion. **B**, Prominent granular cells and koilocytes are present in the more superficial aspect of the proliferation. **C**, HPV 6/11 immunoreactivity.

- Most common sites of occurrence include the lips, palate (hard and soft), and tongue, but any oral mucosal site can be affected.
- Presents as a circumscribed, exophytic white lesion with firm consistency and a papillary appearance protruding from mucosal surface
- Most often a single lesion but multiple lesions may occur
- Caused by HPV types 2 and 4 and less often by types 6, 11, and 16:
 - Route of infection is thought to be by autoinoculation, possibly from the hands from a cutaneous lesion

Pathology

Gross

- Firm, white, sessile, exophytic growth with a papillomatous appearance

Histology

- Histology of oral mucosal VV is the same as the more common cutaneous VV:
 - Characterized by a exophytic papillomatous epithelial proliferation with prominent hyperkeratosis, including thickened external orthokeratosis, acanthosis, and elongated rete ridges:
 - Characteristically rete ridges along the periphery showing angulation toward the center of the lesion
 - Base of the lesion can be sessile or pedunculated.
- Epithelium is cytologically bland, has a prominent granular layer, and koilocytes seen in the majority of cases localized to more superficial aspects:
 - Koilocytes characterized by presence of hyperchromatic, pyknotic (“raisinoid”)-appearing nuclei surrounded by clear cytoplasm
- Mixed chronic inflammatory cell infiltrate may or may not be present in the subjacent stroma.
- No evidence of epithelial dysplasia
- Special studies:
 - Although unnecessary for the diagnosis, presence of HPV can be detected by immunohistochemical, electron microscopic, and molecular diagnostic (in situ hybridization and polymerase chain reaction) studies.

Differential Diagnosis

- Oral squamous papilloma:
 - Also may be associated with HPV
 - From a histologic standpoint, in contrast to verrucae, papillomas typically lack surface keratinization, a prominent granular cell layer, koilocytes, and angulation of the rete ridges at the periphery toward the center of the lesion.
- Condyloma acuminatum

Treatment and Prognosis

- Removal of the lesion is the preferred treatment and can be performed by surgery, cryosurgery, or electrosurgery.
- Recurrences are rare.
- Spontaneous regression/disappearance within 1 to 2 years may occur, especially in children.

Condyloma Acuminatum

Definition: Sexually transmitted, benign papillomatous epithelial proliferation due to HPV.

- Derived from the Greek words *kondylos* (knob or knuckle) and *acumen* (point)

Synonyms: Venereal wart; venereal condyloma

Clinical

- Because condyloma acuminatum is a sexually transmitted disease, it is more apt to develop in areas of sexual contact such as the anogenital region.

Oral Mucosal Condyloma Acuminatum (Fig. 5-19)

- No gender predilection and can be seen in all ages but tends to be most common in teenagers and young adults
- Most common oral mucosal sites of occurrence include the tongue (dorsum), lips (upper and lower), lingual frenum, and soft palate/uvula
- Often asymptomatic
- Solitary (condyloma acuminatum) or multiple (condyloma acuminata) sessile to papillary mucosal-based lesions
- Immunocompromised individuals (e.g., HIV-infected, organ transplant recipients) at increased risk for oral condylomas
- Associated with HPV types 6 and 11 in the majority of oral lesions; HPV types 16 and 18 are present in a minority of cases:
 - Condyloma is very contagious.
 - Primary sexual transmission after direct contact is the principal mode of transmission.
 - Less often, transmission may occur via hematogenous spread, autoinoculation from anogenital lesions, or perinatal transmission from mother to infant.

Pathology

Gross

- Solitary or multiple, broad-based sessile mass with a papillary, cauliflower-like, mulberry growth, reddish-pink appearance
- Tend to be larger than papillomas, usually measuring 1.0 to 1.5 cm but may reach up to 3 cm in greatest dimension

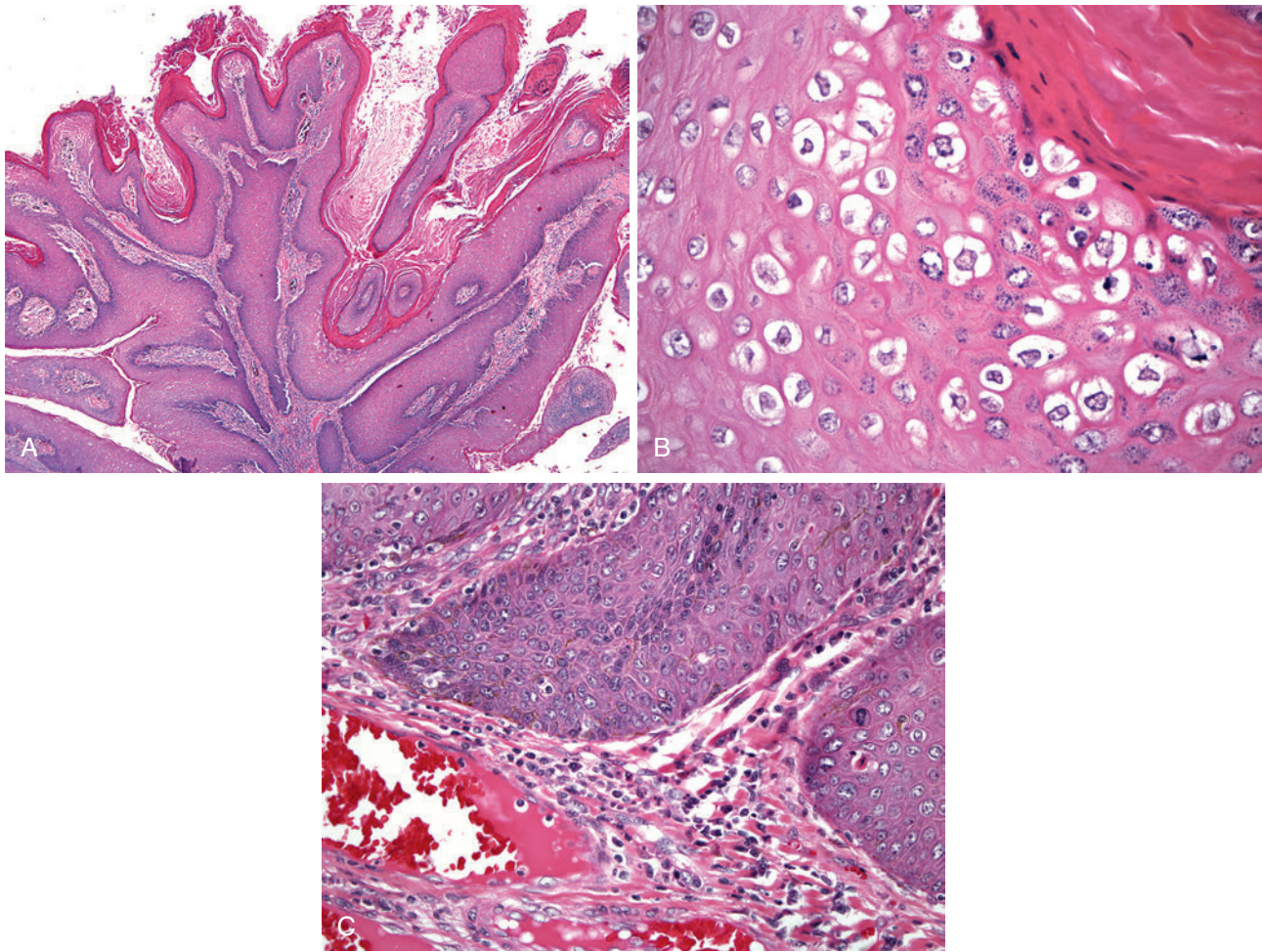


Fig. 5-19. Oral condyloma acuminatum.

A, Broad papillary epithelial fronds with prominent acanthosis. **B**, Koilocytotic cells characterized by hyperchromatic, pyknotic nuclei surrounded by clear zone. **C**, Rounded rete ridges, scattered mitotic figures, and dilated capillaries with mixed chronic inflammatory cell reaction in the submucosa.

Histology

- Broad papillary epithelial fronds with prominent acanthosis, parakeratin crypt formation, and koilocytosis (hyperchromatic, pyknotic nuclei surrounded by clear zone)
- Rete ridges appear bulbous in their depth.
- Numerous mitotic figures can be seen.
- Subjacent stroma shows dilated capillaries and variable mixed chronic inflammatory cell reaction, including mature lymphocytes and plasma cells.
- May involve excretory ducts of minor salivary glands
- Special studies
 - Although unnecessary for the diagnosis, the presence of HPV can be detected by immunohistochemical, electron microscopic, and molecular diagnostic (in situ hybridization and polymerase chain reaction) studies.

Differential Diagnosis

- Squamous papilloma
 - Presence of marked acanthosis, parakeratin crypt formation, numerous koilocytes, and sessile appearance of condyloma acuminatum assists in differentiating it from squamous papilloma.
- Verruca vulgaris
 - Condyloma acuminatum and verruca vulgaris have overlapping histologic features; however, differences include:
 - Presence of marked hyperorthokeratinization and angulated rete ridges along the periphery toward the center of the lesion in verruca vulgaris
 - Condyloma acuminata show more extensive acanthosis as well as the more consistent presence of stromal dilated capillaries and

superficial mixed chronic inflammatory cell infiltrate.

Treatment and Prognosis

- Removal of the lesion is the preferred treatment and can be performed by surgery, cryosurgery, or electrocautery.
- Recurrences are common.
- Spontaneous regression/disappearance may occur.
- Unlike uterine cervical HPV-associated lesions, in which HPV association is considered precancerous, the same precancerous nature is not felt to be true relative to oral mucosal lesions.

Focal Epithelial Hyperplasia (FEH)

(Fig. 5-20)

Definition: Benign oral mucosal epithelial proliferation caused by HPV.

Synonym: Heck disease

Clinical

- Uncommon lesion
- No gender predilection; initially identified in children but affects all age groups
- Propensity to affect specific ethnic groups, including:
 - Native American Indians, Central and South American Indians, Eskimos
- Limited to the oral cavity and most commonly found:
 - Lower and upper lip, buccal mucosa, tongue
- Clinically, typically characterized by multiple, painless, soft, sessile papules, plaques, or nodules, which may coalesce to give rise to larger lesions
- Cause:
 - HPV types 13 and 32 detected in majority of lesions
 - Other subtypes may be identified, including HPV-6 and HPV-11
 - Rarely associated with high-risk HPV (HPV-16)
- Considered to potentially represent an oral manifestation of AIDS

Pathology

Gross

- Soft, tan-pink appearing lesions measuring from 0.1 to 1 cm in greatest dimension

Histology

- Irregular epithelial hyperplasia with hyperkeratosis, parakeratosis, and acanthosis
- Rete ridges are widened and may be fused or appear confluent:
 - Elongation of the rete ridges not usually seen
- Thickened epithelial proliferation extends in an exophytic rather than endophytic manner, resulting in

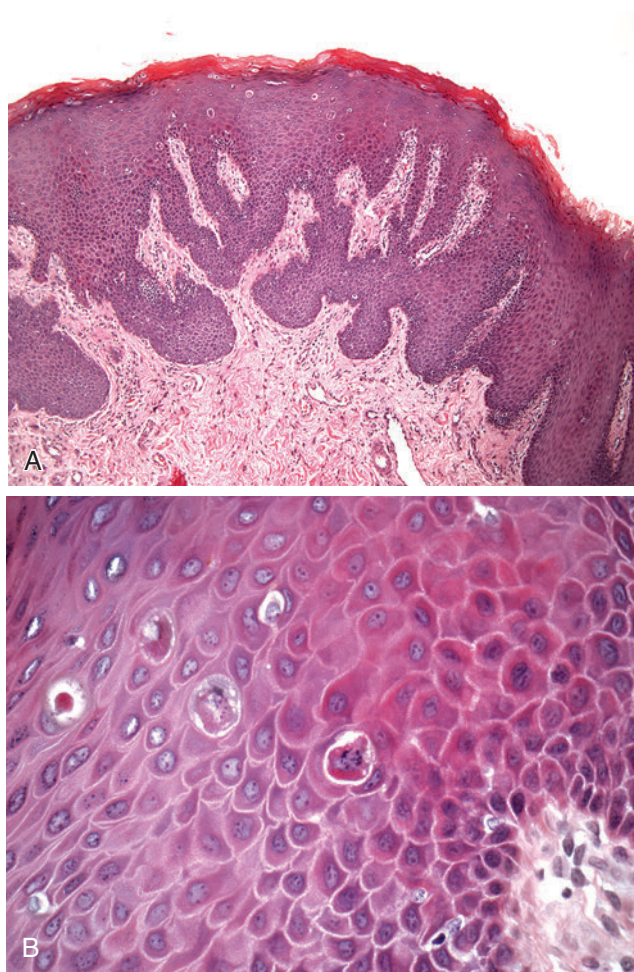


Fig. 5-20. Focal epithelial hyperplasia (Heck disease).

A, Irregular epithelial hyperplasia with hyperkeratosis, parakeratosis, and acanthosis; the lesion has an endophytic growth with widened and fused rete ridges. **B**, A characteristic feature is the presence of mitosoid cells characterized by cells with collapsed nuclei that take on the appearance of a mitotic figure.

rete ridges in the lesion at the same level or depth as adjacent nonlesional epithelial rete ridges.

- Koilocytes can be seen in cells of superficial keratinocytes.
- Mitosoid cells or bodies characterized by the presence of cells with collapsed nuclei taking on the appearance of a mitotic figure can be seen.
- Immunohistochemistry:
 - Identification of HPV-13 and HPV-32
- Electron microscopy:
 - Virus-like particles can be found by ultrastructural analysis in the nuclei and cytoplasm of cells within spinous layer.

- Cytogenetics and molecular genetics:
 - Presence of HPV-13 and HPV-32 identified by in situ hybridization

Differential Diagnosis

- Squamous papilloma
- Verruca vulgaris
- Condyloma acuminatum
- Pseudoepitheliomatous hyperplasia
- Proliferative verrucoid leukoplakia

NOTE: The absence of prominent surface projections, absence of endophytic growth, and presence of mitosoid cells assist in differentiating FEH from these other lesions.

Treatment and Prognosis

- Because these lesions tend to undergo spontaneous regression usually in months (but may take up to a year or more), there is no specific treatment required.
- Some lesions may persist for years.
- Several treatment modalities such as surgical excision, laser ablation, cryotherapy, electrocauterization, topical, intralesional, systemic interferon, and systemic retinoic acid have been used with inconsistent results and many side effects.
- Imiquimod cream has been used with some success for vermilion lesions.
- Transformation to carcinoma does not occur.

ORAL EBV-ASSOCIATED EPITHELIAL LESIONS

Oral Hairy Leukoplakia (OHL)

(Figs. 5-21 and 5-22)

Definition: EBV-induced verruciform hyperkeratotic lesion of the lateral tongue in HIV-infected patients.

Clinical Features

- Affects HIV-infected men more often than HIV-infected women
- Most HIV-infected individuals do not have AIDS at time of diagnosis of OHL but may develop AIDS later in a high percentage of cases:
 - Low CD4 counts
- May occur in non-HIV-positive but immunocompromised patients, including:
 - Organ transplant recipients on immunosuppressive therapy
 - Cancer patients on immunosuppressive oncologic therapies
 - Patients on high-dose corticosteroid treatment
 - Reported as early indicator of EBV-associated posttransplant proliferative disorder
 - Rarely may occur as presenting sign of acute leukemia



Fig. 5-21. Oral hairy leukoplakia.

Oral hairy leukoplakia characterized by the presence of demarcated white plaque to raised, white lesions with vertical corrugations on the lateral aspect of the tongue in a patient with HIV infection.

- Asymptomatic unless secondarily infected (e.g., by *Candida albicans*):
 - OHL often occurs in association with oral cavity *Candida* infestation.
- Lesions typically localize to the lateral tongue but occasionally may involve the ventral or dorsal tongue and infrequently involve other oral sites such as the buccal mucosa.
- White, painless, linear, or plaquelike lesion with white lines running perpendicular to long axis of tongue
- Pathogenesis:
 - Caused by EBV
 - Due to its association with AIDS, OHL was thought to be caused by a variety of microorganisms, including HIV, EBV, human papillomavirus (HPV), and herpes simplex virus (HSV)

Pathology

Gross

- Varies in appearance from a well-demarcated flat, white plaque to a well-demarcated raised, white lesion with vertical striations or corrugations

Histology

- Irregular epithelial hyperplasia characterized by filiform or hairlike keratin projections with associated parakeratosis and acanthosis
- Balloon degeneration of edema may be seen within the deep epithelial layer.
- Koilocytes and cells with Cowdry inclusions (ground glass appearance and intranuclear inclusions) may be seen in superficial epithelial cells lying beneath the parakeratotic layer.

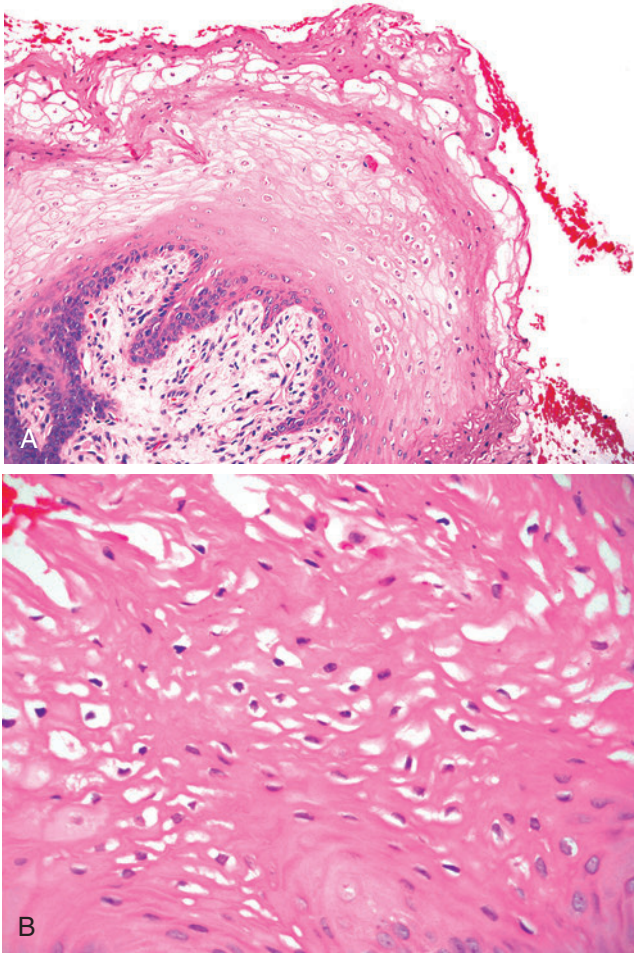


Fig. 5-22. Oral hairy leukoplakia.

A, Oral mucosa in (oral) hairy leukoplakia shows irregular epithelial hyperplasia, band of pale ballooned cells with filiform or hairlike keratin projections associated with parakeratosis and acanthosis. **B,** Cells with perinuclear halos (koilocytes) are identified.

- Absence of intraepithelial dysplasia
- A nonspecific mild chronic inflammatory cell reaction may be seen within the submucosa.
- Exfoliative cytologic examination may prove a useful, simple, cost-effective, and reliable method to diagnose OHL.
- Concomitant fungal (*C. albicans*) microorganisms (spores or hyphae) may be present within the superficial keratin layer:
 - Present in as many as 50% of cases
 - Can be seen by light microscopy and/or by histochemical staining (e.g., GMS, PAS)
- In situ hybridization for Epstein-Barr–encoded RNA (EBER):
 - Used for confirmation of EBV
 - Can be performed on exfoliative cytology material

Differential Diagnosis

- Other oral leukoplakic lesions
- Hairy tongue:
 - Benign condition characterized by hyperkeratosis and enlargement of filiform papillae (see later in this section under oral malignant mucosal melanoma for more detailed discussion)
 - In contrast to OHL, hairy tongue is a poorly demarcated lesion with diffuse involvement of the dorsum of the tongue.
- Verrucous carcinoma:
 - Verrucous carcinoma includes the presence of tiered keratosis and elongated bulbous-appearing rete ridges, features not seen in OHL.

Treatment and Prognosis

- Self-limiting disease and in most cases requires no treatment
- No malignant potential
- Symptomatic lesions usually caused by secondary *Candida* infection require appropriate treatment.
- In HIV/AIDS patients or patients on immunosuppressive therapy, adjustment of antiretroviral and immunosuppressive therapy, respectively, may resolve lesions.
- Owing to its association with HIV, morbidity and mortality may be associated with HIV-associated or AIDS-associated opportunistic infections:
 - Appropriate antibiotic or antiviral therapy may be required.

NONINFECTIOUS BENIGN EPITHELIAL LESIONS

Pseudoepitheliomatous Hyperplasia (PEH) (Fig. 5-23)

Definition: Exuberant reactive or reparative overgrowth of squamous epithelium displaying no cytologic evidence of malignancy that may be mistaken (clinically and histologically) for a squamous cell carcinoma.

Clinical

- Not a distinct clinicopathologic entity; rather it represents a morphologic entity:
 - Wide spectrum in demographics and the clinical presentation
 - May occur as an isolated process or more often is the morphologic process associated with or induced by other diseases or lesions, including:
 - Trauma, chronic denture irritation, tattoo (cutaneous lesions), infections (e.g., due to candida, leprosy, blastomycosis, histoplasmosis, paracoccidioidomycosis, others), and tumors:

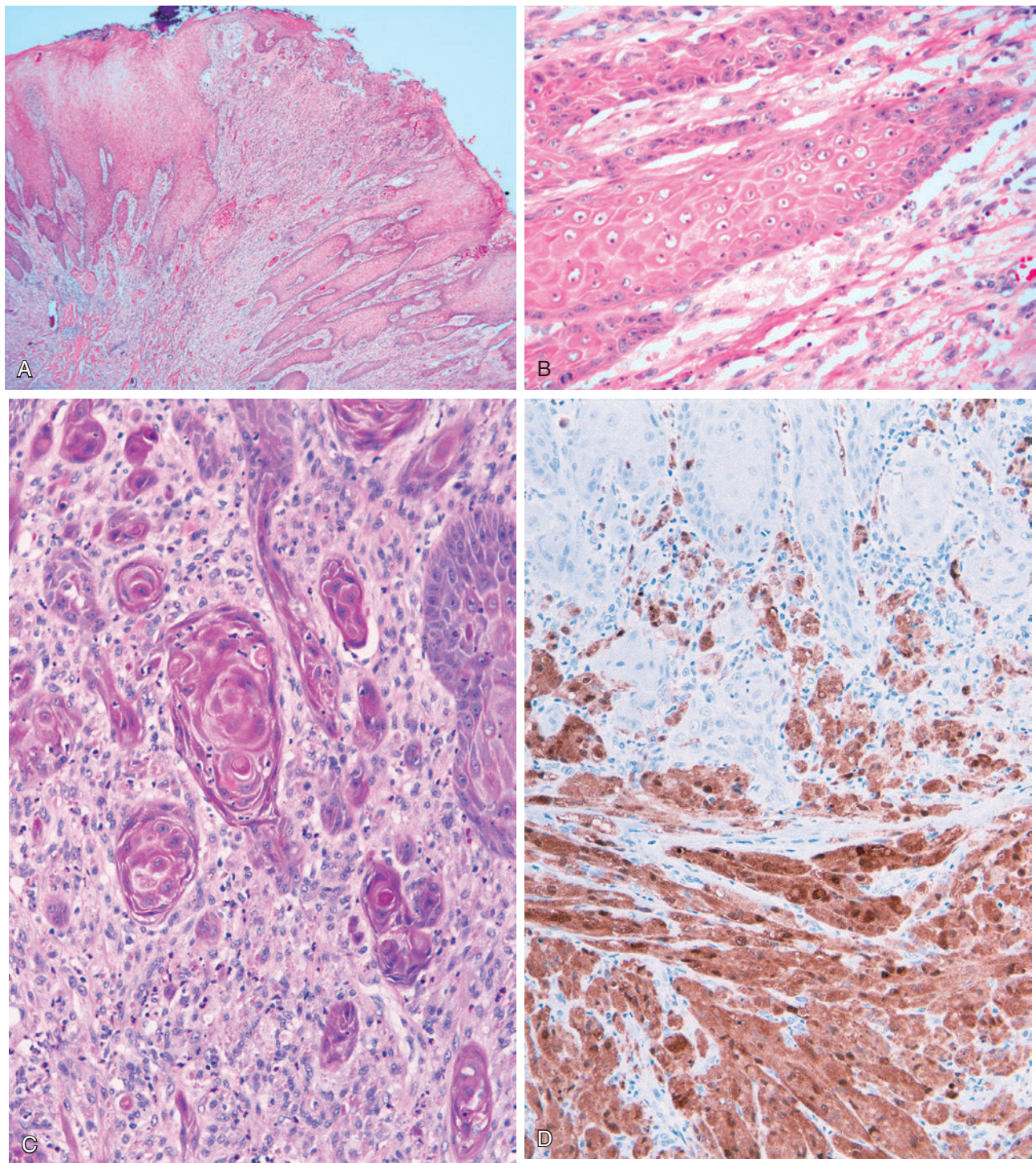


Fig. 5-23. Granular cell tumor with pseudoepitheliomatous hyperplasia.

Pseudoepitheliomatous hyperplasia (PEH) of the oral cavity mucosa secondary to granular cell tumor. **A**, Florid epithelial proliferation with hyperkeratosis, acanthosis, and elongation and downward extension of the rete ridges. **B**, Higher magnification shows rete ridges with rounded or smooth contours and bland cytomorphic features intermixed with the cells of the granular cell tumor. **C**, In other areas the rete ridges have an angulated and irregular appearance with dyskeratotic cells that would raise concern for invasive squamous cell carcinoma, but the granular cell proliferation is seen in and around, as well as deep to the epithelial proliferation. **D**, Diffuse and strong S100 protein immunoreactivity in the granular cell tumor. As long as the granular cells lie deep to the squamous epithelial proliferation without squamous cell nests lying deep to the granular cells, the epithelial proliferation should not be considered as being malignant. The exception to the prior statement would be if metastatic disease was present; then the epithelial proliferation even in conjunction with a granular cell tumor would be considered as carcinoma.

- Classically, PEH has been associated with an underlying granular cell tumor (see later in this section).

Pathology

- Characterized by a florid epithelial proliferation with or without associated hyperkeratosis
- Acanthosis with elongation and downward extension of the rete ridges
 - Rete ridges typically have a rounded or smooth-edged appearance but may be angulated and irregular in appearance.
- In general there is an absence of any significant intraepithelial dysplasia:
 - In association with a granular cell tumor, epithelial dysplasia even reaching more severe degrees may be present.
 - In addition, nests of squamous epithelium may take on a more angulated appearance and simulate an invasive growth pattern that approaches (or even reaches) the morphologic level of squamous cell carcinoma (see later in section).
- Histochemistry:
 - If an infectious cause is suspected, then special stains for microorganisms, in particular for fungi (e.g., Gomori methenamine silver, periodic acid Schiff, others), may be required for the diagnosis.
 - Fungal infestation includes presence of fungal forms (hyphae and/or spores) within the depth of epithelium.
 - Fungal forms limited to the surface keratin and/or superficial epithelium are considered colonization and not infestation.

Differential Diagnosis

- In the majority of cases differentiating PEH from a carcinoma is not problematic given the presence of a bland epithelial proliferation with rounded rete ridges and absence of dysplasia.
- As previously noted in association with granular cell tumor morphologic features virtually identical to squamous cell carcinoma may be present, creating difficulties in differentiating PEH from squamous cell carcinoma:
 - Features that assist in differentiating PEH from squamous cell carcinoma include:
 - In association with a granular cell tumor, nests of PEH should not extend below the depth of the granular cell tumor.
 - S100 protein staining may be required to determine the extent of the PEH (S100 protein negative) relative to the granular cell tumor (S100 protein positive)
 - If PEH does not extend below the deepest part of the granular cell tumor, then the squamous

proliferation should not be considered malignant.

- If the epithelial proliferation does extend below the deepest part of the granular cell tumor and/or there is definitive evidence (i.e., histologic confirmation) of metastatic squamous cell carcinoma (e.g., to cervical lymph node, other sites), then presuming there is no previous history or concurrent presence of another primary mucosal squamous cell carcinoma, a diagnosis of squamous cell carcinoma can be rendered in association with a granular cell tumor.
- More recently, distinctive gene expression profiles identified in squamous cell carcinoma and absent in PEH may offer ability to use DNA microarrays to differentiate these lesions.

Treatment and Prognosis

- There is no specific treatment for PEH:
 - If it is occurring in association with or induced by another disease, then therapy should be oriented to treating the other process, for example:
 - Antifungal therapy in presence of fungal infestation
 - Surgery for a granular cell tumor

Necrotizing Sialometaplasia (Fig. 5-24)

Definition: Benign, self-healing (reactive) inflammatory process of salivary gland tissue, which clinically and histologically mimics a malignant neoplasm.

- See Section 6, Salivary Glands, for a more complete discussion.
- Most commonly involves the minor salivary glands of the palate, but other intraoral sites as well as the minor salivary glands of virtually every site in the upper aerodigestive tract can be affected; major salivary gland involvement occurs as well.
- Most common presenting problem is that of a painless ulcerated lesion or a nodular swelling, which is usually unilateral but may be bilateral; in general, the lesions are asymptomatic but may be associated with pain, numbness, or a burning sensation.
- Palatal-based lesions occur spontaneously and are of unknown causes; the majority of cases involving extrapalatal minor salivary glands and major salivary glands are iatrogenically induced after operative procedures, trauma, or radiotherapy with a mean duration of 18 days from the insult to the development of the lesion.
- Pathogenesis for the iatrogenically induced lesions is primarily but not exclusively thought to be ischemic;

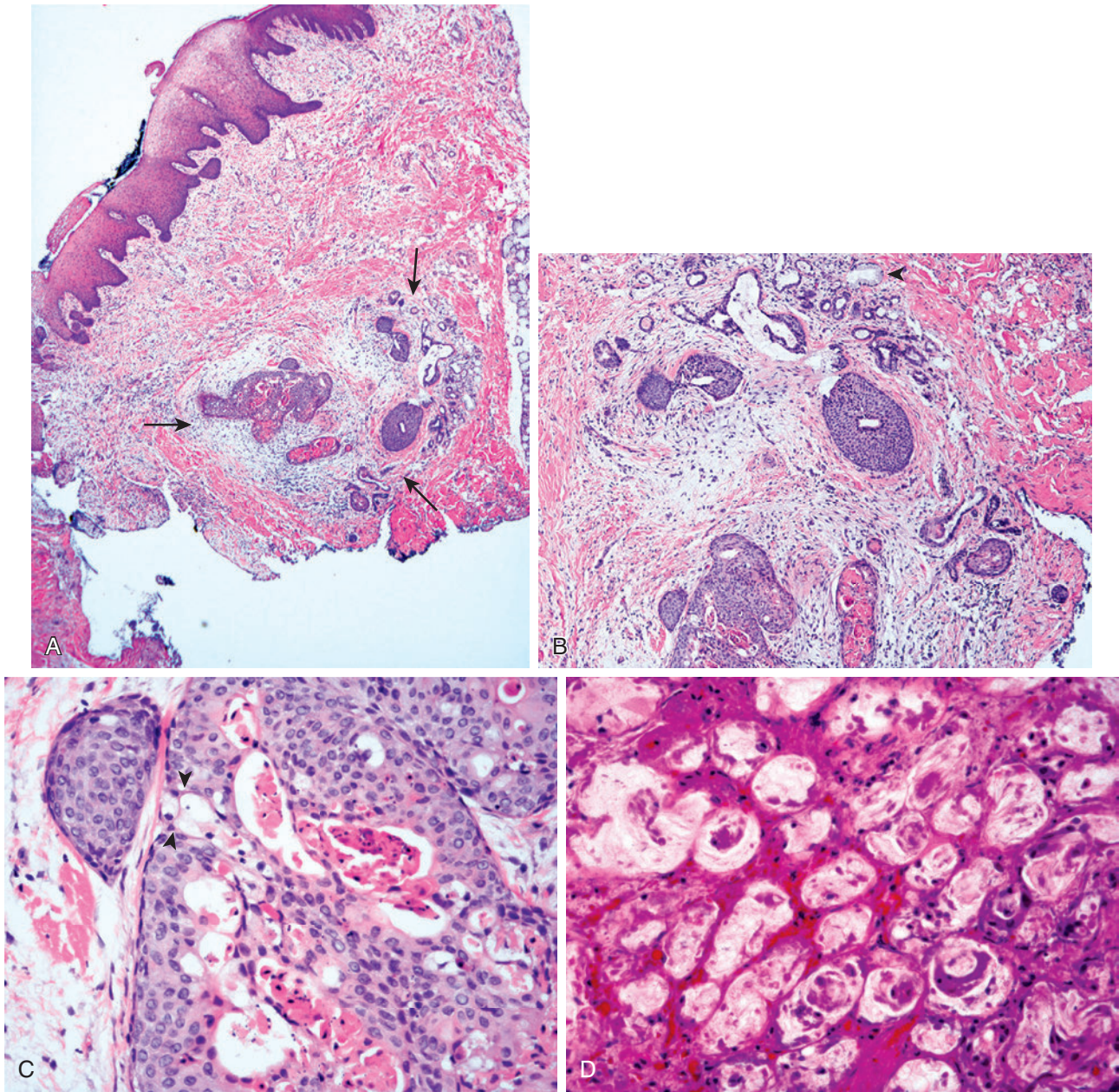


Fig. 5-24. Necrotizing sialometaplasia of the palate.

A, At low magnification the lobular architecture of the minor salivary glands within the submucosa is maintained (*arrows*). **B**, Metaplastic lobules vary slightly to moderately in size and shape, and have smooth contours surrounded by reactive stroma; the lobules in the lower portion of the image show prominent keratinization. **C**, Metaplastic lobule with associated keratinization and identification of residual mucous cells (*arrowheads*). **D**, Necrotic lobules consisting of acinus-sized pools of mucin may or may not be present in any given case.

a similar pathogenesis is implicated for the palate lesions; however, this remains unproven.

- Typical appearance is that of a deep, crater-like ulcerative lesion measuring from 1 to 3 cm; however, the lesion may appear as a submucosal nodular swelling that may slough, leaving a crater-like ulcer.

- Histologically, lobular necrosis of the salivary glands with preservation of the lobular architecture and squamous metaplasia of residual acinar and ductal elements are the histologic hallmarks:
 - Necrotic lobules consist of acinus-sized pools of mucin that may extend into adjacent tissue, eliciting a granulation tissue reaction with associated

acute and chronic inflammation (neutrophils and foamy histiocytes).

- Squamous metaplasia is bland in appearance and composed of squamous cells with uniform nuclei and abundant eosinophilic cytoplasm with occasional preservation of ductal lumina and/or scattered mucous cells.
- Lobular architecture is maintained and the metaplastic lobules vary slightly to moderately in size and shape and have smooth edges surrounded by granulation tissue and an intense mixed acute and chronic inflammatory reaction
- With regeneration, mitoses, individual cell necrosis, enlarged nuclei, and prominent nucleoli can be seen; occasionally, the metaplastic cells have a predominantly basaloid appearance with hyperchromatic nuclei.
- Associated findings may include:
 - Ulcerated mucosa
 - Pseudoepitheliomatous hyperplasia resulting when the metaplastic lobules present in excretory ducts and merges with surface epithelium may be so striking presenting a diagnostic nightmare in separation from an infiltrating squamous cell carcinoma.
- These lesions are self-limiting and heal by secondary intention; depending on the size of the lesion, the healing process in most cases occurs from 3 to 12 weeks; debridement and saline rinses may aid in the healing process.
- Recurrences do not usually occur.

MESENCHYMAL LESIONS

Irritation Fibroma (Fig. 5-25)

Definition: Reactive proliferation of submucosal fibrous tissue covered by benign epithelium.

Synonyms: Traumatic fibroma, focal fibrous hyperplasia, fibrous nodule, fibrous epulis, fibroepithelial polyp

Clinical

- Considered the most common soft tissue lesion of the oral cavity
- Female predilection; majority are found in adults between 20 and 59 years of age:
 - May be seen in children, but less commonly
- Most common location is the buccal mucosa adjacent to crowns of teeth (bite line) followed by the gingiva, lips, and tongue
- Presentation is usually that of slow-growing, non-tender gingival swelling:
 - Duration of the lesion varies considerably, but may range up to 17 months

- Usually solitary; rarely may be bilateral, symmetric lesions

- Periapical radiographs show no evidence of osseous pathology.
- Cause:
 - Major cause is mechanical irritation secondary to trauma/injury from dentures, lip or cheek biting, or sharp edges of teeth or fillings
 - Some lesions occur in the absence of a history of trauma or injury, raising the possibility that these lesions are true neoplasms.

Epulis Fissuratum

- Use of the term *epulis* refers to any mass on the gingiva.
- Unique variant of denture-related fibroma typically occurring in the mucosal vestibule or sulcus adjacent to the alveolar ridge, areas where the edge of an ill-fitting denture may traumatize adjacent tissue:
 - Represents a redundant fold of tissue running parallel to the edge of the denture

Retrocuspid Papule

- Another fibrous oral mass occurring as an asymptomatic, firm papule on the lingual aspect of the mandibular cuspid, either on the gingiva or on the adjacent oral mucosa.

Pathology

Gross

- Well-demarcated, firm, dome-shaped nodule with sessile or pedunculated base and a smooth, dome-shaped elevation varying in size from less than 0.5 to 2.0 cm in greatest dimension, but usually measures from 0.5 to 1.0 cm

Histology

- Bland, nodular submucosal proliferation of fibrous connective tissue with overlying intact but attenuated stratified squamous epithelium:
 - Periphery of lesion is not encapsulated and blends imperceptibly into the surrounding connective tissue.
 - Fibrous tissue ranges from dense and coarse (fibroma durum) to delicate and fibrillar (fibroma molle).
 - Proportion of ground substance varies from sparse to abundant.
 - Surface may be ulcerated.
- Fibroblasts are spindle shaped to stellate with inconspicuous, cigar-shaped nuclei evenly distributed throughout the lesion; cytoplasmic borders are not prominent.
- Collagen may be:
 - Arrayed as interlacing, haphazard, or parallel bundles

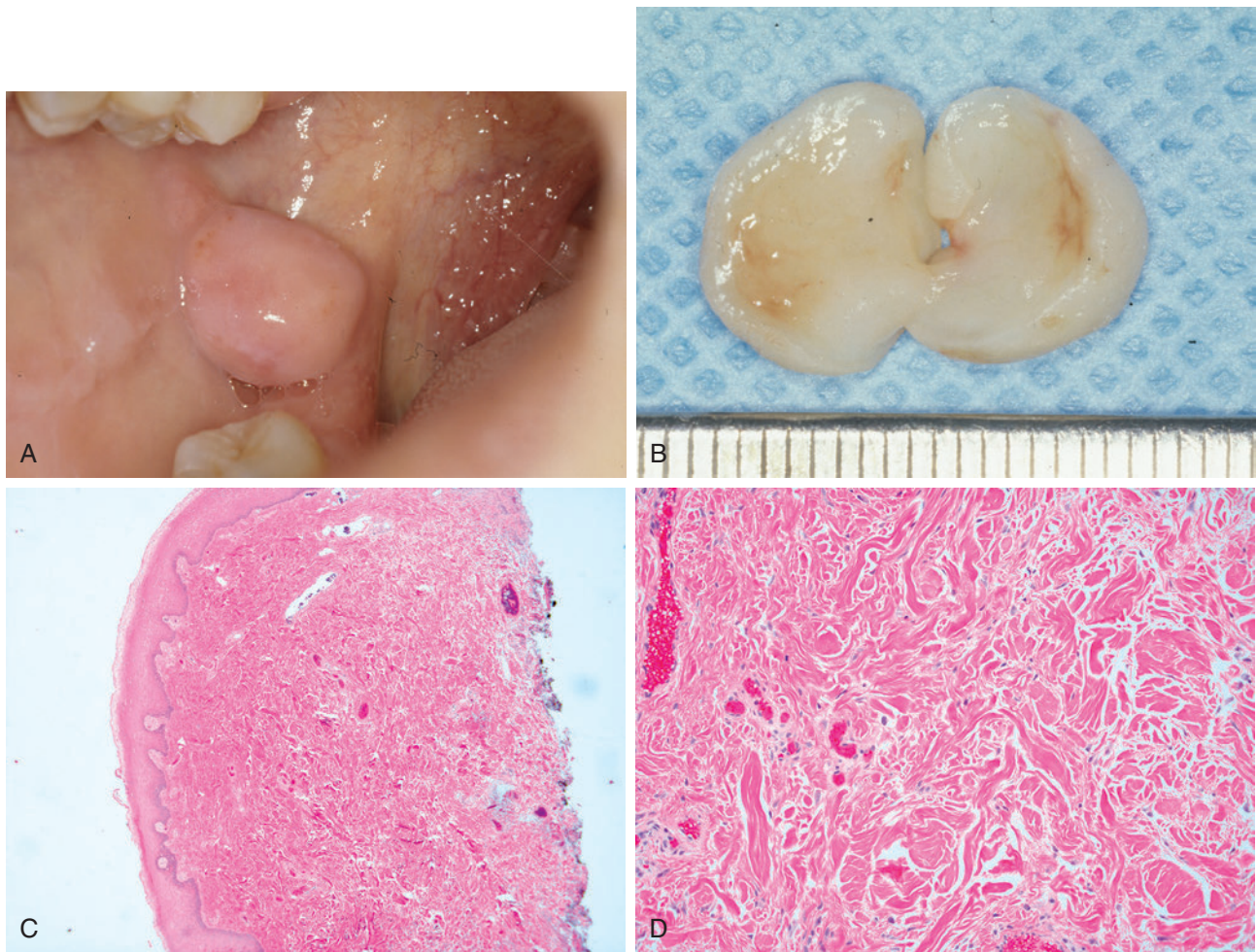


Fig. 5-25. Irritation fibroma.

A, Right buccal mucosa fibroma appearing as a mucosal covered oval to round bulge. **B**, Cut section of the excised lesion shows a white-appearing lesion. **C**, Bland, nodular submucosal proliferation of fibrous connective tissue with overlying intact stratified squamous epithelium. **D**, Submucosal dense collagen with scattered blood vessels.

- Dense, hyalinized bands (keloidal collagen)
- Loose appearing
- Mitoses are not seen.
- Submucosal mild chronic inflammation and edematous change may be present; limited vascularity is present and any given lesion may be avascular.
- Histochemistry:
 - Connective tissue component is a mixture of glycoproteins and fibers, but the pattern of staining does not differentiate between lesions.

Epulis Fissuratum

- Histologically similar to an irritation fibroma except that there is often a denser chronic inflammatory cell reaction and greater tendency for the surface epithelium to be ulcerated

Retrocuspid Papule

- Histology is similar to the giant cell fibroma (see below), except that in occasional cases rests of odontogenic epithelium can be identified.

Differential Diagnosis

- Keloid
- Fibromatosis
- Giant cell fibroma
- Desmoplastic fibroblastoma (collagenous fibroma):
 - Uncommon benign soft tissue lesion with wide anatomic distribution rarely occurring in oral cavity
 - Paucicellular lesion with abundant collagenous or myxocollagenous matrix, low vascularity, and

scattered bland-appearing stellate- and spindle-shaped fibroblastic cells

- Characteristic cytogenetic abnormalities of chromosome 11q12 with presence of identical t(2;11)(q31;q12) translocation

Treatment and Prognosis

- Surgical excision of the lesion, in conjunction with removal of any apparent source of chronic irritation, is the preferred treatment.
- Recurrence of fibroma is uncommon.

Giant Cell Fibroma (Fig. 5-26)

Definition: Benign submucosal fibrous tumor of the oral cavity characterized by large mononuclear and multinucleated giant cells.

Clinical

- No gender predilection; primarily occurs in the first three decades of life with a peak occurrence in the second decade, although a broad age range has been reported
- Most common location is the gingiva, followed by the tongue, palate, buccal mucosa, and lips
- Periapical radiographs show no evidence of osseous pathology.
- Does not appear to be associated with trauma:
 - Some authorities believe giant cell fibroma should not be separated from irritation fibroma.
 - Absence of associated trauma in giant cell fibroma would support separating it from irritation fibroma
 - Differences in demographics, site of location, and histology also support separating these entities.

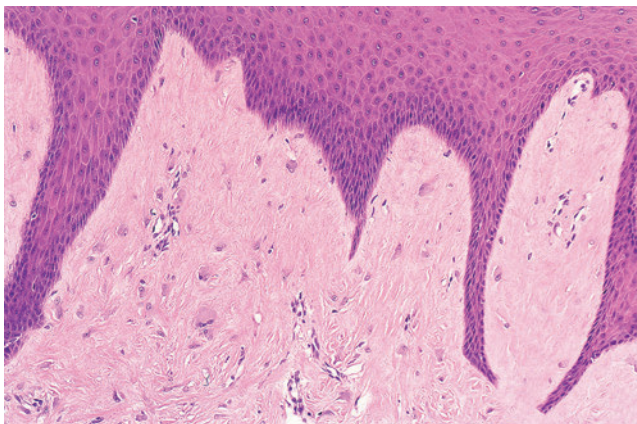


Fig. 5-26. Giant cell fibroma of the oral cavity.

Submucosal fibroblasts include scattered stellate to multinucleated giant fibroblasts in a collagenized stroma; separation artifact is focally seen around the fibroblastic cells.

Pathology

Gross

- Mucosal-covered, nodular, pedunculated, or sessile mass often with a papillary appearance and usually measuring less than 1.0 cm in greatest dimension and often less than 0.5 cm.

Histology

- Bosselated nodule of loose fibrovascular connective tissue composed of fibroblasts and collagenized stroma:
 - Fibroblasts include large, stellate-shaped nuclei, as well as numerous multinucleated giant fibroblasts that can be seen scattered throughout the lesion.
 - Collagen may have a whorled pattern and may range from compact to loose in appearance.
 - Separation artifact is sometimes noted around the stellate cells.
- Vascularity and chronic inflammation varies but may be prominently seen in any given case.
- Surface epithelium remains intact, composed of stratified squamous epithelium; prominent, elongated rete ridges may be present.
- Foci of melanin granules may be seen within the giant cells.
- Mitoses are not seen.
- Electron microscopy:
 - Mononuclear and multinuclear cell cytoplasm contains varying numbers of microfibrils in a perinuclear distribution:
 - Microfibrils are predominantly 50 to 100 angstroms in diameter, with a smaller number of fibrils about 125 angstroms in diameter.
 - Amount of rough endoplasmic reticulum supports a fibroblast-like differentiation.

Differential Diagnosis

- Conventional fibroma
- Peripheral giant cell fibroma:
 - Giant cells of giant cell fibroma are not the “osteoclastic”-type giant cells seen in peripheral giant cell fibroma, and the stroma is not as vascular in giant cell fibroma as it is in peripheral giant cell granuloma.

Treatment and Prognosis

- Simple surgical excision is the preferred treatment; recurrence is uncommon.

Oral Fibrosing Lesions

- Two oral fibrosing lesions include oral submucous fibrosis and gingival fibromatosis.

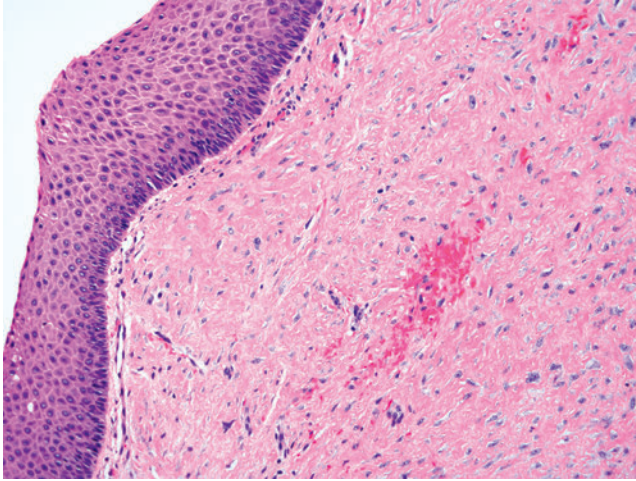


Fig. 5-27. Oral submucous fibrosis.

Oral submucous fibrosis characterized by submucosal hyalinization with replacement of the submucosal soft tissues. The overlying epithelium in this example is essentially unremarkable, although in other examples it may be atrophic and/or show the presence of intraepithelial dysplasia.

Oral Submucous Fibrosis (Fig. 5-27)

Definition: Unique chronic progressive and irreversible generalized fibrosis of oral and oropharyngeal soft tissues characterized by subepithelial fibrosis.

- Associated with chewing areca nut (betel quid), a habit found in rural India
- Symptoms include burning sensation of the oral mucosa, increasing rigidity, and progressive inability to open the mouth (referred to as trismus), causing difficulties in swallowing, speaking, and eating
- Typically involves the buccal mucosa, lips, retromolar areas, and soft palate
- Fiery red (erythroplakic)-appearing areas
- Histologically, in more advanced lesions there is a dense submucosal collagen deposition characterized by thick bands of hyalinization with replacement of the submucosal soft tissues:
 - Hyalinization of minor salivary gland acini can be found.
 - Epithelium is often atrophic, but epithelial dysplasia can be present:
 - Intraepithelial dysplasia varies from 7% to 26%.
 - Ulceration and vesicle formation may occasionally occur.
- Up to 13% of patients with oral submucous fibrosis develop squamous cell carcinoma:
 - Development of squamous cell carcinoma is linked to the presence of tobacco as a component of areca nut
- No effective treatment for oral submucous fibrosis:
 - Restriction or elimination of areca nut use recommended
- Oral dysplasia and/or carcinoma associated with oral submucous fibrosis are treated as any other dysplasia or carcinoma.

Gingival Fibromatosis

Definition: Overgrowth of collagenous portion of non-epithelial gingival tissue.

- Unrelated to aggressive fibromatosis
- May be classified as follows:
 - Hereditary gingival fibromatosis
 - Idiopathic gingival fibromatosis
 - Drug-induced fibrous hyperplasia (also referred to as fibrous gingival hyperplasia)
- Hereditary gingival fibromatosis:
 - May present in early childhood with generalized (or localized) enlargement of attached gingiva
 - Gingiva is characterized as pink, firm, and very fibrous, with little tendency to bleed
 - Linked to a variety of syndromes, including:
 - Byars-Jurkiewicz syndrome (gingival fibromatosis, hypertrichosis, giant fibroadenomas of the breast, and kyphosis)
 - Cross syndrome (gingival fibromatosis, microphthalmia, mental retardation, athetosis, and hypopigmentation)
 - Gingival fibromatosis and growth hormone deficiency
 - Jones-Hartsfield syndrome (gingival fibromatosis and sensorineural hearing loss)
 - Murray syndrome (gingival fibromatosis with juvenile hyaline fibromatosis)
 - Ramon syndrome (gingival fibromatosis, hypertrichosis, cherubism, mental and somatic retardation, and epilepsy)
 - Rutherford syndrome (gingival fibromatosis and corneal dystrophy)
 - Prune-belly syndrome (hypoplastic abdominal muscle, cryptorchidism, obstructive nephropathy, gingival fibromatosis)
 - Zimmerman-Laband syndrome (gingival fibromatosis; ear, nose, bone, and nail defects; and hepatosplenomegaly)
 - Defect in the Son of sevenless-1 (*SOS1*) gene on chromosome 2p21-p22 (HGF1) as a possible cause of this clinical presentation
 - Transmitted through autosomal dominant and recessive modes
- Idiopathic gingival fibromatosis:
 - May present in early childhood with generalized gingival fibromatosis linked to a variety of syndromes or may appear as a papular lesion (papulosis or papular gingival fibromatosis) linked to

- such conditions as acanthosis nigricans, Cowden syndrome, and tuberous sclerosis
- Drug-induced fibrous hyperplasia:
 - Has been linked to a wide variety of drugs
 - Initially becomes noticeable 3 or more months after the use of the medication
 - Drugs associated with gingival fibrous hyperplasia include (but are not limited to):
 - Strongest association: phenytoin (Dilantin), cyclosporine, and nifedipine
 - Others include amlodipine, bepridil, bleomycin, diltiazem, felodipine, isradipine, nicardipine, nimodipine, nisoldipine, nitrendipine, oxidipine, sodium valproate, and verapamil
- A localized form of gingival fibromatosis is the symmetric fibromatosis of the tuberosity:
 - Appears to be a developmental type of phenomenon, although true cause is unknown
 - This form of fibrous hyperplasia may be more common than generalized gingival fibromatosis.

Pathology

- Share similar histology irrespective of clinical occurrence, including:
 - Dense or moderately dense relatively avascular submucosal collagenized connective tissue with scattered chronic inflammatory cells
 - Low cellularity consisting of fibroblasts interspersed with myofibroblasts
 - Myxoid change may be present rarely, calcifications identified

- Gingival epithelium may have extreme elongation of rete ridges including long, narrow anastomosing rete ridges extending into connective tissue
- Crevicular epithelium facing the tooth surfaces usually shows degeneration, subepithelial edema, and more extensive inflammatory cell infiltration due to gingivitis or periodontitis that is often present.

Treatment and Prognosis

- For generalized (hereditary) fibromatosis, treatment includes surgical excision, including gingivectomy and gingivoplasty, to recontour the tissue to achieve satisfactory cosmesis:
 - May recur or progress after surgery requiring repeated surgical resection
 - Improved oral hygiene greatly diminishes the risk of recurrence.
- Drug-induced gingival hyperplasia may also be treated by gingivectomy and plaque control:
 - Discontinuation of drug use often results in cessation and even regression of gingival enlargement.
- Symmetric fibromatosis of the tuberosity usually requires no treatment:
 - Large lesions or those that interfere with function or denture placement may be removed with conservative surgical excision.
 - Recurrence has not been reported.

NON-NEOPLASTIC OSSEOUS-RELATED LESIONS OF THE HEAD AND NECK

GIANT CELL GRANULOMA

(Figs. 5-28 through 5-30)

Definition: Reactive intraosseous and extraosseous proliferation containing numerous osteoclast-like giant cells.

NOTE:

- Because there is no histologic evidence to support a repair phenomenon, the designation “reparative” has been discarded.
- Giant cell granuloma shares many features with solid variant of aneurysmal bone cyst, and in many regards these lesions may be indistinguishable.
- Those lesions predominantly confined to intraosseous sites (e.g., jaws) are referred to as central giant cell granuloma:
 - Controversy whether these represent true neoplasms or reactive process

- Those lesions primarily involving soft tissues (e.g., sinonasal or oral mucosa) are termed peripheral giant cell granuloma:
 - Believed to represent a non-neoplastic reactive process likely occurring secondary to trauma or local irritation

Clinical

- For central (head and neck) lesions:
 - More common in women than in men; occur in patients under 30 years of age
 - Gnathic bones are the most common sites of occurrence:
 - Mandible > maxilla
 - Rare occurrences in other bones include paranasal sinuses and cranial bones.
 - Presents as a painless mass or swelling of affected site

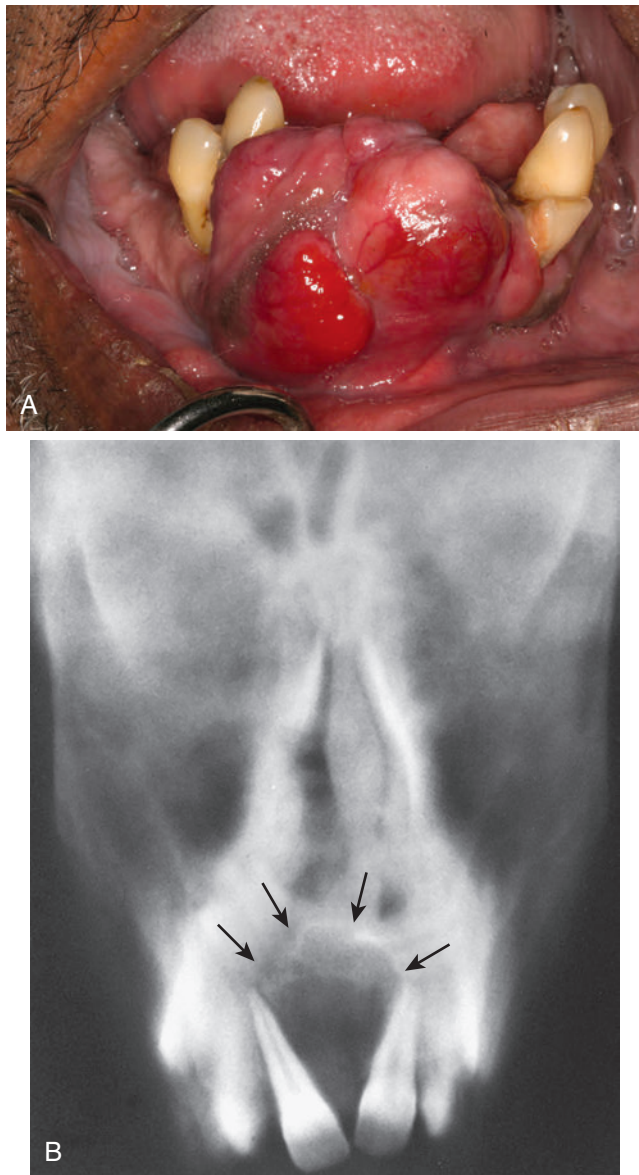


Fig. 5-28. Giant cell reparative granuloma.

A, Giant cell reparative granuloma. This patient presented with a protuberant soft tissue mass that involved bone. If the same lesion were entirely extraosseous, it would be designated as a peripheral reparative giant cell granuloma. **B**, Coronal multidirectional tomogram shows an expansile lesion in the maxillary alveolus and hard palate (arrows). This patient had a central-type giant cell granuloma. (A, Courtesy Dr. Mauricio Wiltz. B, From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, 4-207 and 4-208, p 359.)

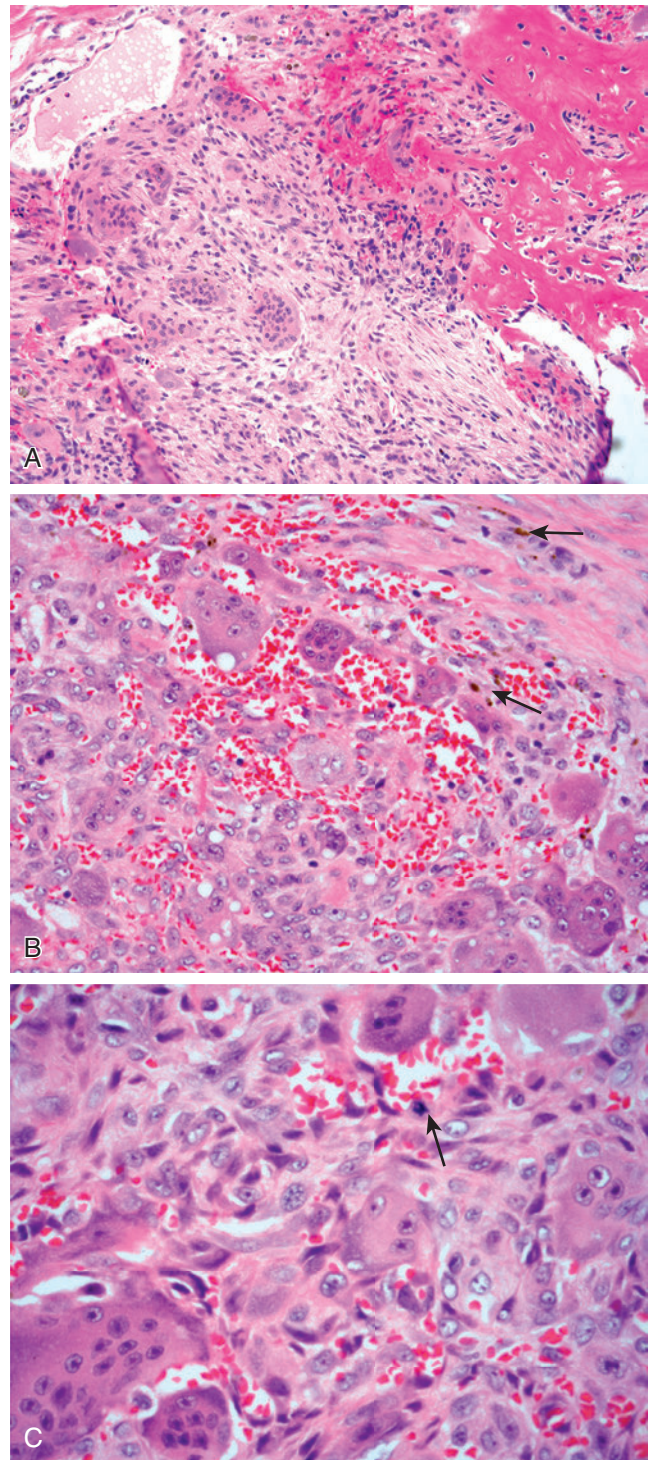


Fig. 5-29. Central giant cell reparative granuloma.

A through **C**, Central giant cell reparative granuloma occurs in bone (upper right in **A**) and includes the presence of cellular fibrous stroma with numerous round to oval to spindle-shaped fibroblasts, variable numbers of multinucleated giant cells, numerous capillaries, and hemorrhage, including fresh hemorrhage and hemosiderin-laden macrophages (arrows in **B**); scattered mitotic figures may be present (arrow in **C**).

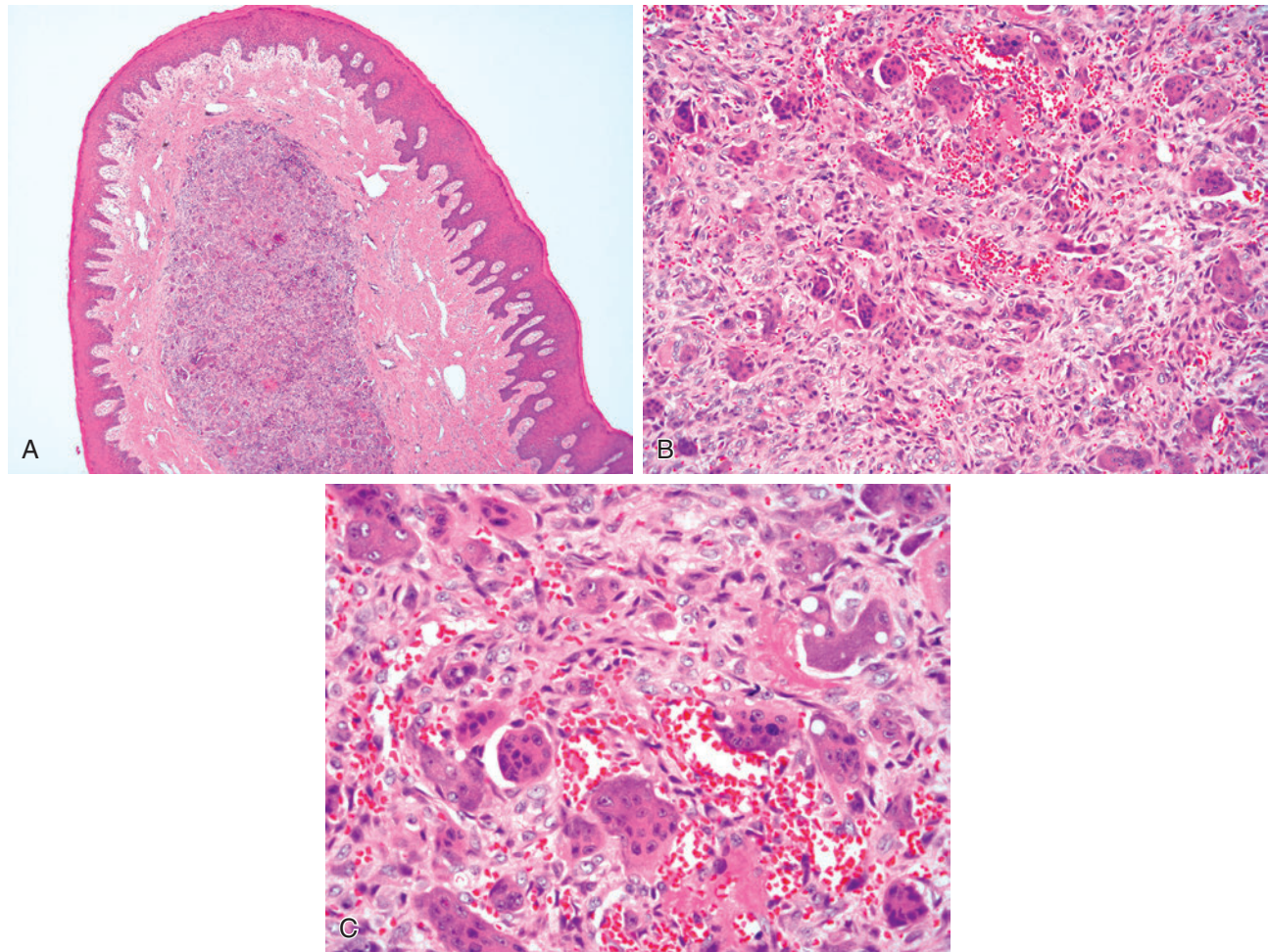


Fig. 5-30. Peripheral giant cell granuloma.

A through **C**, Peripheral (mucosal) giant cell granuloma is histologically similar/identical to central (intraosseous) lesions except that peripheral lesions are localized to a mucosal site without intraosseous involvement. To exclude osseous involvement clinical and radiologic correlation is required. The histologic findings include (**A**) presence of a submucosal proliferation lying subjacent to an intact surface epithelium (surface ulceration may be seen in some cases) composed of (**B, C**) cellular fibrous stroma with numerous round to oval to spindle-shaped fibroblasts, variable numbers of multinucleated giant cells, numerous capillaries, and hemorrhage.

- Radiographic appearance includes:
 - Demarcated, multiloculated, or soap bubble–appearing intraosseous lesion
 - Expansion and thinning of cortical plates
 - Displacement of teeth can be found.
- For peripheral lesions:
 - More common in women than in men; occur in patients under 30 years of age
 - Most often occurs in the oral mucosa (gingiva, alveolar mucosa) overlying the mandible and maxilla; sinonasal tract or nasopharyngeal involvement is uncommon
 - Presents as a painless, firm, sessile or pedunculated mucosal-based mass; overlying mucosa may be intact or ulcerated; sinonasal tract involvement may be associated with pain and swelling
- Radiographic appearance includes:
 - Superficial (not intraosseous) location with saucer-like erosion of subjacent bone
 - Expansion and thinning of cortical plates
- For central and peripheral lesions, laboratory values including serum calcium and phosphorus are within normal limits.
- Multiple lesions in the mandible, particularly if symmetric and bilateral, may suggest a diagnosis of cherubism:
 - Autosomal dominant disease with variable expressivity
 - Sporadic nonfamilial cases also reported

- Characterized by lateral swelling of the jaws (resembling cherubs in Renaissance paintings)
- Bilateral symmetric involvement is almost pathognomonic.
- Usually involves the mandible with the ramus always involved
- Patients have characteristic upturned appearance of the eyes resulting in a cherubic expression.
- Histologic features are those of giant cell granuloma; see below.
- Caused by mutation of *SH3BP2* gene on chromosome 4p16.3:
 - Mutations reported in 75% of cases
 - Mutation of the *SH3BP2* gene believed to increase production of overactive proteins from this gene
 - Overactive protein likely causes inflammation in jaw bones, triggering production of osteoclasts, which break down bone during bone remodeling
 - Bone loss and inflammation lead to increased fibrous tissue and cyst formation
 - Cherubism also found combined with other genetic disorders, including Noonan syndrome, Ramon syndrome, and fragile X syndrome

Pathology

- Central and peripheral giant cell granulomas are histologically identical and are composed of a cellular fibroblastic stroma that includes multinucleated giant cells:
 - Unencapsulated lesion composed of fibrous stroma with numerous round to oval to spindle-shaped fibroblasts, variable numbers of multinucleated giant cells and numerous capillaries, the latter often associated with a prominent endothelial cell proliferation
 - Copious foci of hemorrhage, including fresh hemorrhage and hemosiderin deposition; hemosiderin-laden macrophages are characteristically identified.
 - Giant cells are less diffusely distributed and tend to aggregate in and around foci of hemorrhage.
 - Less often, giant cells are diffusely distributed in the fibroblastic stroma.
 - Mitotic figures are seen in the fibroblasts but not the giant cells.
 - Cyst formation, bone, and osteoid may be present.
 - Peripheral giant cell granulomas are:
 - Submucosal lesions lying underneath an intact and uninvolved respiratory or squamous epithelium:
 - Surface epithelial ulceration may be present.
 - Separation of surface epithelium from subjacent giant cell granuloma by zone of uninvolved fibroconnective tissue
- Associated with chronic inflammatory cell infiltrate that may include mast cells (feature not typically seen in central lesions)
- Hemosiderin-laden macrophages typically seen along periphery of the lesion
- Immunohistochemistry:
 - Not necessarily used in the diagnosis and differential diagnosis
 - Identification of angiogenic factors, including vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) in giant cells, may play a role in the process of osteoclastogenesis, potentially contributing to additional growth in these lesions.
- Cytogenetics and molecular genetics:
 - Lacks mutation of *SH3BP2* occurring in cherubism

Differential Diagnosis

- Giant cell tumor (see below)
- Brown tumor of hyperparathyroidism:
 - Given histologic similarity to brown tumor of hyperparathyroidism, prudent management includes laboratory evaluation of parathyroid gland function:
 - Increased serum levels of calcium, phosphate, alkaline phosphatase, and parathyroid hormone
 - See Section 9, Parathyroid Glands, for complete discussion.
- Aneurysmal bone cyst (ABC) (Figs. 5-31 and 5-32):
 - Represents a benign non-neoplastic osseous lesion characterized by the presence of numerous blood-filled cavities lacking an endothelial lining
 - Occurs as a de novo process unrelated/unassociated with an underlying pre-existing bone lesion or occurs in association with an underlying pre-existing bone lesion; the latter may include:
 - Giant cell tumor (most common)
 - Unicameral bone cyst
 - Osteosarcoma
 - Chondroblastoma
 - Nonossifying fibroma
 - Osteoblastoma
 - Fibrous dysplasia
 - Giant cell granuloma
 - Many other lesions
 - Most common site of occurrence is long bones, where they involve the metaphysis
 - Up to 12% of ABCs occur in the head and neck:
 - Most common site in the head and neck is the jaws with the mandible (body > ramus > angle > symphysis > condylar process) more common than the maxilla
 - Tends to occur in the first two decades of life

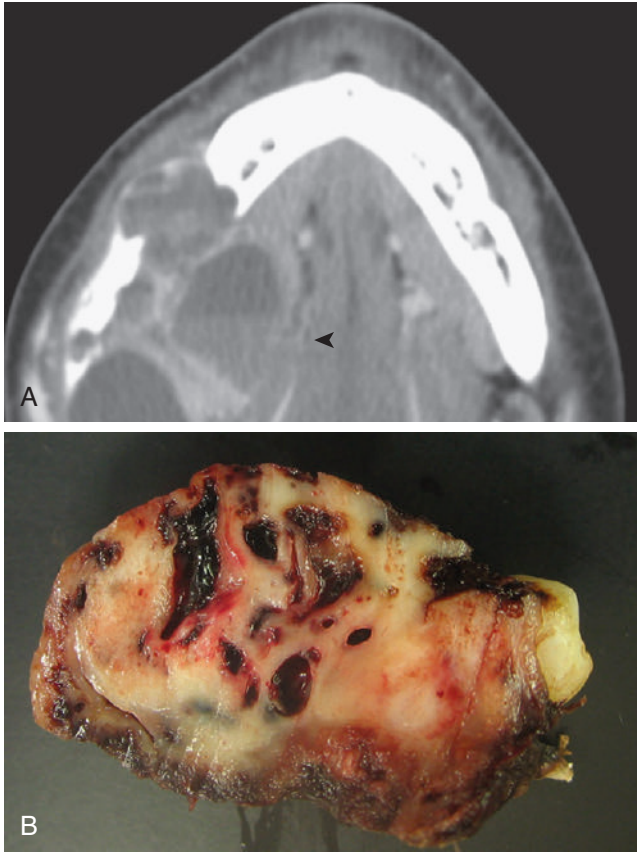


Fig. 5-31. Aneurysmal bone cyst.

A, Expansile multicystic radiolucent mandibular lesion eroding the cortices; a distinctive fluid level within the cyst (*arrowhead*) is seen. **B**, Resected specimen showing multiple blood-filled cysts and intercystic solid areas.

- Presents as a slowly or rapidly enlarging mass with associated swelling and pain; additional symptoms may include, depending on the site of occurrence, headache, visual disturbances (diplopia, decreased vision), proptosis, loosening of teeth, nasal obstruction, paresthesia, limitation of motion, fracture, facial nerve, or abducens nerve paralysis
- Occurrence in the sinonasal tract or nasopharynx may result in a soft tissue mass.
- Radiology:
 - Expansile, uni- or multilocular radiolucency surrounded peripherally by a thin shell of periosteal bone
- Histology:
 - Blood or blood-tinged serous fluid-filled cysts
 - Cysts lack an endothelial-lining and may be lined by fibroblasts, histiocytes, and/or multinucleated giant cells.

- Intercystic stroma is fibrous, well vascularized with mixed chronic inflammatory cells, extravasated erythrocytes and hemosiderin
- Almost all ABCs have areas in which the lesion is more or less solid characterized by a loose arrangement of spindle cells; increased mitotic activity (on average 1 to 3 mitoses per 10 high-power fields) are present but atypical mitoses are not identified
- Osteoid (lace-like), reactive bony trabeculae and osteoclastic giant cells are variably identified
- Mineralized/calcified matrix (so-called blue bone) is characteristically present in ABCs.
- Solid variant of ABC:
 - Characterized by firm and fleshy lesion completely solid microscopically lacking cystic cavities
 - Solid areas composed of spindle cell proliferation with giant cells and osteoid production similar in appearance to the solid areas of a “conventional” ABC
 - Of note, approximately 5% of ABCs lack cystic component.
- Histologic similarities to giant cell granuloma:
 - Differentiating feature is the presence of cysts seen in aneurysmal bone cyst, a feature typically not seen in giant cell granuloma.
 - Solid variant of ABC lacking cysts is histologically indistinguishable for giant cell granuloma.
- Treatment includes curettage or surgical resection:
 - Rate of local recurrence after curettage of the jaws ranges from 20% to 38%.
 - Recurrent lesions should also be managed conservatively.

Treatment and Prognosis

- For central lesions:
 - Conservative but complete surgical resection is the preferred treatment for gnathic and sinonasal lesions.
 - May behave in a locally aggressive manner
 - Recurrence rates vary and reported from 11% to near 50%
 - Radiation treatment generally not indicated
- For peripheral lesions:
 - Conservative but complete surgical resection to include the entire depth of the lesion with curettage of subjacent bone
 - May recur in a small percentage of cases (approximately 10%)

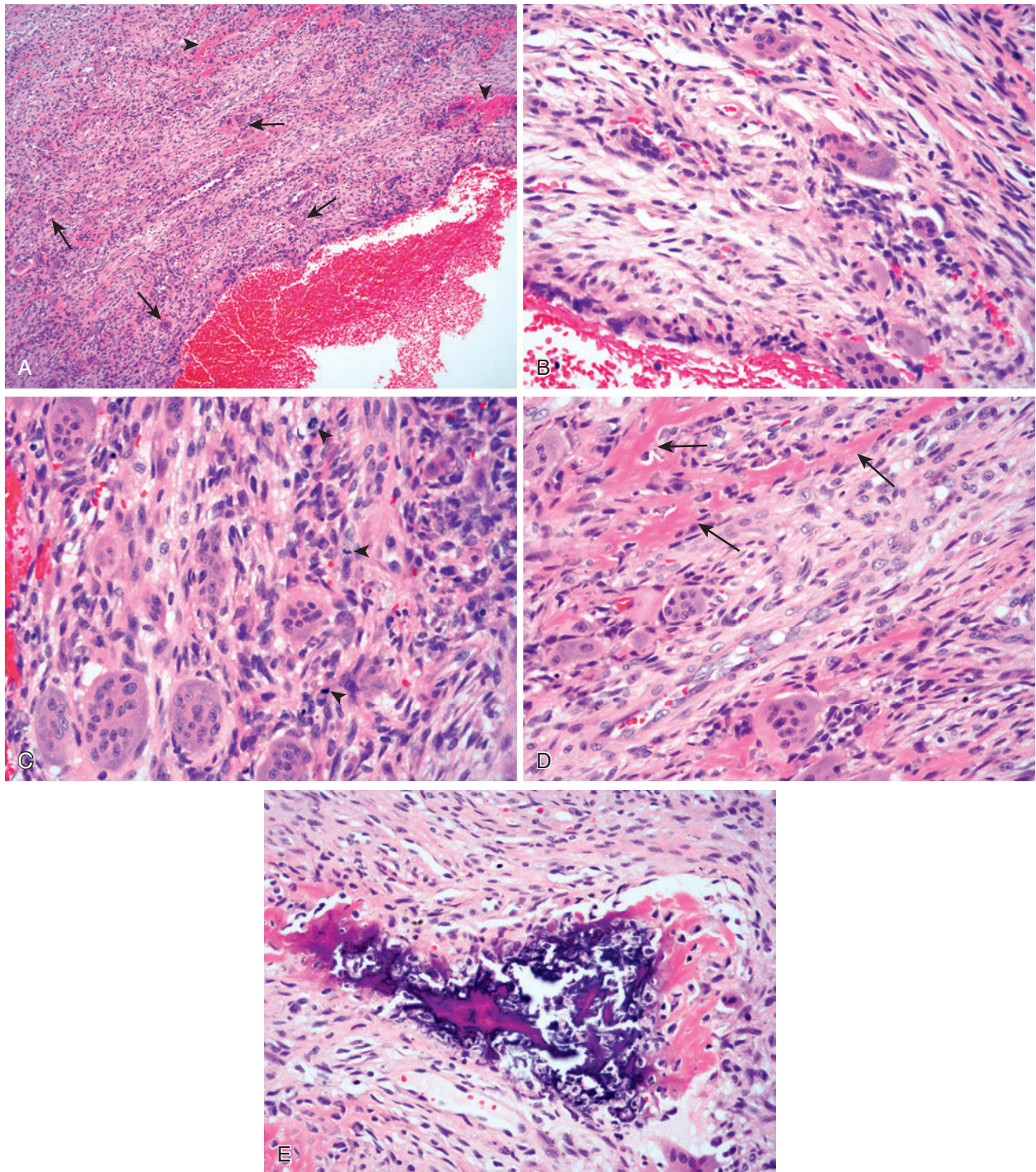


Fig. 5-32. Aneurysmal bone cyst.

A, Blood-filled cyst (*bottom center and right*) with more solid area characterized by spindle cell proliferation, scattered multinucleated giant cells (*arrows*) and lace-like osteoid (*arrowheads*). **B,** Higher magnification shows the blood-filled cyst (*bottom left*) lined by fibroblasts as well as giant cells (*arrowhead*); the solid area is composed of spindle cells and scattered multinucleated giant cells. **C,** Increased mitotic activity is present but atypical mitoses are not identified. **D,** Osteoid (lace-like) reactive bony trabeculae (*arrows*). **E,** Mineralized/calciified matrix (so-called blue bone) is a characteristic finding.

SELECTIVE AUTOIMMUNE, ALLERGIC, SYSTEMIC, CUTANEOUS-TYPE, AND MISCELLANEOUS DISEASES AFFECTING THE ORAL CAVITY

- Oral cavity may be involved by a wide variety of autoimmune, systemic, and cutaneous-type diseases (Box 5-2).
- Many of these lesions/diseases are beyond the scope of this text and the reader is referred to more detailed texts for a discussion of these disease entities.
- This section is limited to select diseases that the pathologist may confront in his/her daily practice.

GRANULOMATOSIS WITH POLYANGIITIS (GPA)

Definition: Non-neoplastic, idiopathic aseptic necrotizing disease with predilection for the upper/lower respiratory tract and the genitourinary system characterized by the presence of vasculitis and destructive properties. This classic definition calls for involvement of the head and neck region, the lung, and the kidney. The majority of GPA patients do not exhibit this classic clinical triad simultaneously at the time of initial presentation. Therefore, it is possible that, in a given patient, the initial biopsy material may originate from lesions of the UADT in the absence of a clinical suspicion for GPA.

- In the UADT, the most common site of occurrence is the sinonasal region with the nasal cavity > maxillary > ethmoid > frontal > sphenoid; other sites of involvement include nasopharynx, larynx (subglottis), oral cavity, ear (external and middle ear including the mastoid), and salivary glands.
- Oral manifestations of GPA may include:
 - An ulcerative lesion and gingivitis
 - Destructive lesions often seen along the palate and alveolar region
- For a more complete discussion see Section 1, Sino-nasal Tract.

RECURRENT APHTHOUS STOMATITIS (RAS)

Definition: Painful ulcerative disorder of unattached oral mucous membrane of unknown cause with tendency to recur.

Synonym: Canker sores

Clinical

- One of the more common recurrent ulcerative processes to affect the oral mucosa, affecting up to 10% to 15% of the world population
- Three clinical forms of aphthous stomatitis (AS) may occur, including minor AS, major AS, and herpetiform AS.

Minor Aphthous Stomatitis

- Most common clinical form of AS, accounting for 80% of cases
- More common in women than in men; often begins in childhood or adolescence
- May occur as a solitary lesion or in groups, tend to measure less than 1 cm in greatest dimension and heal within 7 to 10 days without scarring
- Lesions (ulcers) tend:
 - To occur on nonkeratinized mucosa with the buccal and labial mucosae representing the more common sites of occurrence; other sites of involvement include the tongue (ventral surface), floor of mouth, and soft palate:
 - Involvement of keratinizing mucosa, such as the gingival, hard palate, dorsal tongue, lip vermilion border) usually occurs as extension from an ulcer on an adjacent nonkeratinizing surface and rarely occurs as an isolated lesion of these keratinizing sites
 - To be painful, with the level of pain often out of proportion to the size of the lesion
 - To be covered by a white to yellow, mucopurulent exudate that is removable and is surrounded by an erythematous halo
- Recurrence rate of these ulcers varies from an ulcer every few years to several in a month.

Major Aphthous Stomatitis

- Occurs in a minority of patients (approximately 10%)
- Onset is usually after puberty, with recurring ulcers over decades
- Ulcers:
 - Are painful but are larger and deeper than the ulcers of minor AS
 - Occur over movable mucosa with soft palate, lip, and tonsillar regions most commonly affected, and may take several weeks to heal, with the resolution of the healing process resulting in submucosal scarring
 - May vary from a single ulcer to as many as 10 ulcers

Herpetiform Aphthous Stomatitis

- More common in women than in men; occur in adulthood

- Ulcers:
 - Tend to be smaller (1 to 2 mm) but are typically multiple, may coalesce into larger irregular ulcers
 - Most often occur on nonkeratinizing movable mucosa, take up to 10 days to heal, and have a higher frequency of recurrence over shorter periods of time
 - Resemble ulcers of herpes simplex virus, hence the designation herpetiform

General Comments

- Cause of AS:
 - Not known but thought to be multifactorial
 - Various considerations include trauma, stress, allergies, familial (genetic) predisposition, nutritional deficiencies, and infections (e.g., viral).
- AS has been associated with a number of systemic diseases, including Behçet disease, inflammatory bowel disease, celiac disease, Reiter disease, and immunocompromised conditions (e.g., AIDS/HIV disease).
- No specific laboratory findings associated with or diagnostic of AS:
 - In contrast to such lesions as GPA, serum anti-neutrophil cytoplasmic antibodies (ANCA), and proteinase 3 levels are not elevated in AS.
- Regional lymphadenitis may be present in association with the ulcers.

Pathology

Histology

- Nonspecific findings:
 - Early ulcers show central ulceration with associated fibrinopurulent exudates.
 - Deep to the ulcers there is increased vascularity and a mixed nonspecific acute and chronic inflammation of the submucosa.
- Because the histology is nonspecific and not in and of itself diagnostic for AS, diagnosis requires clinical correlation.
- Biopsies are necessary to exclude other diagnoses.
- Histochemistry:
 - Special stains for microorganisms are negative.
- Immunohistochemistry:
 - Increased activated cytotoxic T-lymphocytes and natural killer (NK) cells
 - Decreased CD4 lymphocytes

Differential Diagnosis

- Wide variety of other oral cavity ulcerative lesions, including (but not limited to):
 - Infections, vasculitic processes, and neoplasms:
 - Special stains for microorganisms may be required to exclude an infectious cause.

- Histologic findings of AS should allow for differentiating it from vasculitic lesions and neoplasms.

Treatment and Prognosis

- Solitary AS ulcers are usually self-limiting and require no therapy:
 - Topical steroids have been used in the treatment of the ulcers of minor AS.
 - Low-dose systemic corticosteroids have been used in the treatment of patients whose ulcers are not responsive to topical steroid.
 - Close monitoring for secondary oral candidiasis is required.
- A broad range of other medications are available with varying success, including antiseptics, anti-inflammatory drugs, and antibiotics (e.g., tetracyclines).
- For major ulcers, intralesional corticosteroid therapy may prove effective:
 - In patients with constant and aggressive outbreaks (major aphthae), pain is intense and topical treatment is unable to afford symptom relief.
 - In such cases, systemic therapy (e.g., corticosteroids) may be indicated.

ORAL LICHEN PLANUS (OLP)

(Fig. 5-33)

Definition: Immunologically mediated mucocutaneous disorder that often presents as a chronic dermatologic disease but also commonly affects the oral mucosa.

Synonym: Lichenoid mucositis

Clinical

- Represents the second most common site of occurrence to cutaneous sites:
 - Up to 35% of patients with LP have only oral manifestations.
- More common in women than in men; disease of middle-aged people; pediatric LP is uncommon (2% to 3%)
- May occur in several forms, including reticular (papular, plaque-like), erythematous (atrophic), and erosive (ulcerative or bullous):
 - Reticular and erosive forms are most common.
- Reticular form:
 - Most commonly affects the posterior buccal mucosa and may be bilateral; other sites of involvement include the tongue (lateral and dorsal), gingiva, palate, and lip (vermillion border)
 - Concurrent sites of involvement may occur.
 - Designation as reticular is due to the fact that the lesions have a characteristic pattern of interlacing white lines (so-called Wickham striae):

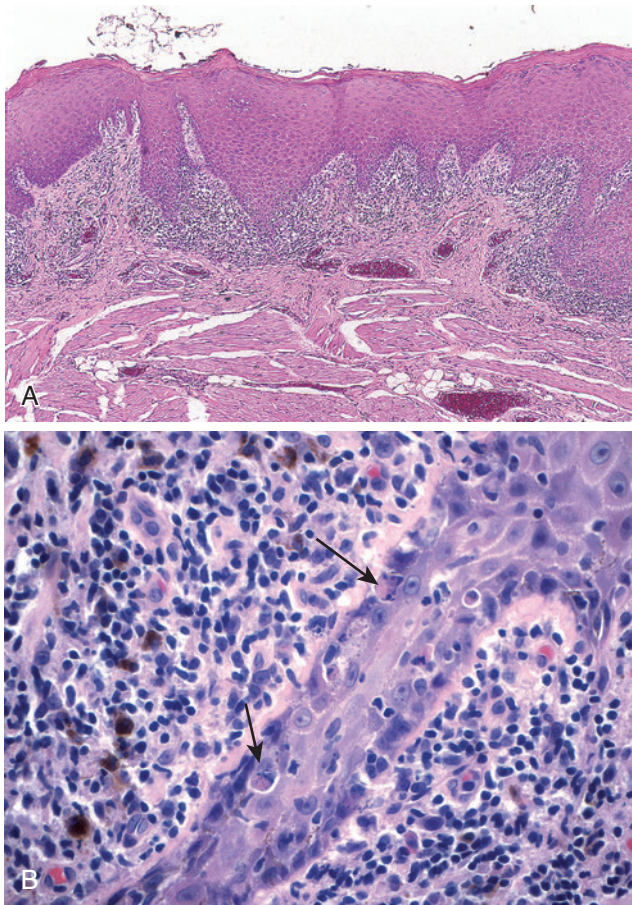


Fig. 5-33. Oral lichen planus.

A, Irregular epithelial hyperplasia with acanthosis, hyperkeratosis, and a saw-tooth configuration of the rete ridges with characteristic dense, bandlike chronic inflammatory cell infiltrate hugging the basal epithelium within the superficial submucosa. **B**, Dyskeratotic (apoptotic) basal keratinocytes (Civatte bodies) are present.

- In contrast, reticular OLP of the dorsal tongue appears as a keratotic plaque.
- Lesions of reticular OLP tend to be asymptomatic.
- Erosive form:
 - Often symptomatic with patients complaining of associated pain
 - Appear as atrophic, erythematous areas with central ulceration
 - Peripheral to the ulcer, interlacing white striations (Wickham striae) may be seen.
 - Gingival involvement may result in a clinical picture of desquamative gingivitis, necessitating biopsy to exclude other disease (e.g., cicatricial pemphigoid).

- In severe cases there may be epithelial separation, resulting in bullous form.
- Pathogenesis:
 - Unknown but evidence points to cell-mediated immune response
 - Numerous medications have been implicated in lesions that clinically simulate LP with similar histologic findings:
 - These lesions are referred to as lichenoid drug eruptions, and more specifically, relative to the oral mucosa have been termed lichenoid mucositis:
 - Appear to represent a systemic anaphylactic reaction
 - List of the medications associated with lichenoid drug eruption is extensive; a partial list includes antibiotics (ketoconazole, streptomycin, tetracycline), antihypertensive drugs (chlorothiazide, methyldopa, propranolol, spironolactone), nonsteroidal anti-inflammatory medication (naproxen, indomethacin, ibuprofen), antimalarials, and sulfonylureas

Pathology

Histology

- Overall histologic findings are not specific or pathognomonic but need to be correlated to the clinical picture to correctly diagnose the lesion.
- Epithelial alterations include:
 - Epithelial atrophy or acanthosis, hyperkeratosis (parakeratosis and orthokeratosis), and a saw-tooth configuration of the rete ridges
 - Hydropic degeneration (liquefaction) of the basal cell layer and dyskeratotic basal keratinocytes referred to as Civatte bodies
- In addition, a characteristic feature is presence of a dense, bandlike chronic inflammatory cell infiltrate predominantly composed of mature T-lymphocytes in the superficial submucosa hugging the basal epithelium.
- Absence of intraepithelial dysplasia:
 - Lesions with superimposed candida infection may appear dysplastic.
- Histochemistry:
 - Special stains for microorganisms are negative (except in the presence of fungal infestation).
- Immunohistochemistry:
 - Band-like lymphocytes are predominantly T-lymphocytes.
- Direct immunofluorescence:
 - Not diagnostic
 - Presence of fibrinogen in granular or linear pattern along basement membrane
 - Deposits of IgM, IgG, IgA, and C3 can be identified.

Differential Diagnosis

- Histologically, there are numerous pathologic processes with a lichenoid inflammatory reaction:
 - In contrast to LP, the inflammatory cell infiltrate in lichenoid lesions:
 - May have associated lymphoid follicles
 - May contain a higher number of plasma cells
 - May include a perivascular distribution

Treatment and Prognosis

- Treatment predicated on the extent of disease:
 - Reticular form:
 - Does not necessarily require treatment because it is often asymptomatic and may undergo spontaneous remission in more than 50% of cases
 - Superimposed fungal infection (e.g., candidiasis) requires antifungal therapy.

- Limited erosive form:
 - Topical corticosteroids used
- Extensive erosive form:
 - Systemic corticosteroids used
 - Close monitoring for secondary oral candidiasis is required.
- Whether the erosive form of LP can undergo malignant transformation is still debatable:
 - Development of squamous cell carcinoma in the setting of LP may be more coincidental than causative.

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References may be accessed online at ExpertConsult.com.

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Neoplasms of the Oral Cavity

GENERAL CONSIDERATIONS

- Similar to tumors of other upper aerodigestive tract sites, the most common tumors of the oral cavity are of epithelial origin:
 - Most common benign tumor is a (squamous) papilloma
- Most common malignant tumor is squamous cell carcinoma or variant thereof
- Although epithelial neoplasms are the most common tumor type, other epithelial tumors including those of minor salivary gland origin, as well as nonepithelial tumors, occur in the oral cavity.

BENIGN NEOPLASMS

CLASSIFICATION OF ORAL CAVITY BENIGN NEOPLASMS (Box 6-1)

BOX 6-1 Classification of Neoplastic Lesions of the Oral Cavity

Benign

Epithelial

- Squamous papilloma
- Minor salivary gland tumors
- Ectomesenchymal chondromyxoid tumor of the anterior tongue
- Others

Mesenchymal/Neuroectodermal

- Peripheral nerve sheath tumors (e.g., schwannoma, neurofibroma, granular cell tumor, mucosa neuroma, others)
- Fibrous tumors (e.g., fibromatosis, myofibroma/myofibromatosis)
- Vascular neoplasms (e.g., angiofibroma, hemangioma, lymphangioma)
- Lipoma(s)
- Leiomyoma(s)
- Rhabdomyoma(s)
- Fibrous histiocytic tumors (e.g., fibrous histiocytoma)
- Osseous (e.g., ossifying fibroma, giant cell tumor, osteoma, osteoblastoma, others)
- Cartilaginous (e.g., chondroma, chondroblastoma, others)
- Others

Odontogenic

- Ameloblastoma
- Squamous odontogenic tumor
- Odontogenic keratocyst (keratocystic odontogenic tumor)
- Adenomatoid odontogenic tumor
- Calcifying epithelial odontogenic tumor
- Calcifying cystic odontogenic tumor
- Odontogenic myxoma/fibromyxoma

Malignant

Potentially Malignant Disorders

- Leukoplakia
- Proliferative verrucoid leukoplakia

- Erythroplakia
- Actinic cheilitis
- Keratinizing and nonkeratinizing dysplasias

Epithelial

- Squamous cell carcinoma including conventional-type and variants (e.g., verrucous carcinoma, papillary [exophytic] squamous cell carcinoma, spindle cell squamous carcinoma, basaloid squamous cell carcinoma, adenosquamous carcinoma, carcinoma cuniculatum, others)
- Minor salivary gland tumors
- Cribriform adenocarcinoma of minor salivary glands
- Others

Nonepithelial

- Mucosal malignant melanoma
- Neuroendocrine carcinomas
- Malignant hematolymphoid (e.g., non-Hodgkin lymphomas, Hodgkin lymphoma, plasma cell neoplasms)
- Sarcomas
- Rhabdomyosarcoma
- Leiomyosarcoma
- Liposarcoma
- Malignant peripheral nerve sheath tumors
- Fibrosarcoma
- Undifferentiated pleomorphic sarcoma
- Alveolar soft part sarcoma
- Angiosarcoma
- Kaposi sarcoma
- Matrix-forming malignant neoplasms (e.g., osteosarcoma, chondrosarcoma, others)
- Malignant odontogenic tumors
- Secondary neoplasms

PAPILLOMA (Figs. 6-1 and 6-2)

Definition: Benign, exophytic epithelial neoplastic growth composed of branching fronds of squamous epithelium with fibrovascular cores.

Synonym: Squamous papilloma

Clinical

- Most common benign neoplasm of the oral cavity
 - No gender predilection; most commonly seen in the third to fifth decades of life:
 - May occur in pediatric ages
 - Any site can be affected but most frequently involves tongue, palate, buccal mucosa, tonsil, and uvula
 - Symptoms relate to a painless mass.
 - Majority are solitary but may be multiple:
 - Multiple papillomas may occur in association with focal dermal hypoplasia syndrome or in focal epithelial hyperplasia (Heck disease)
 - Focal dermal hypoplasia:
 - Autosomal dominant disorder with incomplete penetrance
- Predominantly occurs in women
 - Features include:
 - Multiple papillomas
 - Dermal hypoplasia with fatty penetrance
 - Syndactyly
 - Colobomas of the iris and choroids
 - Strabismus
 - Ductal hypoplasia
 - Focal epithelial hyperplasia or Heck disease includes:
 - Multiple oral papillomas
 - Caused by HPV types 13 and 32
 - Papillomas may occur anywhere in the oral cavity but most common on the labial and buccal mucosa and the tongue
 - Florid oral papillomatosis:
 - Clinical term for diffuse papillomatous change but not a defined clinicopathologic entity
 - May be associated with:
 - Cowden syndrome:
 - ◻ Autosomal dominant disease characterized by facial trichilemmomas associated with

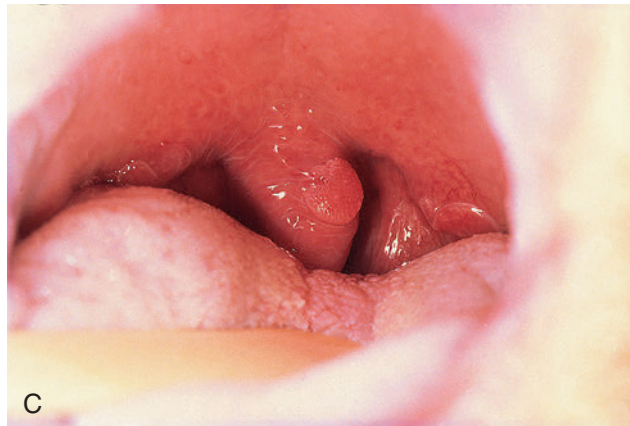
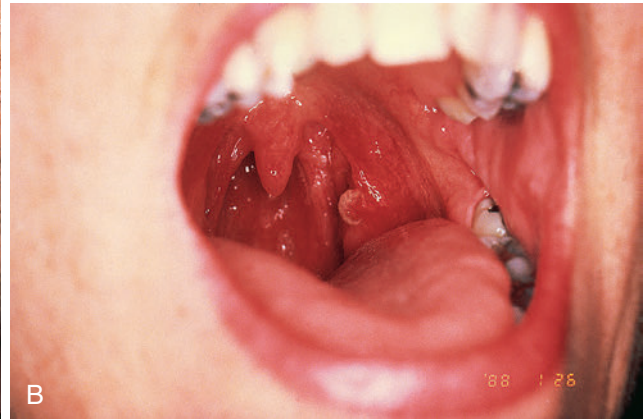


Fig. 6-1. Oral cavity squamous papillomas.

Squamous papillomas of the oral cavity include exophytic tan-white, warty or cauliflower-like lesions involving the (A) tongue, (B) tonsil, and (C) uvula.

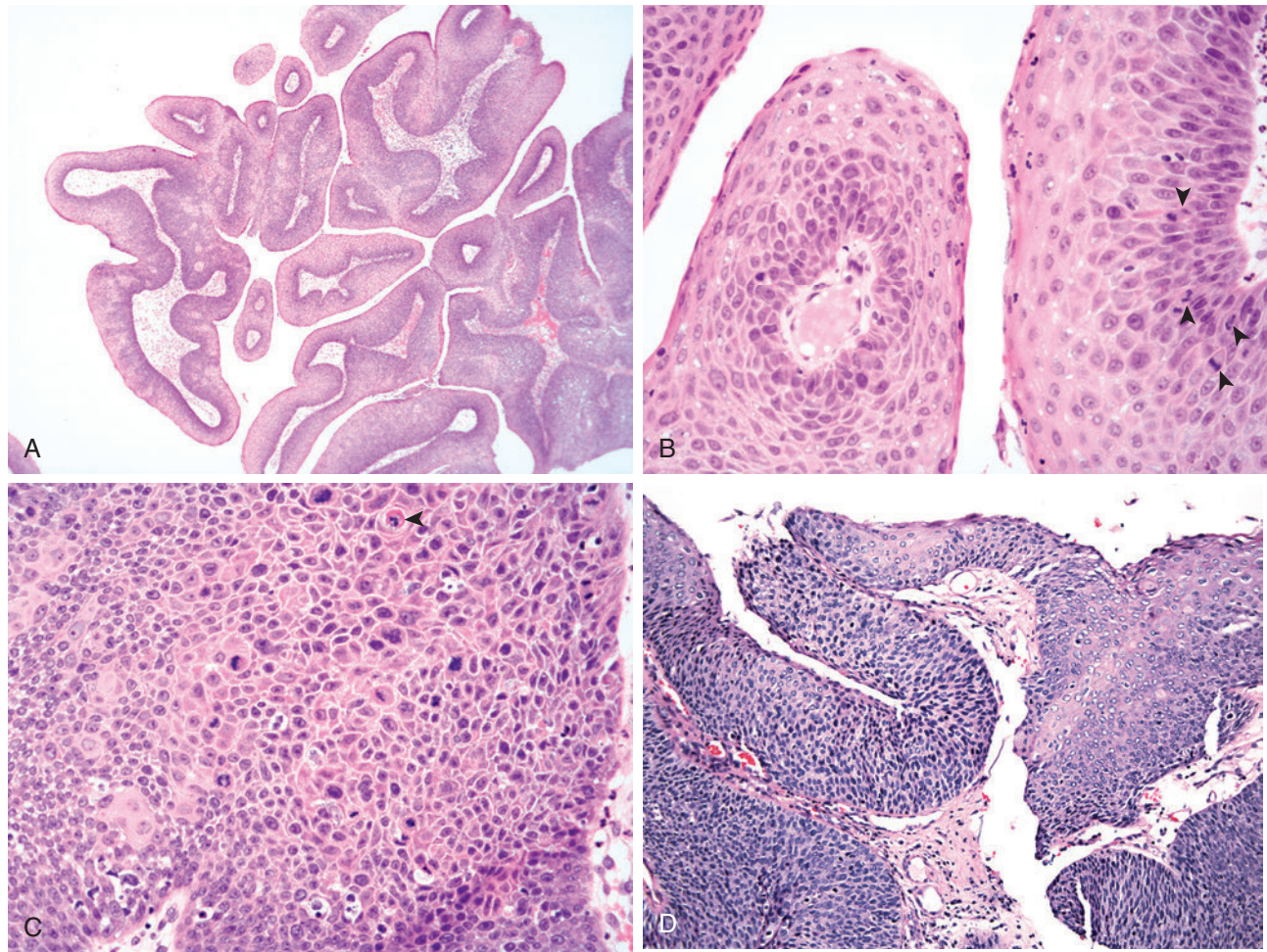


Fig. 6-2. Histology of squamous papilloma.

Typical histologic features of squamous papilloma include (**A** and **B**) benign epithelial proliferation with fingerlike projections and fibrovascular cores lacking surface keratinization and intraepithelial dysplasia; increased mitotic figures can be seen (*arrowheads*) but there is retention of cellular polarity as well as maturation lacking features of dysplasia; (**C**) area of high-grade dysplasia in a papilloma characterized by loss of polarity, nuclear pleomorphism and hyperchromasia, with increased nuclear-to-cytoplasmic ratio, increased mitotic activity including atypical mitoses and dyskeratotic cells (*arrowhead*); (**D**) squamous papilloma with transformation to carcinoma in situ showing transition from benign epithelium (*right*) to areas of carcinoma in situ (*left*); invasive squamous cell carcinoma was present (not shown).

GIT, CNS, musculoskeletal, and thyroid abnormalities

- Down syndrome, nevus unis lateris syndrome (ichthyosis hystrix), acanthosis nigricans, tuberous sclerosis, and focal dermal hypoplasia syndrome (Goltz-Gorlin syndrome)
- Immunosuppressed patients, in particular HIV infection, may be associated with florid oral papillomas/papillomatosis (immunodeficiency and papillomas/papillomatosis):
 - Entire oral mucosa may be papillomatous.
 - Lesions tend to be larger than nonimmunosuppressed-related lesions and may be

multiple; lesions may coalesce to form extensive mucosal patches.

- Multiple HPV subtypes, including unusual ones, may be identified.
- Cause:
 - Human papillomavirus (HPV) proposed as causative:
 - Many HPV subtypes have been detected, but most common are HPV types 6 and 11.
 - HPV DNA identified in greater than 80% of cases
 - No definitive association between HPV type and the type of papilloma

Pathology

Gross

- Exophytic, pink to tan-white lesion with a warty or cauliflower-like appearance; variation in size from a few millimeters up to 3.0 cm in greatest dimension

Histology

- Multiple finger-like projections with prominent fibrovascular cores covered by hyperplastic squamous epithelium:
 - Typically there is an absence of keratosis.
 - Squamous cell component generally is free of any dysplastic change.
 - Variable amount of hyperkeratosis, parakeratosis, and orthokeratosis may be seen.
 - On rare occasions, an “inverted” growth may be seen.
- Viral-associated cytopathic changes (i.e., koilocytes) may be seen in uppermost epithelial cell layers.

Differential Diagnosis

- Verruca vulgaris
- Syringocystadenoma papilliferum
- Verrucous carcinoma
- Exophytic squamous cell carcinoma
- Inflammatory papillary hyperplasia:
 - Benign, reactive oral epithelial hyperplasia often associated with an intraoral inflammatory process (e.g., stomatitis)
 - Relatively common oral lesion
 - More common in men than in women; typically occur in the third through fifth decades of life
 - May occur in any intraoral site but is most often found on the palate
 - Painless, appearing as multiple warty or papillary, red-appearing lesions
 - Development linked to:
 - Patients with stomatitis, the result of ill-fitting dentures or dental prostheses, especially in those people who retain their prosthesis while sleeping and who exhibit poor oral hygiene
 - *Candida*
 - May also occur in dentulous patients without known history of dental prosthesis use
 - Histologically:
 - Similar to pseudoepitheliomatous hyperplasia with hyperkeratosis, parakeratosis, and an absence of epithelial dysplasia
 - Edematous change and a mixed chronic inflammatory cell reaction can be seen in the submucosa.
 - Secondary reactive or degenerative changes of seromucous glands, including squamous metaplasia, fibrosis, atrophy, mucin pool formation, and mixed inflammation may be present in

areas overlying minor salivary glands; despite these findings the lobular configuration of the seromucous glands is retained.

- Fungi (i.e., *Candida albicans*) may be present.
- Resolution may occur by initial treatment approach that includes:
 - Replacement of prosthesis with a better fitting one and education in the proper oral hygiene indicated
 - Topical antifungal (e.g., miconazole) used to treat presence of fungi
- Failure for lesions to regress/resolve after conservative (nonsurgical) approach may require surgical excision
- Not considered to be a premalignant lesion

Treatment and Prognosis

- Complete surgical excision usually is curative.
- Recurrences occur infrequently and relate to inadequate excision.
- Malignant transformation does not occur.

BENIGN MINOR SALIVARY GLAND TUMORS

- Benign salivary gland tumors of the oral cavity are fairly common.
- Pleomorphic adenoma is the dominant histologic type seen; less often, monomorphic adenomas such as myoepithelioma and oncocytoma occur.
- For a more complete discussion see Section 6, Salivary Glands.

Ectomesenchymal Chondromyxoid Tumor of the Anterior Tongue

(Figs. 6-3 and 6-4)

Definition: Benign tumor of the anterior dorsal tongue of presumed origin from an undifferentiated ectomesenchymal cell but owing to morphologic and immunohistochemical resemblance to soft tissue myoepitheliomas it is more likely a myoepithelial neoplasm of soft tissues.

Synonyms: Oral myoepithelioma of soft tissue origin; reticulated myxoid tumor of the tongue; myoepithelioma of the tongue

Clinical

- Uncommon tumor
- No gender predilection; occurs over wide age range including first to eighth decades of life; median age of 32 years
- Asymptomatic, slow-growing, painless, submucosal nodular lesion of the anterior dorsal tongue

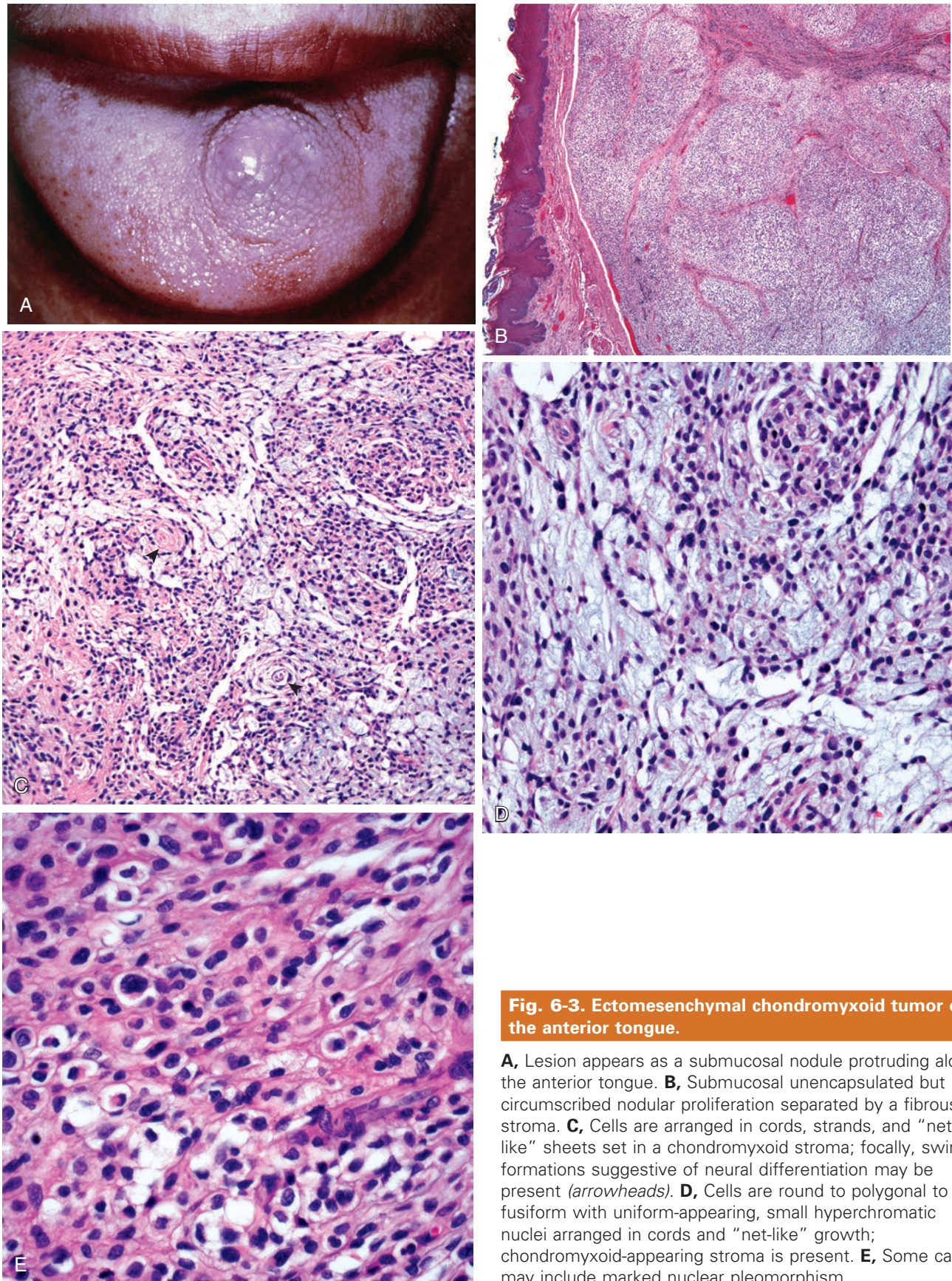


Fig. 6-3. Ectomesenchymal chondromyxoid tumor of the anterior tongue.

A, Lesion appears as a submucosal nodule protruding along the anterior tongue. **B**, Submucosal unencapsulated but circumscribed nodular proliferation separated by a fibrous stroma. **C**, Cells are arranged in cords, strands, and "net-like" sheets set in a chondromyxoid stroma; focally, swirling formations suggestive of neural differentiation may be present (*arrowheads*). **D**, Cells are round to polygonal to fusiform with uniform-appearing, small hyperchromatic nuclei arranged in cords and "net-like" growth; chondromyxoid-appearing stroma is present. **E**, Some cases may include marked nuclear pleomorphism.

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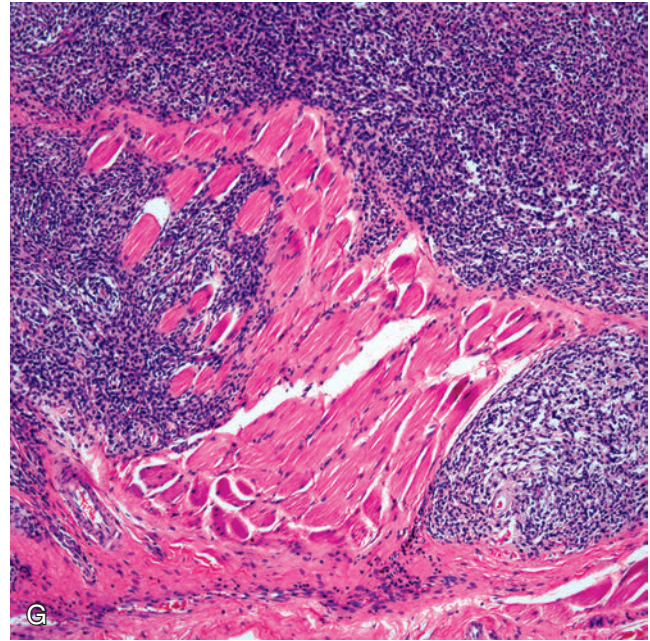
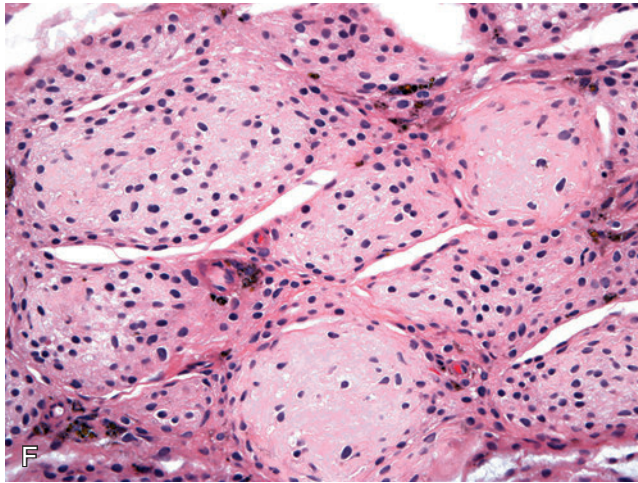


Fig. 6-3, cont'd

F, Nodular foci with chondromyxoid stroma. **G**, Infiltration and entrapment of skeletal muscle may be identified.

Pathology

Gross

- Submucosal nodular growth appearing tan-yellow and measuring from 0.5 to 3 cm in greatest dimension; on cut section has a gelatinous appearance/consistency

Histology

- Submucosal unencapsulated but well-delineated or circumscribed nodule(s) separated by a fibrous stroma
- Cells are round to polygonal to fusiform with uniform-appearing small hyperchromatic nuclei and ample basophilic-appearing cytoplasm.
- Cells may be arranged in cords, strands, and so-called net-like sheets set in a chondromyxoid stroma; hyalinized foci may be present.
- Generally, nuclear pleomorphism, multinucleation, and mitotic figures are not present but in occasional cases hyperchromatic and pleomorphic nuclei as well as mitotic figures may be identified.
- Atypical mitoses and necrosis are not identified.
- Swirling formations suggestive of neural differentiation may be present.
- Absence of glands and/or myoepithelial cells (spindle shaped, plasmacytoid)
- Lesional cells may extend into and/or entrap soft tissue structures, including:
 - Skeletal muscle
 - Nerves

- Histochemistry:
 - Tumor cells:
 - Mucicarmine, periodic acid Schiff with and without diastase negative
 - Extracellular matrix:
 - Alcian blue (pH 0.4 and 2.5) positive
 - Mucicarmine faintly positive
- Immunohistochemistry:
 - Glial fibrillary acidic protein (100%), cytokeratins (>90%), S100 protein (60%), smooth muscle actin (>50%); vimentin positive
 - Epithelial membrane antigen, desmin negative
 - No reports include staining for p63 or calponin.
- Electron microscopy (limited to a single case):
 - Presence of partial basal lamina
 - Absence of desmosomes or thin filaments
- Cytogenetics and molecular genetics:
 - No reported cases with *EWSR1* gene rearrangements as identified in association with soft tissue myoepitheliomas

Differential Diagnosis

- Monomorphic adenoma of salivary glands:
 - Myoepithelioma:
 - Myoepithelioma of the anterior dorsal tongue is rare.
 - Immunohistochemical findings would be compatible with myoepithelial cells, but presence of chondromyxoid stroma and absence of plasmacytoid and/or spindle-shaped myoepithelial

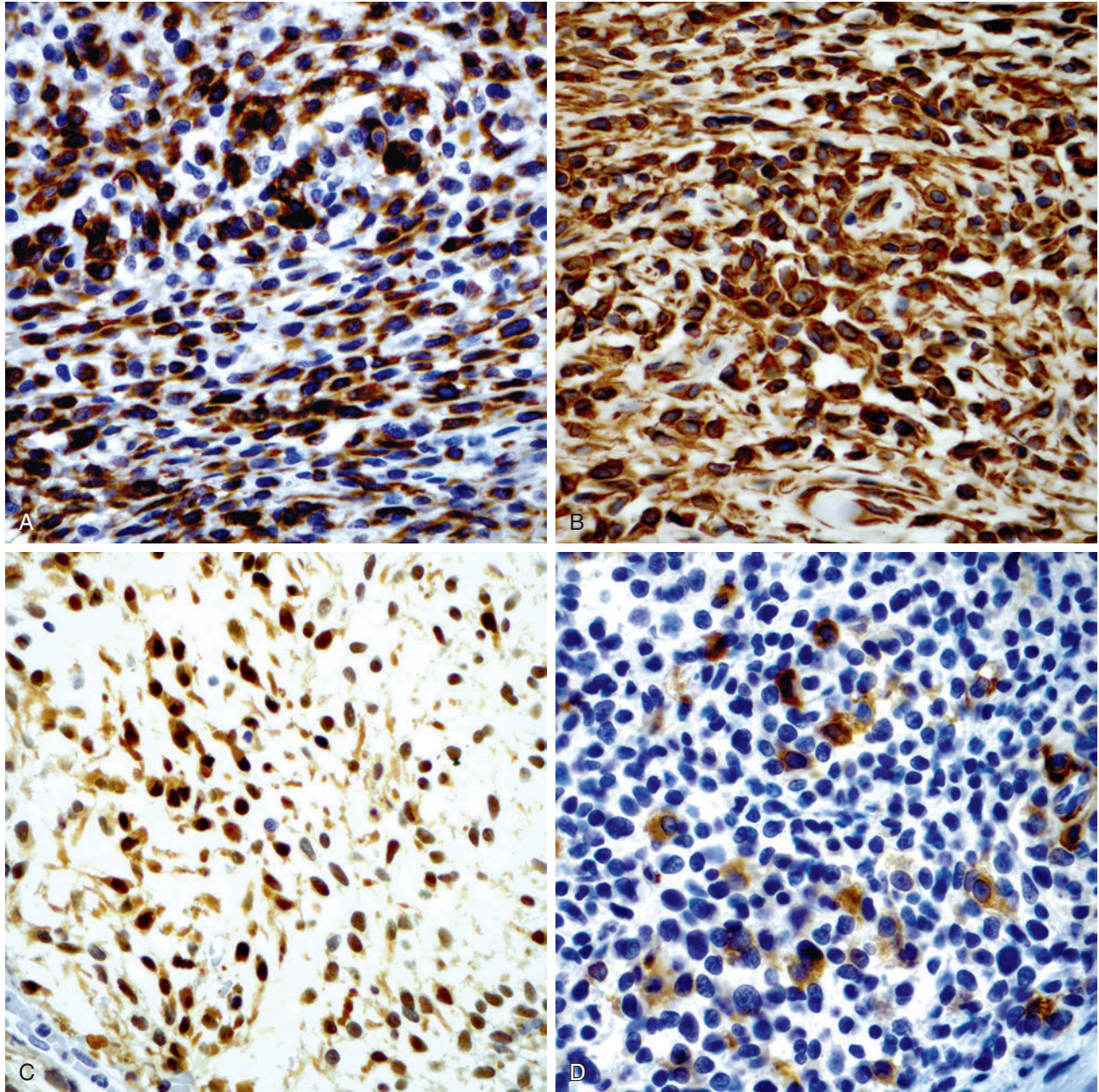


Fig. 6-4. Immunohistochemical reactivity in ectomesenchymal chondromyxoid tumor.

Lesional cells of ectomesenchymal chondromyxoid tumor may show immunoreactivity for (A) GFAP (positive in 100% of cases), (B) cytokeratin, (C) S100 protein, (D) smooth muscle actin.

- cells by light microscopy weigh against this diagnosis.
- Pleomorphic adenoma:
 - Rarity of salivary gland tumors localized to the anterior dorsal tongue and absence of identifiable glandular differentiation by light microscopy weigh against this diagnosis.
- Extraskeletal myxoid chondrosarcoma:
 - Location is rare for chondrosarcomas of any type
 - Presence of cytokeratin and glial fibrillary acidic protein are not features seen in chondrosarcomas.

Treatment and Prognosis

- Conservative but complete excision is curative
- Rarely (<10%) recur; recurrence likely a function of inadequate excision

MESENCHYMAL NEOPLASMS

Benign Peripheral Nerve Sheath Neoplasms

General Considerations

- Benign peripheral nerve sheath tumors include neurilemoma and neurofibroma (see Section 4, Neck).
- Other benign tumors of nerve sheath or presumed peripheral nerve sheath origin include:
 - Granular cell tumor
 - Mucosal neuroma
 - Palisaded encapsulated neuroma (solitary circumscribed neuroma)
 - Dermal nerve sheath myxoma (neurothekeoma) (see Section 4, Neck)
 - Perineurioma (see Section 4, Neck)
- See Section 5, Larynx, for discussion of mucosal granular cell tumor.

Granular Cell Tumor

Definition: Benign tumor of neural (Schwann cell) origin.

- Two forms of granular cell tumor can occur:
 - Mucosal granular cell tumor
 - Congenital granular cell epulis

Mucosal Granular Cell Tumor

- See Section 6, Larynx, for a more complete discussion, including illustrations.

Congenital Granular Cell Epulis

(Fig. 6-5)

Synonyms: Congenital epulis; gingival granular cell tumor of newborn; congenital granular cell myoblastoma.

- Use of the term epulis refers to any mass on the gingiva.

Clinical

- More common in females than males; occurs exclusively in newborns (at or immediately after birth)
- Identified on gum pads in oral cavity on the crest of the alveolar ridge in the incisor region:
 - Localizes to labial aspect of the dental ridge with a predilection of the upper jaw
- Affects the maxilla more often than the mandible but can occur in both locations simultaneously
- Approximately 10% are multiple.



Fig. 6-5. Congenital granular cell epulis.

A, Newborn with a polypoid mass on the anterior mandibular ridge. **B**, Cells are similar to those seen in granular cell tumor but there is a greater degree of vascularity characterized by arborizing capillaries; although not shown, other features that contrast from granular cell tumors include absence of associated pseudoepitheliomatous hyperplasia, incorporation of odontogenic epithelium, absence of S100 protein, and presence of vimentin, neuron-specific enolase, and CD68 immunoreactivity.

- Radiology:
 - May be diagnosed prenatally by ultrasound:
 - Ultrasound examination shows marked blood flow in the tumor.
- Histogenesis:
 - Owing to absence of S100 protein reactivity, this tumor is felt to originate from a non-neural cell of origin but the histogenesis remains uncertain.
 - Some authorities believe it to be a nonneoplastic (hamartomatous) lesion.

Pathology

Gross

- Smooth, pink multilobulated mass ranging in size from millimeters up to 5 cm

Histology

- Similar to granular cell tumor with the following exceptions:
 - Greater degree of vascularity
 - Absence of associated pseudoepitheliomatous hyperplasia
 - Less conspicuous nerve bundles
 - Incorporation of odontogenic epithelium may be seen
 - Absence of S100 protein and laminin immunoreactivity
 - Immunoreactivity for:
 - Vimentin, CD68 (KP1), alpha-1-antitrypsin
 - Smooth muscle differentiation may be present.

Treatment and Prognosis

- Usually require complete surgical excision
- May regress spontaneously

Mucosal Neuroma (Fig. 6-6)

Definition: Benign tumor of nerve sheath origin involving mucosal surfaces of the oral cavity, eyelids, and intestines occurring associated with multiple endocrine neoplasia (MEN) syndrome type 2B.

Synonyms: Multiple endocrine neoplasia 2B-associated mucosal neuroma; oral mucosal neuroma

- MEN 2B (see Section 10 for a more complete discussion):
 - Occurs sporadically or inherited in autosomal dominant manner
 - Caused by germline mutations of *RET* proto-oncogene
 - Characterized by:
 - Medullary thyroid carcinoma
 - Pheochromocytoma
 - Parathyroid proliferative disease (adenoma, hyperplasia)
 - Mucosal neuromas, intestinal ganglioneuromatosis, and musculoskeletal abnormalities

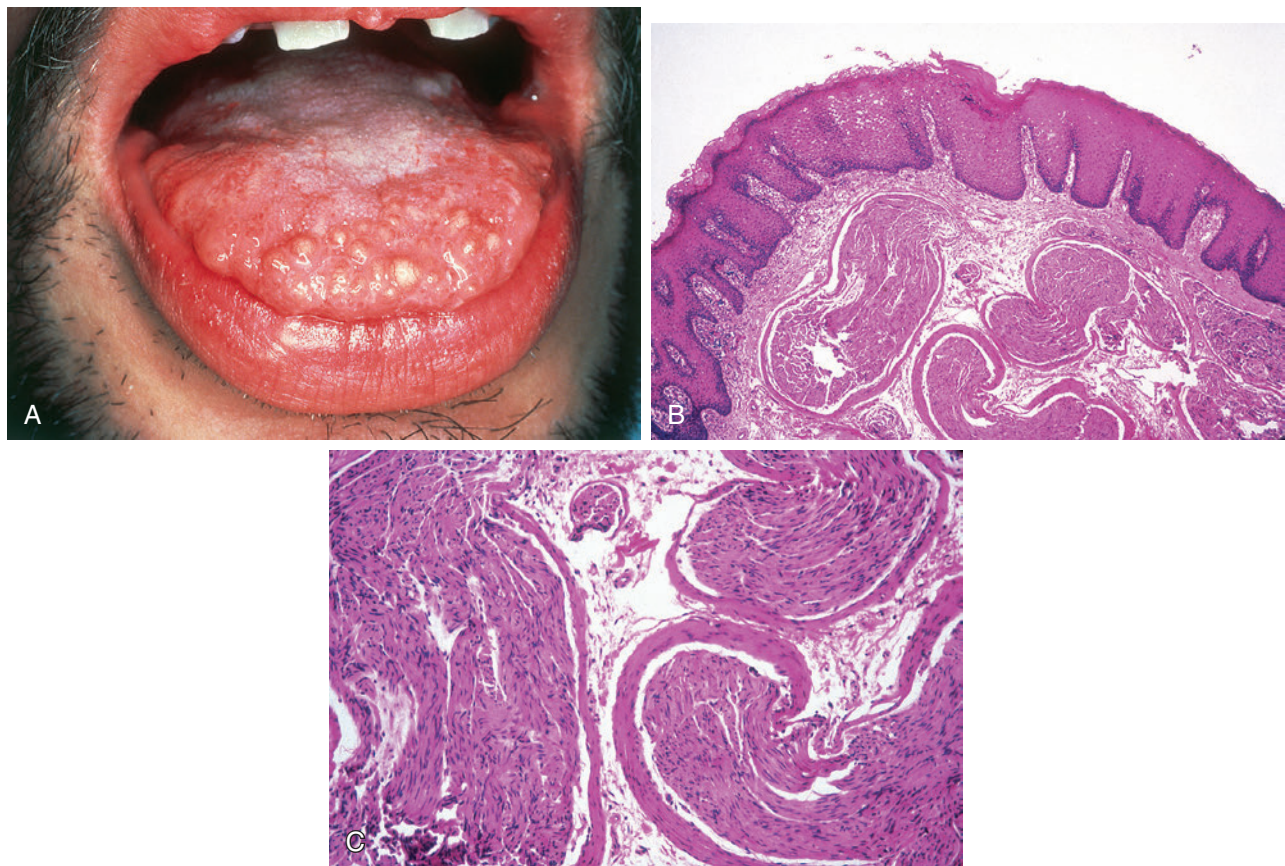


Fig. 6-6. Oral mucosal neuroma.

Oral mucosal neuroma in a patient with multiple endocrine neoplasia (MEN) syndrome type 2B. **A**, Multiple nodules of the anterior tongue. **B** and **C**, Submucosal proliferation of irregular tortuous bundles of nerves with prominent perineurium.

Clinical

- Slightly more common in females than males; noted at birth or during first few years of life
- Common sites of involvement include lips, tongue, and eyelids:
 - Oral cavity:
 - Vermilion border of the lips, anterior third of the ventral or dorsal tongue, buccal mucosa
 - Ocular:
 - Eyelids
- Clinical appearance includes the presence of multiple small, sessile, mucosal-covered nodules.

Pathology

Histology

- Polypoid, dome-shaped, or diffuse submucosal proliferation of numerous irregular tortuous, highly branched and loosely arrayed nerves of varying size with prominent perineurium and presence of focal myxoid change:
 - Perineurium of affected nerve is thickened.
 - Mucoïd or myxoid endoneurial matrix may separate nerve fibers.
 - Reactive perineurial fibrosis not a feature.
 - Absence of ganglion cells (present in intestinal ganglioneuromatosis, noted in cases of mucosal neuromas of lingual and ciliary nerves and lesions in the roof of the iris and uveal meshwork)
- Immunohistochemistry:
 - S100 protein positive (Schwann cells)
 - Neurofilament protein positive (axons)

Differential Diagnosis

- Traumatic (amputation) neuroma:
 - Exuberant, non-neoplastic proliferation of nerves occurring in response to injury or surgery
 - Presents as firm nodule occasionally tender or painful
 - Circumscribed nodule(s) located in continuity with proximal end of injured or transected nerve
 - Unencapsulated lesion consisting of haphazard proliferation of nerve fascicle including axons Schwann cells and fibroblasts:
 - Less well-myelinated than parent nerve
 - Enveloped in collagen
 - May be embedded in mucoïd matrix
 - Immunoreactivity present for neurofilament protein (axons), S100 protein (Schwann cells), and EMA (perineurial cells)
- Plexiform neurofibroma
- Palisaded encapsulated neuroma (solitary circumscribed neuroma) (Fig. 6-7):
 - Distinct form of true neuroma consisting of Schwann cells as well as axons within a perineurial-derived capsule

- No association with NF-1 or MEN 2B
- Usually a cutaneous lesion
- May occur in the oral cavity (palate, lips)
- Small asymptomatic solitary circumscribed nodule
- No gender predilection; occurs in adults
- Histology:
 - Submucosal circumscribed nodular or multinodular, solid proliferation of Schwann cells lacking stromal alterations, including hyalinization or myxoid change often associated with schwannomas or neurofibromas
 - Most are small, measuring approximately 3 mm, and localized to the reticular dermis or submucosa.
 - In spite of its description most do not show “palisading” and are not encapsulated but often are incompletely encapsulated.
 - Composed of bland-appearing spindle cells set in a variably fibrous stroma and focally separated by artifactual clefts or cracking artifact:
 - Clefts or cracks likely related to fixation
 - Surrounds or results in slit-like spaces between cell bundles
 - Schwann cells are diffusely and strongly S100 protein positive.
 - Presence of axons traverse the lesion in close association with Schwann cells:
 - Not evident on hematoxylin and eosin staining
 - Best seen with silver stains
 - May be highlighted by neurofilament protein (NFP) immunostaining
- Simple surgical excision is curative.

Treatment and Prognosis

- Surgical excision may be performed for cosmetic purposes.
- Diagnosis should prompt work-up for possibility of MEN 2B:
 - Early diagnosis of MEN 2B, especially evaluation for the possibility of medullary thyroid carcinoma, allows for initiation of earlier treatment.

BENIGN FIBROUS TUMORS

Fibromatosis/Extraabdominal Fibromatoses

Definition: Locally aggressive, nonmetastasizing (myo) fibroblastic neoplasm characterized by locally infiltrative growth.

Synonyms: Desmoid-type fibromatosis; desmoid tumor; aggressive fibromatosis; extraabdominal desmoid, extraabdominal fibromatosis; tumefactive fibroinflammatory tumor; inflammatory pseudotumor

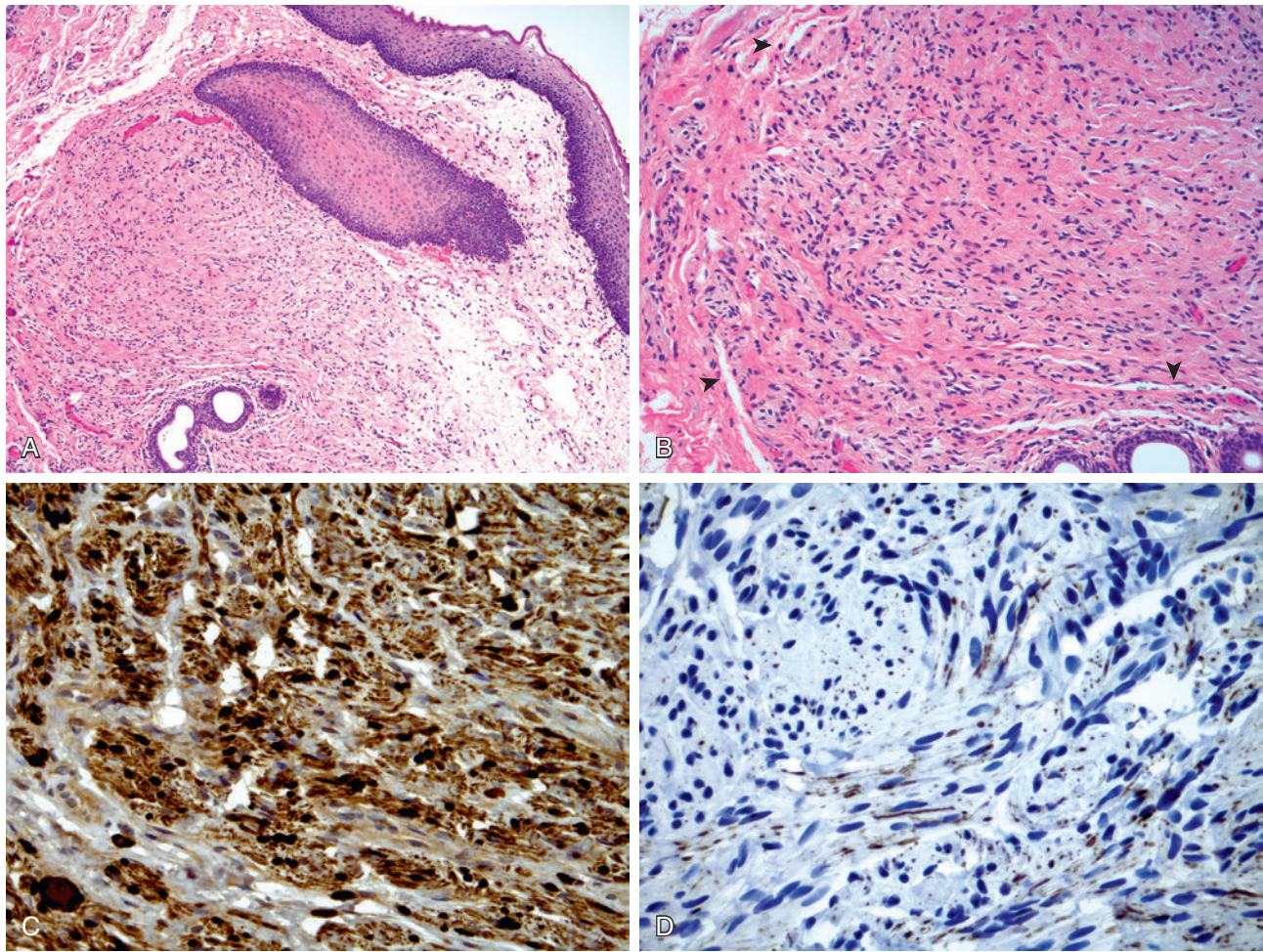


Fig. 6-7. Palisaded encapsulated neuroma (solitary circumscribed neuroma).

A, Submucosal circumscribed but not encapsulated nodular, solid proliferation of Schwann cells. **B**, Bland-appearing spindle cells set in a variably fibrous stroma and focally separated by artifactual clefts or cracking artifact (*arrowheads*). **C**, Diffuse and strong S100 protein staining. **D**, Neurofilament protein (NFP) immunostaining highlights axons traversing the lesion in close association with Schwann cells.

- See Section 5, Neck, for a more complete discussion.
- Fibromatosis of the head and neck region occurs primarily in the soft tissues of the neck, including the supraclavicular region and the anterolateral neck.
- Excluding the neck, the common sites of occurrence are the sinonasal tract, nasopharynx, tongue, and oral cavity.
- Approximately 10% to 15% of fibromatoses occur in the head and neck; in children, more than one third of cases occur in the head and neck.

Myofibroma and Myofibromatosis (Fig. 6-8)

Definition: Benign neoplasm composed of myoid cells arranged around thin-walled blood vessels.

- Two types:
 - Solitary (myofibroma)
 - Multicentric (myofibromatosis)
- Synonym:** Infantile myofibromatosis

Clinical

- Myofibromas:
 - Most common type occurring three times more often than multicentric form
 - More common in males than females; occurs over a wide age range, including infants and adults but represents the type most commonly seen in adults
 - Tend to occur in the head and neck region:
 - Most common in bone (mandible and skull) followed by the oral cavity, especially the buccal mucosa and tongue; less common intra-oral sites of involvement include the gingival, palate, lip, retromolar trigone

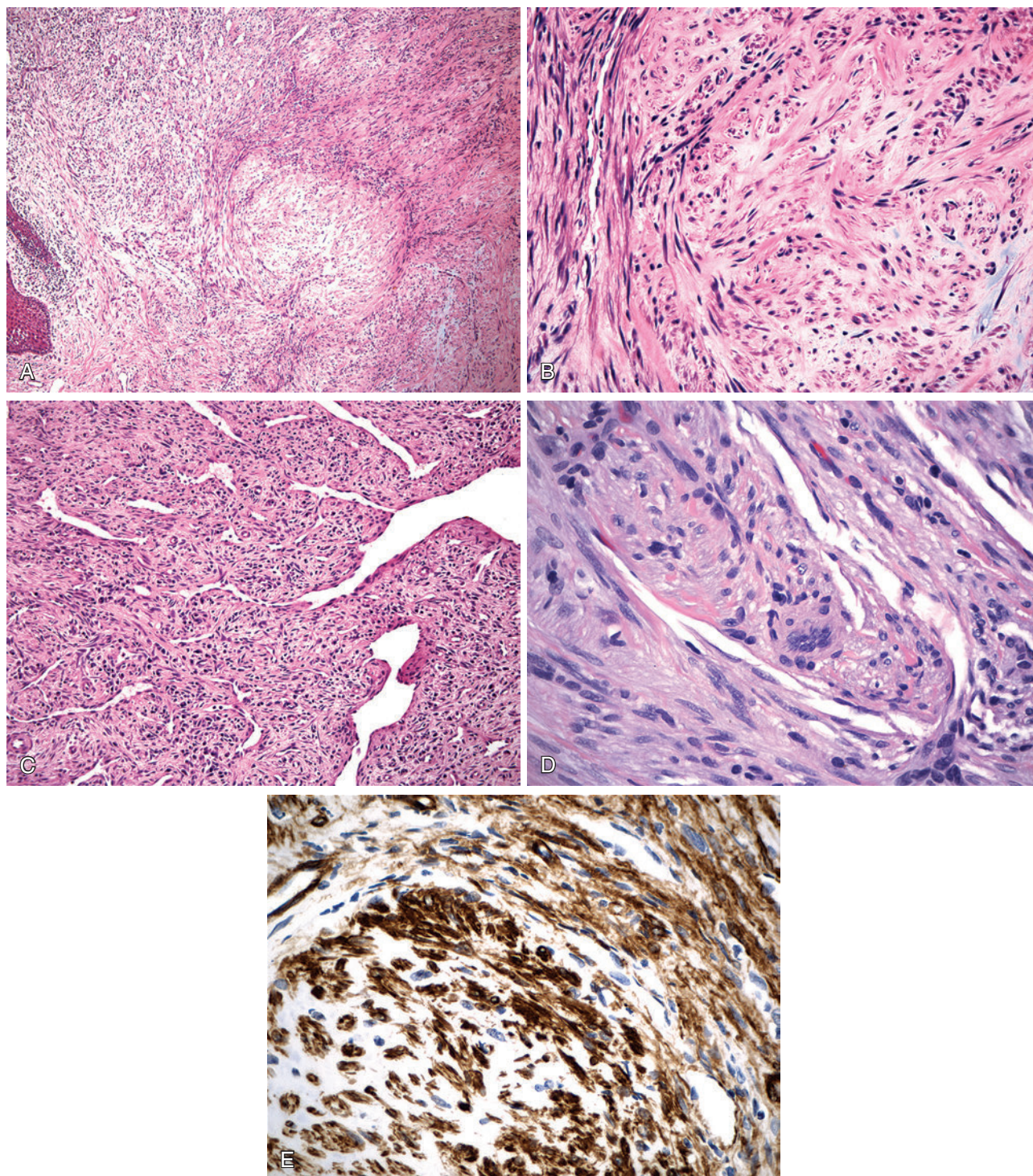


Fig. 6-8. Oral myofibroma.

A, Submucosal nodular growth. **B**, Nodule composed of spindle-shaped cells with elongated, cigar-shaped vesicular nuclei arranged in short fascicle at periphery with round cells having round to polygonal to spindle-shaped hyperchromatic nuclei and scant eosinophilic cytoplasm more centrally located. **C**, Irregularly branching blood vessels similar in appearance to those associated with hemangiopericytoma. **D**, Subendothelial intravascular growth. **E**, Diffuse immunoreactivity for smooth muscle actin.

- May rarely involve other head and neck sites, including sinonasal tract and neck
- Presents as a painless mass usually measuring less than 3 cm
- Myofibromatosis may occur with or without visceral involvement:
 - Without visceral involvement:
 - More common in males than females; majority (up to 90%) occurs within the first 2 years of life with many presenting at birth
 - Sites of involvement include skin, subcutis, soft tissue, and bone:
 - Multiple lesions may be limited to a single general anatomic site (e.g., only head and neck) or may be generalized in distribution
 - Absence of visceral involvement
 - Presents as a painless mass usually measuring less than 3 cm
 - Possible but not definitive for familial inheritance
 - With visceral involvement:
 - Up to 40% have visceral involvement
 - More common in males than females; majority (up to 90%) occur within the first 2 years of life with many presenting at birth
 - Sites of involvement include skin, subcutis, soft tissue, and bone as well as visceral involvement, the latter including:
 - Lungs, heart, gastrointestinal tract, liver, kidney, pancreas, and rarely central nervous system
 - Present with symptoms related to the organs involved
 - Possible but not definitive for familial inheritance
- Radiology:
 - Osseous lesions appear as circumscribed radiolucent lesions often with sclerotic margin
 - Central mineralization may be present.
- Familial occurrence has been reported:
 - Inherited in autosomal dominant manner
- Peripheral (light staining) zone composed of plump-appearing, spindle-shaped cells with elongated, cigar-shaped vesicular nuclei, small nucleoli, and pale pink cytoplasm; cells are arranged in short fascicles or whorls
- Central (dark staining) zone composed of primitive-appearing round cells with round to polygonal to spindle-shaped, vesicular to hyperchromatic nuclei, and scant eosinophilic to clear cytoplasm arranged around thin-walled, irregularly branching blood vessels showing features similar to the vascularity seen in hemangiopericytomas
- No significant pleomorphism or increase in mitotic activity
- Extensive coagulative necrosis may be identified.
- Hemorrhage, cystic degeneration, calcification, and stromal hyalinization may be focally present.
- Intravascular growth is frequently present:
 - Subendothelial location
 - No prognostic significance
- Peripherally located chronic inflammatory cells, including lymphocytes and plasma cells, may be present.
- Immunohistochemistry:
 - Vimentin positive
 - Actins (smooth muscle and muscle specific) focally and weakly positive
 - S100 protein, desmin, and epithelial markers are negative.
 - Proliferation rate indices of up to 10% seen by Ki67 (MIB1) staining
- Electron microscopy:
 - Findings compatible with myofibroblasts, including prominent rough endoplasmic reticulum, intracytoplasmic filament bundles with dense bodies, and focal basal lamina
- Cytogenetics and molecular genetics:
 - Absence of *ETV6-NTRK3* gene fusion that is identified in infantile fibrosarcoma

Pathology

NOTE: Pathologic findings remain similar, whether solitary or multifocal.

Gross

- Well-circumscribed, rubbery to firm, gray-white to tan-brown mass ranging in size from 0.5 to 7 cm with a median size of 2.5 cm
- Degenerative changes may be present, including cyst formation, hemorrhage, and necrosis.

Histology

- Nodular or multinodular growth with characteristic biphasic or “zoning” appearance due to regional variation of cell types, including:

Differential Diagnosis

- Fibromatosis
- Nodular fasciitis
- Smooth muscle neoplasms (leiomyoma, leiomyosarcoma)
- Sarcomas:
 - Due to increased cellularity, rich vascularity, and presence of necrosis, myofibromas/myofibromatosis may be mistaken for a sarcoma.

Treatment and Prognosis

- Spontaneous regression may occur in solitary or multifocal (without visceral involvement) lesions.
- Simple excision of solitary lesions is curative.
- Surgical resection of multiple lesions may be indicated in cases in which there is functional impairment or involvement of vital organs.

- Recurrence rates after surgery usually are less than 10% of cases.
- Prognosis less favorable in newborns and infants with multiple visceral lesions:
 - Increased morbidity and mortality:
 - Mortality rates >70% reported
 - Death may be due to cardiopulmonary or gastrointestinal complications.
 - Low-dose chemotherapy (methotrexate and vinblastine) may be effective in treating patients with multicentric visceral involvement.

BENIGN VASCULAR TUMORS

- See Section 1 on the Sinonasal Tract for a more complete discussion.
- May include a variety of hemangioma subtypes, including capillary, cavernous, mixed capillary-cavernous
- Majority occurs in adults
- Most common sites of occurrence include lips, buccal mucosa, and tongue.
- These tumors may be mucosal based or within muscle (intramuscular) or bone (intraosseous).

BENIGN LIPOGENIC TUMORS

- Benign lipogenic tumors of the oral cavity are uncommon.
- See Sections 4, Neck, and 5, Larynx and Trachea, for discussion.

BENIGN MYOGENIC TUMORS

- Benign myogenic tumors of the oral cavity are uncommon and include tumors of smooth muscle differentiation (leiomyomas) and skeletal muscle differentiation (rhabdomyomas).
- For leiomyoma see Section 1, Sinonasal Tract.
- For rhabdomyoma see Section 4, Neck.

BENIGN FIBROHISTIOCYTIC TUMORS

- Benign fibrohistiocytic tumors of the oral cavity are uncommon and include fibrous histiocytoma; see Section 1, Sinonasal Tract.

BENIGN FIBRO-OSSEOUS LESIONS OF CRANIOFACIAL BONES (Table 6-1)

- Gnathic (jaw bones) benign fibro-osseous lesions include ossifying fibromas (and variants thereof) and fibrous dysplasia.

- Fibrous dysplasia is not a neoplastic lesion but is included here as part of the broader category of benign fibro-osseous lesions.
- Gnathic fibro-osseous lesions (ossifying fibroma and fibrous dysplasia) may be histologically indistinguishable; therefore a definitive diagnosis may not be achievable on morphology alone, and the diagnosis rests on the clinical-radiologic-histopathologic correlation.
- In the head and neck, benign fibro-osseous lesions occur most often in relation to gnathic (maxillary and mandibular) bones.
- Given its localization to the sinonasal tract, psammomatoid ossifying fibroma is discussed in Section 1, Sinonasal Tract.

Ossifying Fibroma (Fig. 6-9 and 6-10)

Definition: Well-demarcated, slow-growing benign fibro-osseous neoplasm composed of fibrocellular tissue admixed with varying amounts of mineralized material (i.e., bone, cementum) of varying appearances.

Synonyms: Cemento-ossifying fibroma; cementifying fibroma; central intraosseous ossifying fibroma; fibrous osteoma; osteofibroma

Clinical

- More common in women than men; occurs over a wide age range but is most frequently seen in the second to fourth decades of life
- Most common site of occurrence is the mandible, especially molar or posterior area followed by the premolar area, incisor area, and cuspid area
 - May also occur in association with the maxilla, but maxillary involvement occurs much less often as compared with the mandibular region
- Generally asymptomatic unassociated with pain or swelling and diagnosed incidentally after radiographic examination; symptomatic tumors manifest by displacement of teeth or as an expansile mass that may include facial asymmetry.
- Typically presents as solitary mass but infrequently may be multifocal:
 - Multifocal tumors can occur in the mandible, in the maxilla, or in both regions.
 - Polyostotic involvement of extragnathic bones as seen in fibrous dysplasia is not a finding associated with ossifying fibromas.
- Radiology:
 - Well-circumscribed lesion with smooth contours having a variation in appearance based on the maturity of the tumor, including:
 - Completely radiolucent:
 - Immature lesion
 - Completely radiopaque:
 - Mature lesion

TABLE 6-1 Benign Fibro-osseous Lesions: Clinicopathologic Comparison

	OF	POF	FD
Gender/age	F > M; 2nd-4th decades	F = M; younger age groups (1st-2nd decades), but may occur in older individuals	MFD: F = M; 2nd-3rd decades PFD: F > M; 1st decade
Location	Most common in the mandible (posterior or molar region)	Ethmoid sinus; supraorbital frontal region	No specific site of involvement
Focality	Single site	Single site or involvement of multiple (contiguous) sites/sinuses	MFD (75%-80%) PFD (20%-25%) MAS (1%-3%)
Radiology	Well-circumscribed or sharply demarcated lesion with smooth contours	Lytic or mixed lytic/radiopaque osseous and/or soft tissue mass varying from well demarcated to invasive with bone erosion	Poorly defined expansile osseous lesion with a thin intact cortex; predominantly fibrous lesions are radiolucent; predominantly osseous lesions are radiodense; lesions with an equal admixture of fibrous and osseous components have a ground glass appearance
Histology	Randomly distributed mature (lamellar) bone spicules rimmed by osteoblasts admixed with a fibrous stroma; central portions may be woven bone with lamellar bone at the periphery	Bony spicules and distinctive mineralized or calcified "psammomatoid" bodies or ossicles admixed with a fibrous stroma; psammomatoid bodies vary from a few in number to a dense population of innumerable spherical bodies; osteoclasts are present within the ossicles, and osteoblasts can be seen along their peripheral aspects; the bony trabeculae vary in appearance and include odd shapes with a curvilinear pattern; trabeculae are composed of lamellar bone with associated osteoclasts and osteoblastic rimming.	Fibrous tissue component is nondescript and of variable cellularity; osseous component includes irregularly shaped trabeculae of osteoid and immature (woven) bone that is poorly oriented with misshapen bony trabeculae with odd geometric patterns including C- or S-shaped configurations; the trabeculae typically lack osteoblastic rimming
Syndromes	No known association	No known association	MAS (1% to 3%)
Treatment	Surgical resection	Surgical resection	Disease may stabilize at puberty and, in children, therapy should be delayed if possible until after puberty; surgical resection indicated in cases with compromise of function, progression of deformity, associated pathologic fracture(s), or the development of a malignancy
Prognosis	Excellent	Good after complete excision; recurrence(s) often occurs due to incomplete excision; may behave in an aggressive manner with local destruction and potential invasion into vital structures	Good prognosis; recurrence rates are low and death due to extension into vital structures rarely occurs
Malignant transformation	Not known to occur	Not known to occur	Malignant transformation (osteosarcoma) occurs in less than 1%; dismal prognosis

FD, Fibrous dysplasia; MAS, McCune-Albright syndrome; MFD, monostotic fibrous dysplasia; OF, ossifying fibroma; PFD, polyostotic fibrous dysplasia; POF, psammomatoid ossifying fibroma.

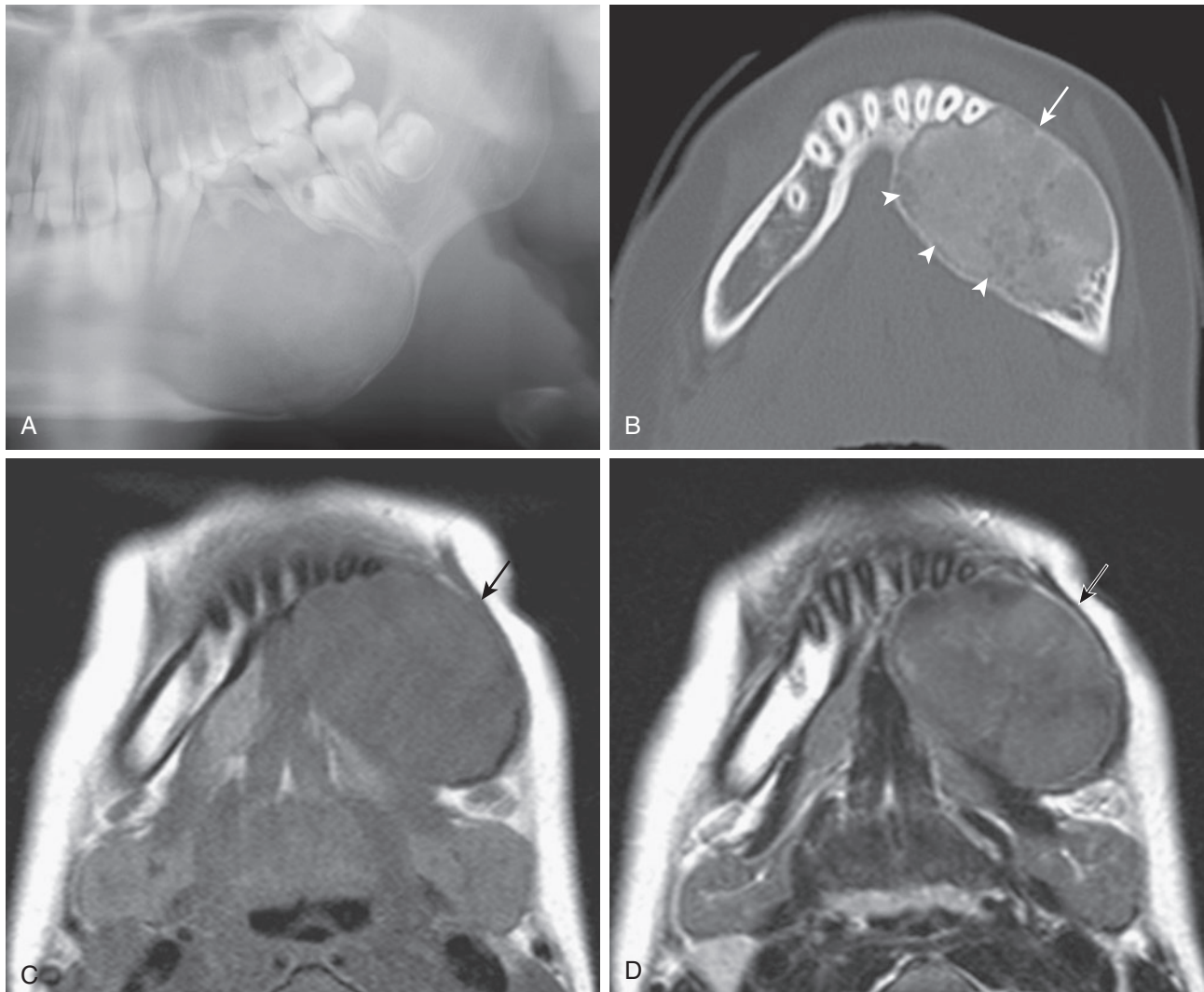


Fig. 6-9. Ossifying fibroma in the mandible.

A, Pantomogram of the mandible. **B**, Axial CT image shows a homogeneous radiopaque internal structure (*arrow*) and radiolucent band at the periphery (*arrowheads*). **C**, Axial T1-weighted MR image shows an intermediate signal intensity. **D**, Axial T2-weighted MR image shows a heterogeneous intermediate signal intensity. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-62, p 1509.)

- Mixed radiolucent and radiopaque:
 - Increased mineralization with age results in radiopaque foci admixed with radiolucent areas
- Presumptive origin is from the periodontal ligament, which:
 - Is a layer of fibrous connective tissue surrounding and attaching the roots of teeth to alveolar bone
 - Is capable of forming cementum, bone, and fibrous tissue
 - Supports close relationship to cementifying fibroma and cemento-ossifying fibroma; in fact, all of these lesions are considered variants of ossifying fibroma

Pathology

Gross

- Well-demarcated, tan/gray to white, gritty and firm lesions varying in size from 0.5 to as large as 10 cm

Histology

- Well-delineated, demarcated, or encapsulated proliferation composed of randomly distributed mature (lamellar) bone spicules rimmed by osteoblasts admixed with a fibrous stroma
- Although the osseous component is generally described as mature, the central portions may be woven bone with lamellar bone at the periphery.

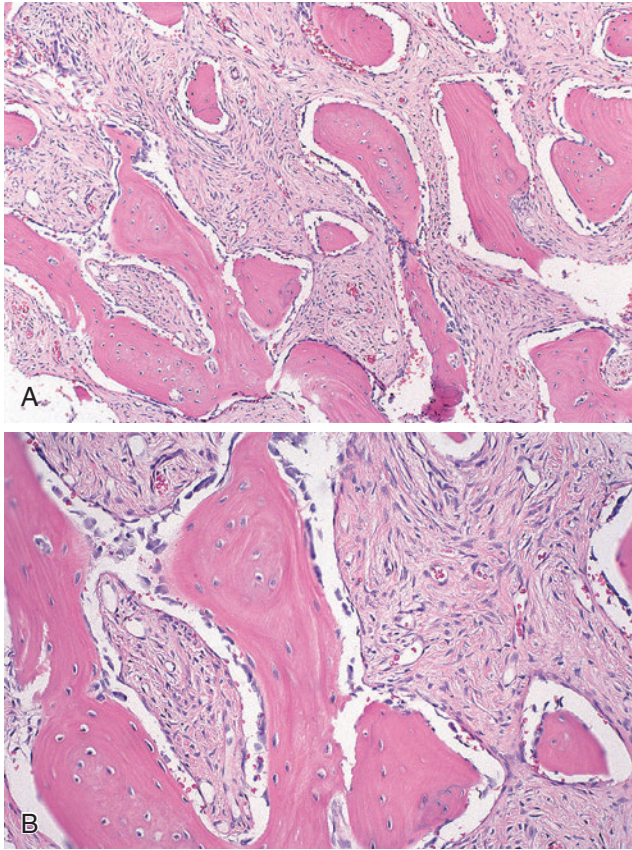


Fig. 6-10. Ossifying fibroma.

Histologically, ossifying fibroma is characterized by an admixture of mature (lamellar) bone and a fibrous stroma; bony spicules are rimmed by osteoblasts. The fibrous stroma is similar to that seen in fibrous dysplasia. Although these features support a diagnosis of ossifying fibroma, there are overlapping features with fibrous dysplasia so that clinical and radiologic correlation is required in rendering a diagnosis.

- Complete bone maturation is seldom seen.
- Fibrous stroma may be densely cellular; mitotic figures are rare to absent.
- Secondary changes, including hemorrhage, inflammation, and giant cells, may be seen.
- Lesions with associated cementum are referred to as cementifying fibroma and those lesions with cementum and bone are referred to as cemento-ossifying fibroma:
 - Cementum is mineralized material covering the surface of roots of teeth.
 - There is no clinical relevance in distinguishing cementum from bone.
- Immunohistochemistry:
 - Reactivity for osteocalcin:
 - Weak in ossifying fibroma
 - Strong throughout calcified regions in fibrous dysplasia

- Cytogenetics and molecular genetics:
 - Guanine nucleotide-binding protein/ α -subunit (GNAS) mutational analysis by PCR reported to be:
 - Absent in ossifying fibromas, cemento-ossifying fibromas, and cemento-ossifying dysplasias:
 - Also reported to be absent in odontogenic myxomas
 - Present in fibrous dysplasia

Differential Diagnosis

- Primarily with fibrous dysplasia (see below and Table 6-1)
 - Differentiation of ossifying fibroma from fibrous dysplasia is important because the therapeutic rationale differs for these lesions.

Treatment and Prognosis

- Surgical excision is the preferred treatment:
 - Well-circumscribed nature of this lesion allows for relatively easy removal.
- Prognosis is excellent after complete excision.
- Recurrences are rare.

Peripheral Ossifying Fibroma

- Represents an oral mucosal or soft tissue (nonintraosseous) ossifying fibroma:
 - Similar to intraosseous (central) ossifying fibroma; also presumably arises from periodontal ligament
- Believed to represent a reactive process rather than a neoplastic proliferation
- More common in women than in men; most common in the second decade of life
- Unique to gingival mucosa:
 - Majority occurs anterior to molar region, equally affecting mandible and maxilla.
- Presents as firm, sessile to pedunculated mass measuring up to 1 cm in greatest dimension:
 - Overlying epithelium may be intact and smooth in appearance or ulcerated.
- Histology includes:
 - Unencapsulated cellular lesion composed of connective tissue, plump-appearing fibroblasts with large, round to oval vesicular nuclei and mineralized material, the latter including interlacing trabeculae of bone or osteoid, calcification, or spherules of cementum
 - Multinucleated giant cells associated with bone and calcified material may be present.
 - Chronic inflammatory cell infiltrate may be present along the periphery of the lesion.

- Complete surgical resection is the preferred treatment, often requiring excision of the lesion as well as the periodontal ligament and periosteum:
 - Tooth extraction is not usually required.
- Up to 20% of cases may recur.

Fibrous Dysplasia (Figs. 6-11 and 6-12)

Definition: Idiopathic nonneoplastic bone disease in which normal medullary bone is replaced by structurally weak fibro-osseous tissue.

- Three variants are identified: monostotic, polyostotic, polyostotic with endocrinopathy (McCune-Albright syndrome).

Monostotic Fibrous Dysplasia

- Only a single osseous site is involved.
- Represents greater than 75% to 80% of all cases
- Frequently occurs in older children and young adults
- Most commonly affects ribs, femur, and tibia
 - Involves head and neck bones in up to 25% of cases:
 - In head and neck most common sites of involvement include maxilla (zygomatic process) > mandible (region of premolar and molar teeth)

> frontal bone > ethmoid and sphenoid bones
> temporal bone

Polyostotic Fibrous Dysplasia

- Involvement of two or more bones
- Represents approximately 20% to 25% of all cases
- May be limited to a few bones in one anatomic region or may be diffuse, affecting virtually every bone in the skeleton
- In greater than half the cases osseous involvement includes the long bones of the extremities, pelvic bones, ribs, metacarpals, metatarsals, and the humerus:
 - Craniofacial or jaw regions are included in up to 50% of patients.

Polyostotic with Endocrinopathy or McCune-Albright Syndrome

- Triad includes:
 - Polyostotic fibrous dysplasia
 - Endocrine dysfunction:
 - Hyperthyroidism and/or sexual precocity, the latter predominantly identified in females
 - Cutaneous hyperpigmentation

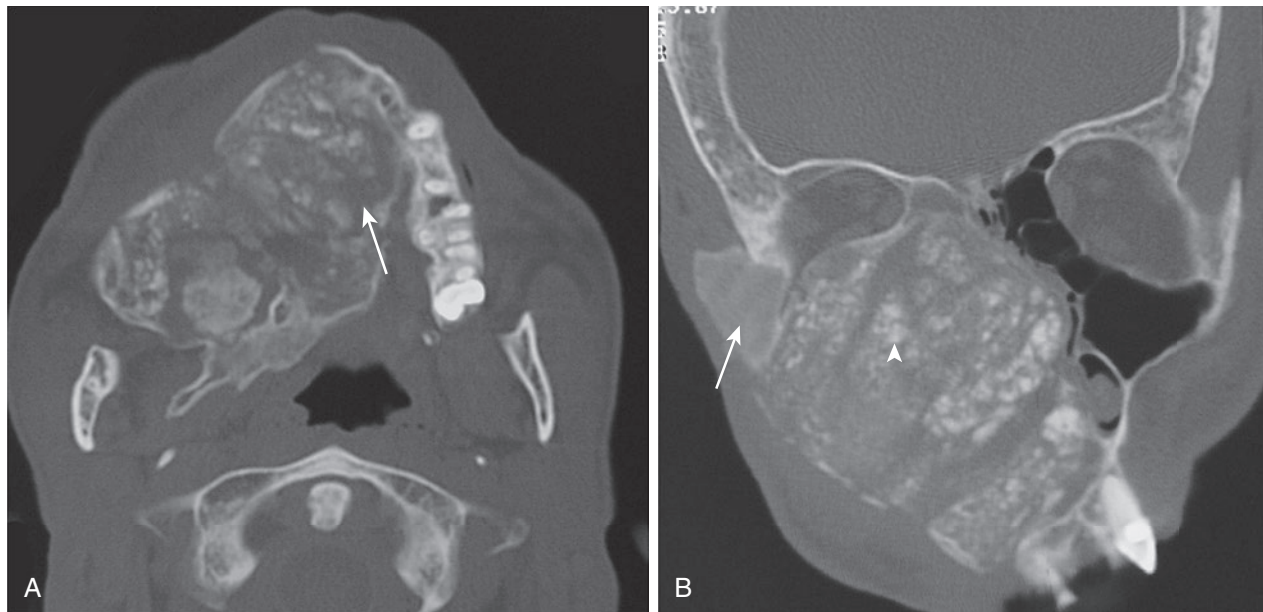


Fig. 6-11. Fibrous dysplasia of the maxilla.

There is gross expansion of the maxilla. The lesion contains multiple consistencies including soft tissue, bone, and perhaps cartilage. **A**, Axial image with multiple punctate areas of mineralization (*arrow*). The low density may represent fibrous tissue or a cystic component. **B**, Coronal image shows small foci of calcifications (*arrowhead*) that may represent chondroid matrix. This makes differentiation from chondrosarcoma difficult. The lateral part of the abnormality (*arrow*) has a typical “ground glass” appearance. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-55, p 1506.)

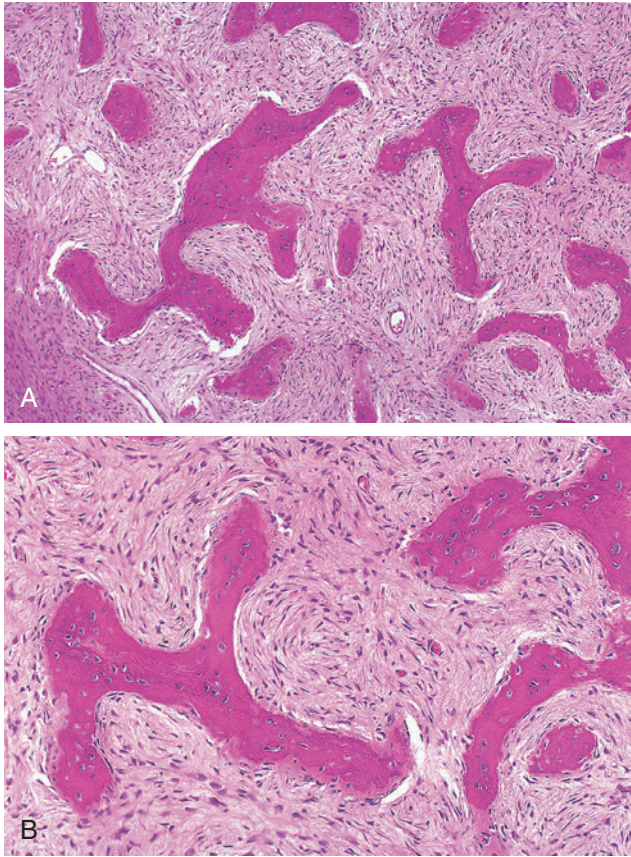


Fig. 6-12. Fibrous dysplasia.

Histologically, fibrous dysplasia is characterized by proliferation of fibrous tissue and osseous components; the osseous component includes immature (woven) bone, in which the trabeculae form odd geometric patterns ("Chinese" characters) and typically lack osteoblastic rimming; the fibrous tissue component is nondescript without pattern and of variable cellularity.

- Least common variant representing approximately 1% to 3% of all cases

General Clinical Features

- Monostotic type:
 - No gender predilection or slightly more common in women
- Polyostotic type:
 - More common in women than men
- Regardless of type, majority of patients affected are under 30 years of age, although older individuals may be affected:
 - In monostotic type most common in second to third decades of life
 - In polyostotic type and McCune-Albright syndrome tend to occur in the first decade of life

- Craniofacial symptoms include:
 - Painless, asymmetric, nonmobile swelling associated with functional disturbances
 - Displacement or malocclusion of teeth, failure of tooth eruption in children
 - Headaches, proptosis, nasal obstruction, especially for sinonasal tract lesions
 - Hearing loss (conductive)
- Laboratory findings:
 - Serum calcium and phosphorous levels are normal; alkaline phosphatase may be elevated.
- May be associated with:
 - Oncogenic osteomalacia
 - Cholesteatoma
- Radiology:
 - Poorly defined expansile osseous lesion with a thin intact cortex
 - Predominantly fibrous lesions are radiolucent.
 - Predominantly osseous lesions are radiodense.
 - Equal admixture of fibrous and osseous components results in a ground glass appearance.
 - Usually no periosteal reaction is seen unless there is an associated fracture.
- Cause remains unknown:
 - No familial or hereditary origin
 - Cherubism is congenital form of fibrous dysplasia:
 - Autosomal dominant disease with variable expressivity
 - Characterized by lateral swelling of the jaws:
 - Bilateral symmetric involvement is almost pathognomonic.
 - Usually involves the mandible with the ramus always involved.
 - Patients have characteristic upturned appearance of the eyes, resulting in a cherubic expression.
- Rarely may be associated with soft tissue myxomas referred to as Mazabraud syndrome:
 - Defined as combination of one or more intramuscular myxomas and fibrous dysplasia of bone
 - Association is more common with polyostotic fibrous dysplasia and McCune-Albright syndrome
 - Myxomas tend to appear years (decades) after bone lesions
 - Soft tissue myxomas most common in the thigh (intramuscular)
 - Often multiple and tend to occur near to abnormal bones
 - These patients are at increased risk for malignant transformation:
 - Risk is greater than in those with fibrous dysplasia alone
 - Risk increases when patient has both McCune-Albright and Mazabraud syndromes

Pathology

Gross

- Tan-white to yellow, soft, rubbery, gritty, or firm tissue
- Thin cortex

Histology

- Fibrous tissue component is nondescript and of variable cellularity
- Osseous component includes:
 - Irregularly shaped trabeculae of osteoid and immature (woven) bone arising metaplastically from fibrous stroma
 - Poorly oriented with misshapen bony trabeculae, increased cellularity, and irregular margins and forms odd geometric patterns including C- or S-shaped configurations, so-called Chinese characters
 - Trabeculae typically lack osteoblastic rimming.
- Multinucleated giant cells, macrophages, increased vascularity, and calcification may be seen.
- Under polarized light bone appears woven rather than lamellar; however, lamellar bone can be seen in fibrous dysplasia, and its presence does not exclude the diagnosis.
- Immunohistochemistry:
 - Reactivity for osteocalcin:
 - Strong throughout calcified regions in fibrous dysplasia
 - Weak in ossifying fibroma
- Cytogenetics and molecular genetics:
 - Guanine nucleotide-binding protein/ α -subunit (GNAS) mutational analysis by PCR showed:
 - Presence in fibrous dysplasia
 - Absence in ossifying fibromas, cemento-ossifying fibromas, and cemento-ossifying dysplasias
 - Also reported to be absent in odontogenic myxomas

Differential Diagnosis

- Ossifying fibroma (see [Table 6-1](#)):
 - Gnathic fibro-osseous lesions (fibrous dysplasia and ossifying fibromas) may be histologically indistinguishable; therefore the diagnosis and differentiation rest on the clinical–radiologic–histopathologic correlation.
 - Differentiation of ossifying fibromas from fibrous dysplasia is important because the therapeutic rationale differs for these lesions.

Treatment and Prognosis

- Conservative surgical excision is the preferred treatment and is indicated only in cases with compromise of function, progression of deformity, pain,

associated pathologic fracture(s), or the development of a malignancy.

- Disease may stabilize at puberty and, in children, therapy should be delayed if possible until after puberty.
- Radiation treatment is not used because of the risk of inducing malignant change.
- Recurrence rates are low and death due to extension into vital structures rarely occurs.
- Malignant transformation:
 - Occurs in less than 1% of cases but is most feared complication
 - When it occurs is most often an osteosarcoma > chondrosarcoma > fibrosarcoma:
 - Also associated with angiosarcoma, Ewing sarcoma, and malignant mesenchymoma, including osteosarcomatous, chondrosarcomatous, and rhabdomyosarcomatous elements
 - Most common in craniofacial bones (maxilla and mandible) followed by femur and tibia
 - Peaks in third and fourth decades
 - May occur spontaneously or in patients treated by prior radiation
 - Identified more often in association with the monostotic type:
 - Risk increases when patient has both McCune-Albright and Mazabraud syndromes
 - Risk is greater than in those with fibrous dysplasia alone
 - Tends to occur years to decades after development of fibrous dysplasia
 - Treatment is similar to that of a primary malignant bone tumor.
 - Prognosis is poor with tendency to metastasize to lungs and short survival periods.

Giant Cell Tumor of the Head and Neck ([Figs. 6-13](#) and [6-14](#))

Definition: Benign but potentially aggressive primary tumor of bone composed of stromal mononuclear cells and osteoclast-like giant cells.

Synonym: Osteoclastoma

Clinical

- Most occur at ends (epiphyses) of long bones with distal femur the most common site followed by proximal tibia
- Rare in the head and neck:
 - Less than 2% of all giant cell tumors occur in head and neck.
 - Propensity to affect sphenoid, temporal, and ethmoid bones
- More common in women than in men; occur over a wide age range

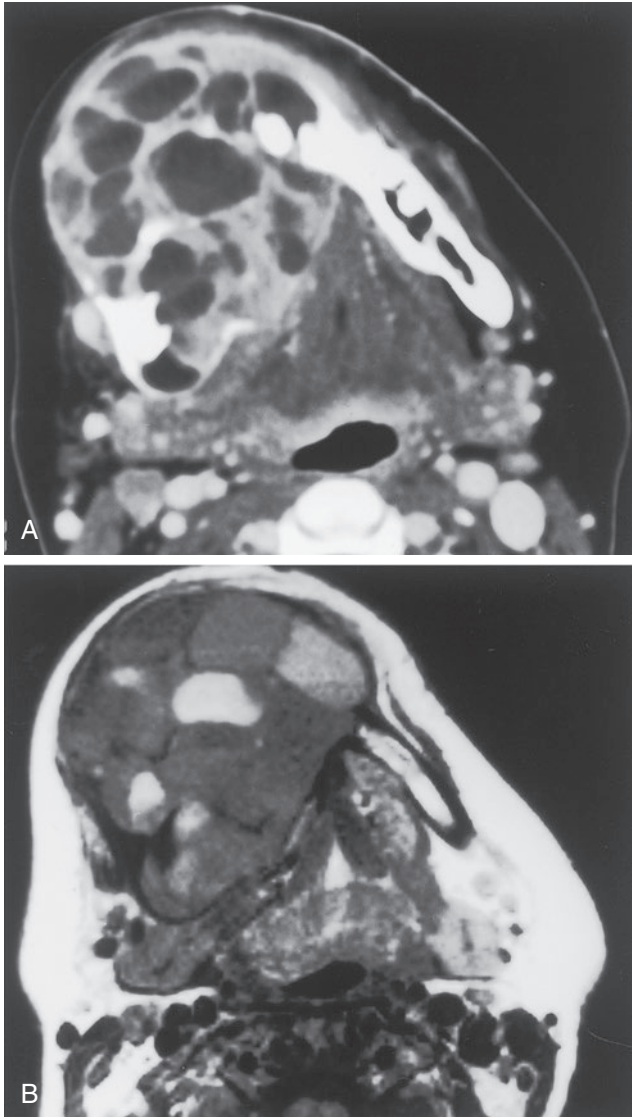


Fig. 6-13. Giant cell tumor.

Contrast-enhanced CT scan (A) and axial T1-weighted (B) and T2-weighted (C) MR images demonstrate a large, septated destructive mass of the right mandible. The tumor is well defined and multiseptated. Multiple fluid levels are obvious, especially in C. (From Som P, Curtin H: *Head and neck imaging*, ed 4, St Louis, 2003, Mosby.)

- Symptoms vary per site of involvement:
 - Sphenoid and ethmoid bones
 - Headaches, diplopia, visual disturbances, proptosis
 - Middle ear, temporal bone, petrous bone:
 - Conductive hearing loss
 - Vertigo and sensorineural hearing loss
- Laboratory:
 - No abnormalities of serum calcium

- Radiology:
 - Lytic lesions with or without involvement/destruction of adjacent bones

Pathology

Histology

- Characterized by the presence of abundant multinucleated giant cells and stromal mononuclear cells
- Multinucleated giant cells:
 - Diffusely and evenly distributed, are large and have numerous nuclei (10 to 100)
 - Nuclei are round to oval with or without nucleoli and tend to cluster in the center of the giant cells.
 - Cause bony destruction
 - Are thought to be recruited from normal mononuclear stromal cells
- Mononuclear cell stromal component:
 - Plump, ovoid, or spindle-shaped
 - Nuclei similar to those seen in the giant cells
 - No cytologic atypia
- Variable associated thin-walled blood vessels:
 - Identification of intravascular tumor especially at the periphery of the tumor may be seen but has no clinical import.
- Mitoses are seen in the stromal mononuclear cells and may be abundant but atypical mitoses are not present:
 - Presence of atypical mitoses identified as an indicator of malignancy
- Additional findings may include the presence of foam cells, osteoid, and rarely chondroid:
 - Foam cells frequently present and in some case may be abundant
 - Reactive bone may be focal or abundant, usually in the form of seams of osteoid with prominent osteoblastic rimming.
 - Cartilage formation is uncommon, and presence of chondroid material should engender consideration of another lesion.
 - Secondary aneurysmal bone cysts are not uncommon:
 - May be present as microscopic cysts
- Absence of collagenized or fibroblastic background unless previously biopsied or traumatized
- Immunohistochemistry:
 - Multinucleated giant cells:
 - Express strong CD68 (KP1) staining (monocytic/histiocytic lineage) and vimentin staining
 - Smooth muscle actin negative
 - Exhibited an osteoclast phenotype expressing tartrate-resistant acid phosphatase and vitronectin receptor

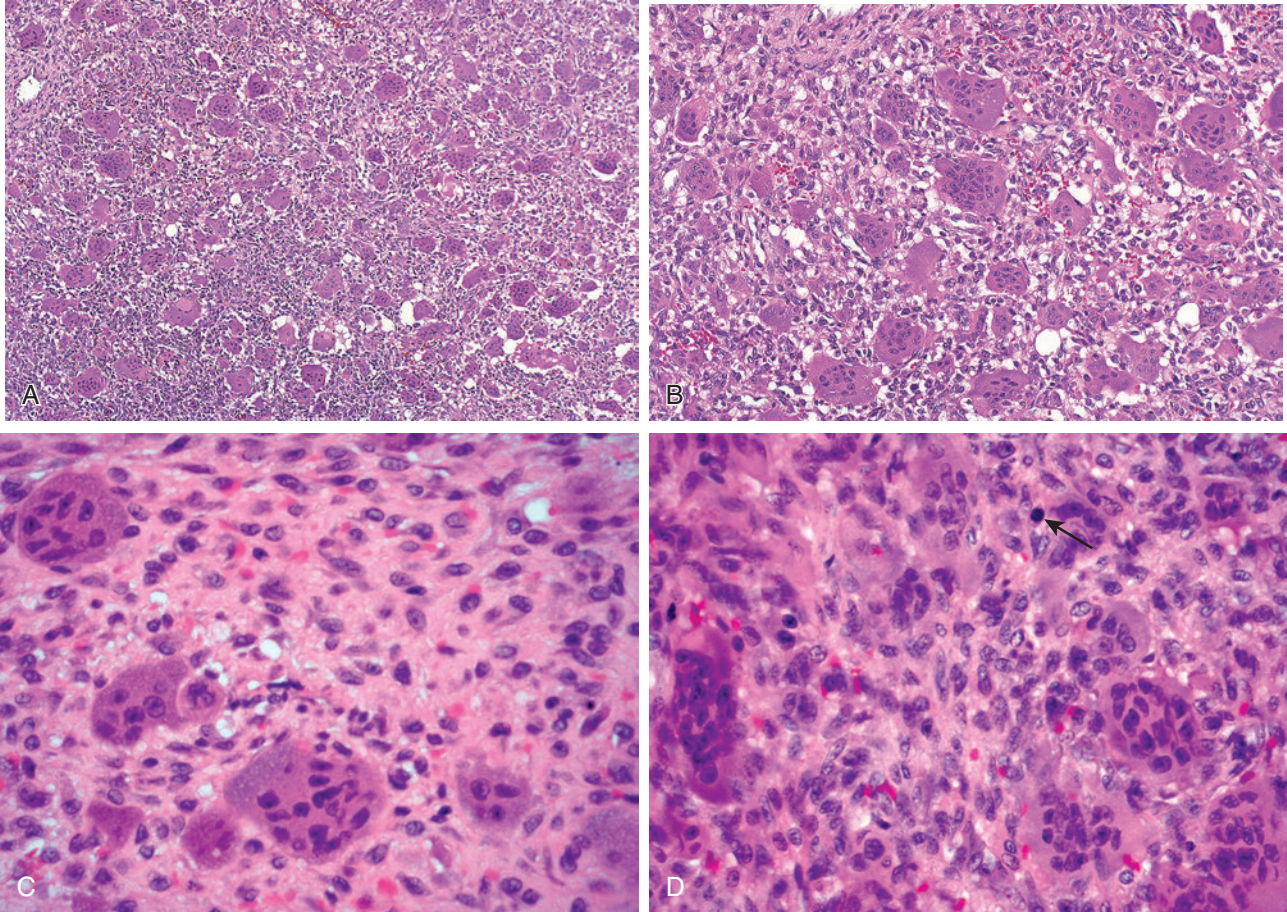


Fig. 6-14. Giant cell tumor.

A and B, Histology is characterized by the presence of diffusely and relatively evenly distributed multinucleated giant cells. **C,** Multinucleated giant cells are large and have numerous nuclei that are round to oval with nucleoli with tendency to cluster in the center of the giant cells; around the giant cells is the mononuclear cell stromal component composed of plump, ovoid-appearing cells with nuclei similar in appearance to those seen in the giant cells. There is an absence of cytologic atypia. **D,** Mitotic figures (*arrow*) may be seen and in any given case may be numerous, but atypical mitotic figures should not be present.

- Mononuclear stromal cells:
 - p63 reactivity (strong nuclear staining)
 - Exhibited an osteoblast phenotype, expressing:
 - Alkaline phosphatase, and the receptor activator for nuclear factor kappa B ligand (RANKL), a factor that is essential for osteoclast formation
 - Also expressed osteoprotegerin (OPG), an inhibitor of osteoclastogenesis, and TNF-related apoptosis-inducing ligand (TRAIL), a receptor that binds OPG:
 - These findings indicate that the mononuclear and giant cell components of giant cell tumor have similar phenotypic features and that the accumulation of osteoclasts in these giant cell-rich tumors occurs by a receptor activator of nuclear factor kappa-B ligand (RANKL)-dependent process
 - RANKL expression by osteoblast-like mononuclear stromal cells in these tumors stimulates osteoclast formation and resorption accounting for the osteolysis associated with these giant cell-rich tumors
 - Inhibitors of osteoclast formation and activity are likely to be effective in controlling the osteolysis associated with GCTB and possibly other giant cell-rich lesions.
 - Identification of angiogenic factors, including vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) in mononuclear cells and giant cells, may play a role in the process of osteoclastogenesis, potentially contributing to additional growth in these lesions.
- Cytogenetics and molecular genetics:
 - Telomeric associations (TAS) represent the most frequent chromosomal translocation.

- Telomeric associations on 11p and dicentric chromosomes
- Clonal abnormalities, such as del(17p), and losses of chromosomes 4, 13, and 18 and gains on chromosome 7
- Comparative genomic hybridization: chromosomal imbalances with gains on chromosomes 1p31-q44, 6q12-q23, and 12q15-q22

Differential Diagnosis

- Giant cell granuloma:
 - Share histologic similarities with giant cell tumor:
 - Divergent opinion whether giant cell tumor and giant cell granuloma represent spectrum of a single entity
 - Features in giant cell granuloma differing from giant cell tumor include:
 - Predilection to the gnathic bones, especially the mandible
 - Overall fewer numbers of giant cells with less even distribution of the giant cells
 - Frequent areas of hemorrhage and tendency for giant cells to cluster in areas of hemorrhage, as well as in proximity to vascular spaces
 - Greater amount of stromal collagenization
- Brown tumor of hyperparathyroidism:
 - Absence of abnormalities of serum calcium in giant cell tumor assists in differentiating these lesions.
- Chondroblastoma

Treatment and Prognosis

- Surgical excision (i.e., curettage) is the preferred treatment:
 - Treatment recommendation is based on the more common giant cell tumors of long bones.
 - In long bones recurrence rates vary from 20% to 50% after surgical curettage.
- Radiation is not recommended because:
 - These tumors are not felt to be radiosensitive.
 - There is believed to be increased risk of malignant transformation after radiation treatment.
- Medical therapies include diphosphonates and denosumab (RANKL inhibitors):
 - May be used in patients with untreatable disease, including refractory, recurrent, or metastatic giant cell tumor
- Rarely (less than 10%) morphologically benign giant cell tumors may metastasize:
 - May be referred to as benign metastasizing giant cell tumor
 - No reliable predictors of which lesions may metastasize
 - Metastasis may be solitary or multiple.
 - Metastatic disease most often to lungs; less often to lymph nodes and other visceral sites

- If solitary surgical resection is achievable (metastasectomy), prognosis is good.
- Rarely, more diffuse metastatic disease occurs and may result in death.
- Malignant transformation of giant cell tumors is uncommon, representing presence of histologically benign giant cell tumor in association with sarcomatous component:
 - Malignant giant cell tumors, primary and secondary:
 - Primary malignant giant cell tumor represents a de novo malignancy (i.e., at presentation).
 - Secondary malignant giant cell tumor represents malignant transformation of a previous tissue-verified benign giant cell tumor:
 - Most occur secondary to radiation treatment.
 - Could be considered postirradiation sarcoma
 - For primary and secondary malignant giant cell tumors, malignancy includes osteosarcoma, undifferentiated pleomorphic sarcoma, and fibrosarcoma.
 - Metastatic disease is most often to the lungs.
 - Poor prognosis with greater mortality associated with secondary as compared with primary malignant giant cell tumor
 - Rare malignant giant cell tumor of the sphenoid arising in setting of Paget disease.

Giant Cell Tumor of Soft Tissue (Osteoclastoma of Soft Tissue)

- Primary soft tissue neoplasm that is clinically and histologically similar to giant cell tumor of bone
- Majority occurs in upper and lower extremities but approximately 7% may occur in soft tissues of the head and neck
- Histology and immunoreactivity similar to that of giant cell tumor of bone
- Complete surgical resection is the preferred treatment.
- May locally recur in up to 12% of cases (often a function of inadequate excision)
- Rarely metastasizes

Osteoblastoma (Figs. 6-15 and 6-16)

Definition: Benign bone-forming neoplasm characterized by osteoblastic rimming of woven bony trabeculae (histologically similar to osteoid osteoma) but with potential for progressive/aggressive growth.

Synonym: Giant osteoid osteoma

Clinical

- Represent approximately 1% to 4% of all benign tumors of bone

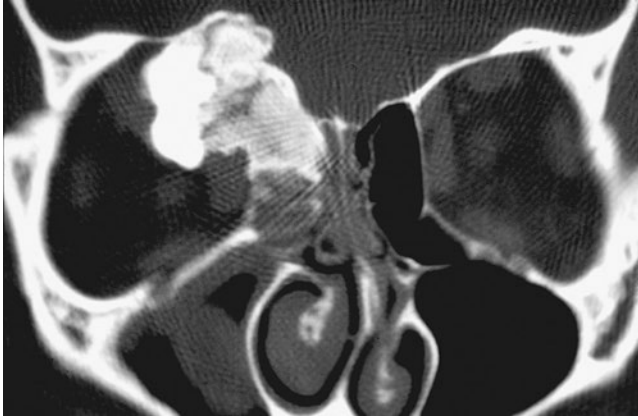


Fig. 6-15. Osteoblastoma.

Coronal CT scan shows a bone density lesion in the right frontal and ethmoid bones. The bone is expanded, and the cortices are intact. Part of the lesion has a “ground glass” appearance; however, the lateral portion of the mass has very dense bone cap. This patient had a benign osteoblastoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 4-184, p 344.)

- Most common site of occurrence is in the vertebra:
 - Uncommon tumor of head and neck
 - In head and neck occurs most commonly in gnathic (jaw) bones:
 - More common in the mandible (body) than maxilla
 - Less common sites of occurrence include the cervical vertebrae, skull, sinonasal tract, and middle ear/temporal bone.
- More common in men than in women; overwhelming majority of cases (greater than 90%) occur in patients under 30 years of age
- Presentation is usually that of localized pain to involved site:
 - Unlike osteoid osteoma, pain is not nocturnal and aspirin does not typically assist in resolving the pain.
 - In addition to pain, other symptoms related to site of occurrence may include:
 - Jaws: swelling, loosening of teeth
 - Sinonasal tract: epistaxis, nasal obstruction
 - Middle ear/temporal bone: conductive hearing loss
- Radiology:
 - Well-defined or sharply circumscribed to poorly defined radiolucent/radiopaque lesion with variable mineralization:
 - Depending on the degree of mineralization may appear:
 - Predominantly lytic
 - Predominantly sclerotic
 - Mixed lytic and sclerotic

- Expansion of bone with cortical erosion and extension into adjacent soft tissue may be identified
- Usually measure more than 2 cm but rarely larger than 10 cm
- Absence of a nidus as seen in osteoid osteoma
- In gnathic bones may be intimately associated with roots of teeth
- Significant percentage of cases may radiographically show features similar to those identified in osteosarcoma.

Pathology

Gross

- Intact lesions are rarely seen by the pathologist, because curettage is the usual means of surgical treatment.
- Intact lesions are:
 - Usually well circumscribed with a hemorrhagic appearance and granular to somewhat gritty texture, depending on the degree of calcification
 - Older lesions may be more heavily calcified, resembling cancellous bone.
 - In all skeletal locations range in size from 1.5 cm to 10 cm in greatest dimension
 - Often lack the sclerotic rim, which is so prominent in osteoid osteomas

Histology

- Well-circumscribed/sharply demarcated lesion composed of intricate complex (anastomosing) bony trabeculae in loose fibrovascular stroma:
 - Trabeculae may connect with cortical bone at periphery of the lesion, suggesting maturation
 - Bony trabeculae are lined by a single layer of plump osteoblasts, which may have small bland nuclei or may have enlarged nuclei with prominent nucleoli:
 - Scattered typical mitotic figures may be identified in osteoblastic cells.
 - May lack mineralization or may be rather heavily calcified
 - Lace-like osteoid may be present in small percentage of cases
- Intertrabecular spaces contain a richly vascularized loose fibroblastic stroma.
- Chondroid areas are uncommon but may be seen focally.
- Rarely large atypical but degenerated-appearing hyperchromatic nuclei may be seen.

Aggressive Osteoblastoma

- Designation ascribed to those osteoblastomas with atypical features suggestive of malignancy, including:
 - Increase in epithelioid-appearing osteoblasts
 - Increased mitotic figures

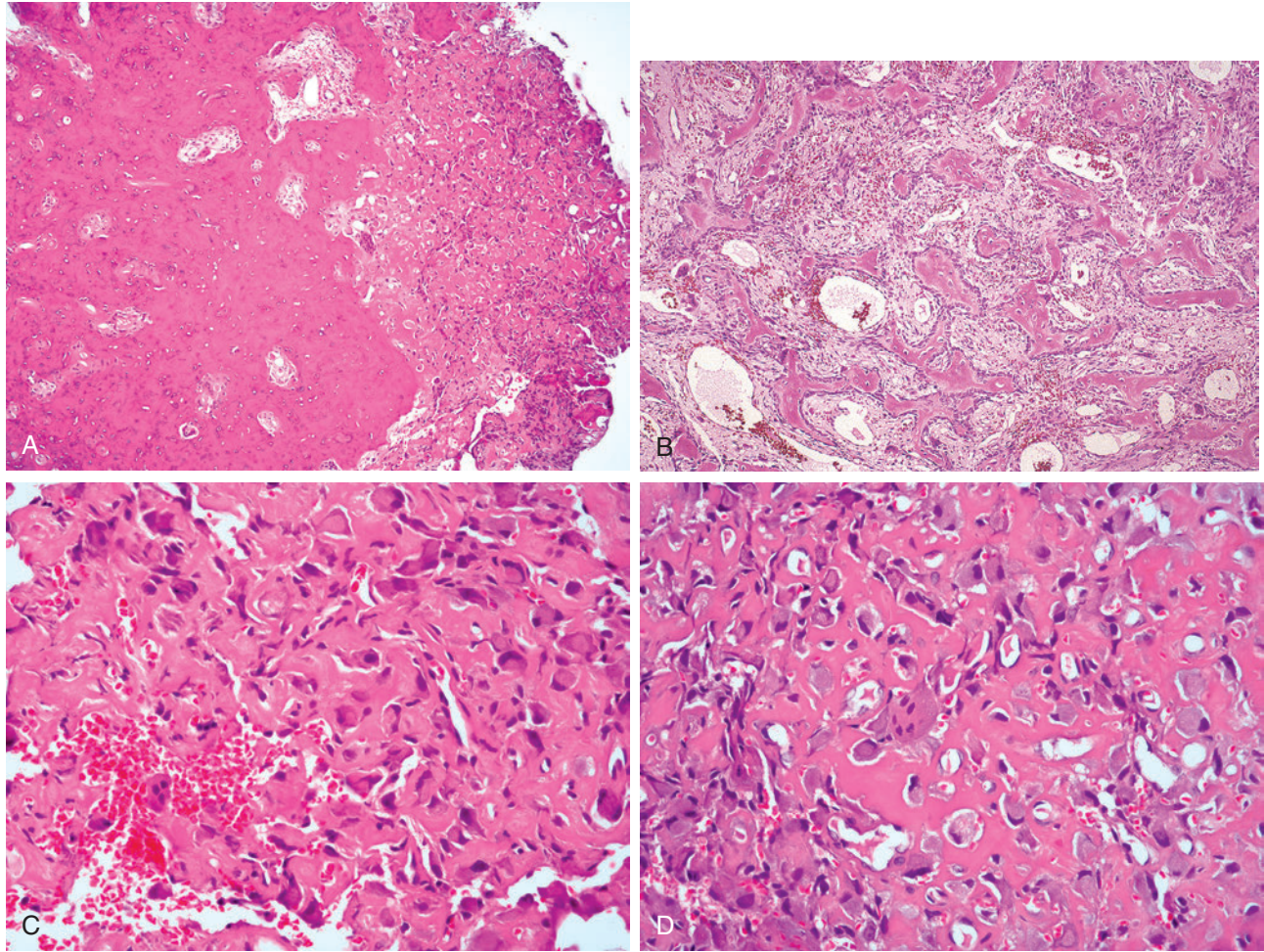


Fig. 6-16. Osteoblastoma.

A, The interface between the tumor (*right*) and adjacent host bone (*left*) is rather well demarcated, contrasting with the destructive nature typically seen in osteosarcomas. **B**, Complex of bony trabeculae lacking mineralization and lined by a single layer of osteoblasts; intertrabecular space is vascularized and composed of loose fibroblastic stroma. **C**, Osteoblasts have an epithelioid appearance with low nuclear-to-cytoplasmic ratio. **D**, Lace-like pattern of osteoid suggesting a possible diagnosis of osteosarcoma but the cells lack cytologic atypia.

- Sheetlike or trabecular areas of osteoid
- Osteoclastic activity
- Absence of radiographic distinctive findings
- Metastatic disease and/or death not seen in the lesions
- Validity of existence of aggressive osteoblastoma questioned

Malignant Osteoblastoma

- Another entity whose validity as a distinct lesion with reproducible features has been questioned:
 - Designation used for lesion showing borderline features between osteoblastoma and osteosarcoma, including:
 - Cellular pleomorphism of osteoblasts
 - Large number of giant cells

- Speculated blue bone similar to that found in osteosarcoma
- May recur but metastatic disease not reported

Differential Diagnosis

- Osteoid osteoma:
 - Benign bone forming tumor with limited growth potential
 - Represents approximately 14% of all benign bone tumors
 - More common in men than in women; most common in the first to third decades of life
 - Majority occurs in femur and tibia
 - Rare in head and neck sites, where most common sites of occurrence include mandible and cervical vertebrae

- Pain, especially occurring at night (nocturnal pain), is most common presenting complaint; pain typically responds (i.e., pain relief) to non-steroidal anti-inflammatory drugs.
- Radiology:
 - Circumscribed dense cortical radiolucency surrounding marked sclerosis (nidus)
- Usually measures 1 cm or less
- Essential identical histology to osteoblastoma:
 - Exception is presence in osteoid osteoma of a nidus representing interconnecting mass of osteoid and immature (woven) bony trabeculae of variable length and thickness rimmed by osteoblasts
 - Because of shared histologic features (except for the nidus), differentiation may not be achievable in curetted material, thereby requiring radiographs to assist in differentiating osteoid osteoma from osteoblastoma.
- Complete surgical excision or ablation of the nidus (en bloc) is curative:
 - Depending on the site of occurrence may require multiple procedures
 - Medical management (nonsteroidal anti-inflammatory drugs) may be an option if surgical treatment is contraindicated.
- Aneurysmal bone cyst
- Fibrous dysplasia
- Giant cell tumor
- Odontogenic lesions/neoplasms:
 - Cementoblastoma, cemento-ossifying fibroma, cemento-osseous dysplasia
- Osteosarcoma:
 - Features in osteoblastoma that assist in excluding osteosarcoma include:
 - Sharp circumscription with no permeation or entrapment of surrounding host bone
 - Bony trabeculae embedded in loose connective tissue; lining of trabeculae by a single layer of osteoblasts
 - Features in osteosarcoma that contrast to those of osteoblastoma include:
 - Greater nuclear pleomorphism and hyperchromasia
 - Greater number of mitoses with atypical mitotic figures
 - More compact stromal component
 - Penetration of neoplastic cells between existing bone/bony trabeculae
 - Presence of sheets of osteoblasts without osteoid production

Treatment and Prognosis

- Conservative but complete surgical resection by curettage or local excision is the preferred treatment and is curative in majority of cases.
- Recurrent tumor is uncommon.
- Features potentially associated with aggressive behavior include:
 - Location of lesion:
 - Tumors of the central neuroaxis associated with increased morbidity and mortality
 - Presence of secondary aneurysmal bone cyst component:
 - Associated with more destructive behavior
 - Local control of disease:
 - Ability to completely resect tumor associated with excellent long-term prognosis
 - Histology alone is not predictive of aggressive behavior.
- Metastatic disease rarely, if ever, occurs.

BENIGN ODONTOGENIC NEOPLASMS

- Odontogenic tumors represent a broad group of relatively rare heterogeneous neoplasms.
- The full spectrum of odontogenic neoplasms is beyond the scope of this text.
- This section focuses on some of the more common odontogenic neoplasms with which the surgical pathologist may be confronted in daily practice.

Ameloblastoma

(Figs. 6-17 through 6-19)

Definition: Slow-growing, locally aggressive epithelial odontogenic jaw tumor recapitulating enamel organ development during tooth crown formation with a high propensity for recurrence:

- Thought to arise from reduced enamel epithelium of the dental follicle, remnants of odontogenic epithelium, lining of odontogenic cysts, or basal cells of the overlying oral (alveolar) mucosa
- May develop from an odontogenic cyst (e.g., dentigerous cyst, odontogenic keratocyst) or develop in association with another type of odontogenic neoplasm (e.g., adenomatoid odontogenic tumor, others) referred to as hybrid tumor.
- Based on various clinical and pathologic features, ameloblastomas can be divided into four categories, including:
 - Solid/multicystic:
 - Are intraosseous
 - Unicystic:
 - Are intraosseous
 - Desmoplastic:
 - Are intraosseous
 - Peripheral:
 - Arise in extraosseous (mucosal) locations

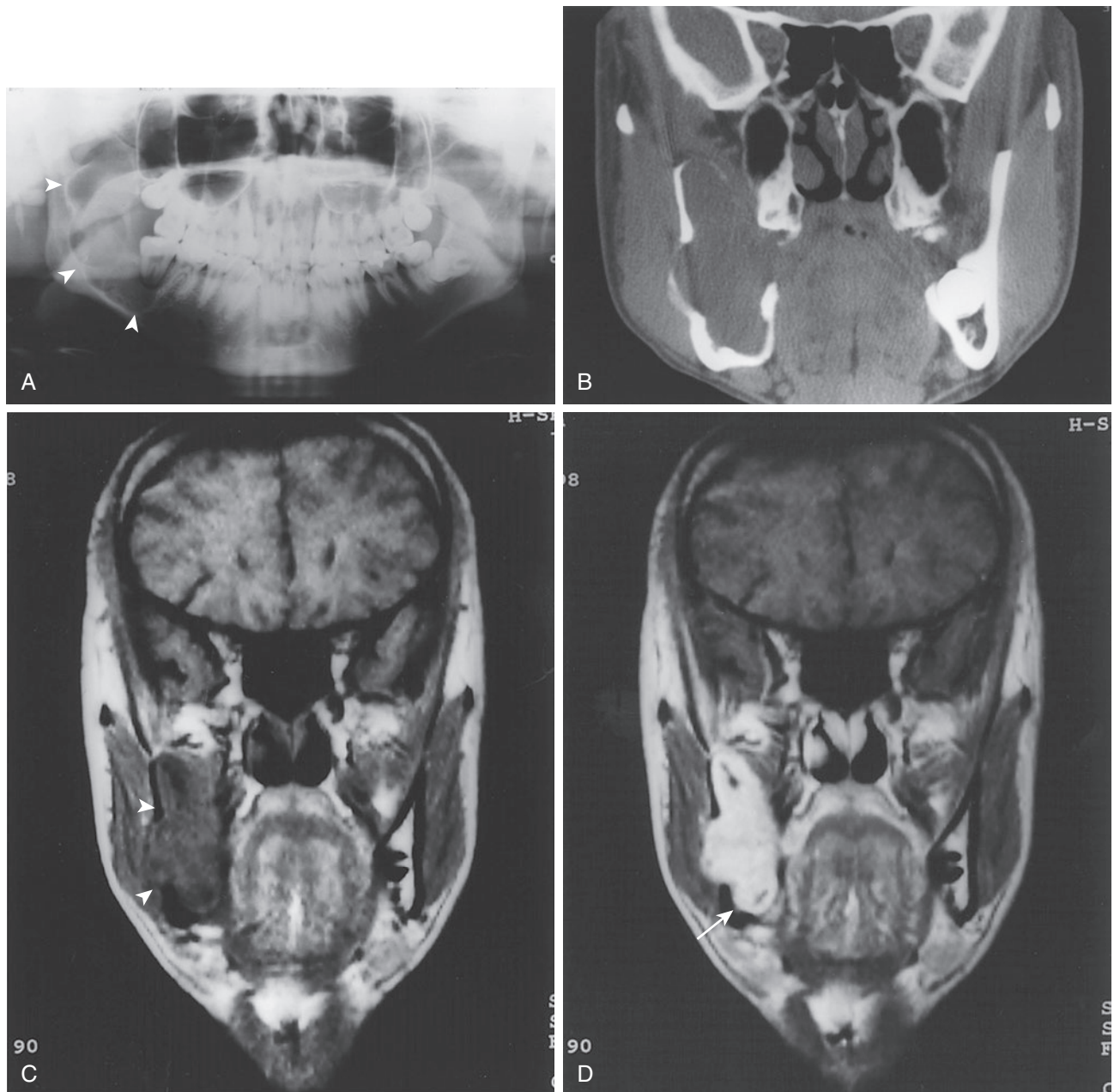


Fig. 6-17. Ameloblastoma.

Ameloblastoma, solid/multilocular type in a 25-year-old man. **A**, Pantomogram shows a large, multilocular, expansile lesion in the right side of the mandible (*arrowheads*). There is no root resorption of adjacent teeth. A cystic lesion is suspected. **B**, Coronal CT shows the expansile multilocular lesion, with bulging of the bony cortex without perforation. **C**, Coronal T1-weighted MR image reveals a lesion of homogeneously low signal intensity in the mandible (*arrowheads*). **D**, Enhanced coronal MR image shows the markedly enhanced solid lesion in the mandible. The mandibular canal can be seen under the solid mass (*arrow*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-22, p 1484 [panels A through D]).

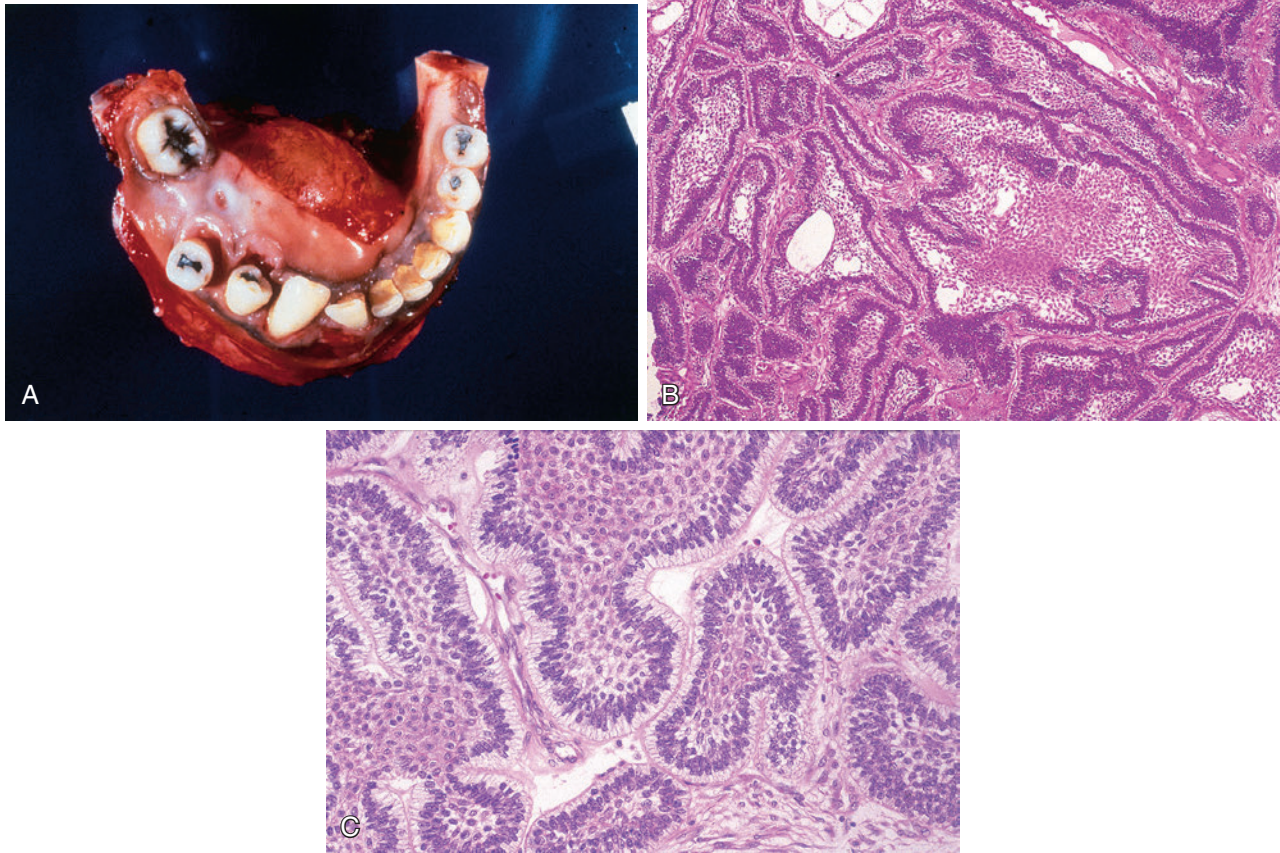


Fig. 6-18. Ameloblastoma, follicular (solid and cystic) variant.

A, Expansile lesion of the right mandible with displacement of teeth. **B** and **C**, Solid and cystic tumor composed of proliferating nests or islands of odontogenic (ameloblastic) epithelium including central area of loosely arranged cells similar to the stellate reticulum of the enamel organ and a peripheral area of palisading columnar or cuboidal cells with hyperchromatic small nuclei oriented away from the basement membrane (reverse polarity).

Ameloblastoma, Solid/Multicystic Type

Clinical

- Second most common odontogenic tumor (odontoma is considered the most common odontogenic tumor)
- Most common type of ameloblastoma, representing greater than 80% of all cases
- No gender predilection; occurs over a wide age range but most commonly occurs in the fourth to sixth decades of life; rare under 20 years of age
- Greater than 80% involve the mandible with predilection for the posterior mandibular region (molar-ramus area > premolar area > symphysis); often associated with unerupted third molar teeth:
 - Predilection to the molar-ramus area is thought to be the result of:
 - Aberrant tooth germs often found in this region
 - Posterior end of the dental lamina proliferates continuously.

- Maxillary ameloblastomas occur primarily in the posterior (molar) region
- May occur as a primary sinonasal tract neoplasm; see Section 1, Sinonasal Tract, for detailed discussion.
- Most common clinical presentation is a painless swelling of the affected area; pain or paresthesia is rare
- Radiology:
 - Unilocular or multilocular radiolucent lesion resembling cysts with a honeycomb appearance and scalloped borders
 - Extensive thinning of cortical bone can often be seen.
 - Desmoplastic type may present as mixed radiolucent/radio-opaque lesions

Pathology

Gross

- Predominantly solid but microcyst may be identified

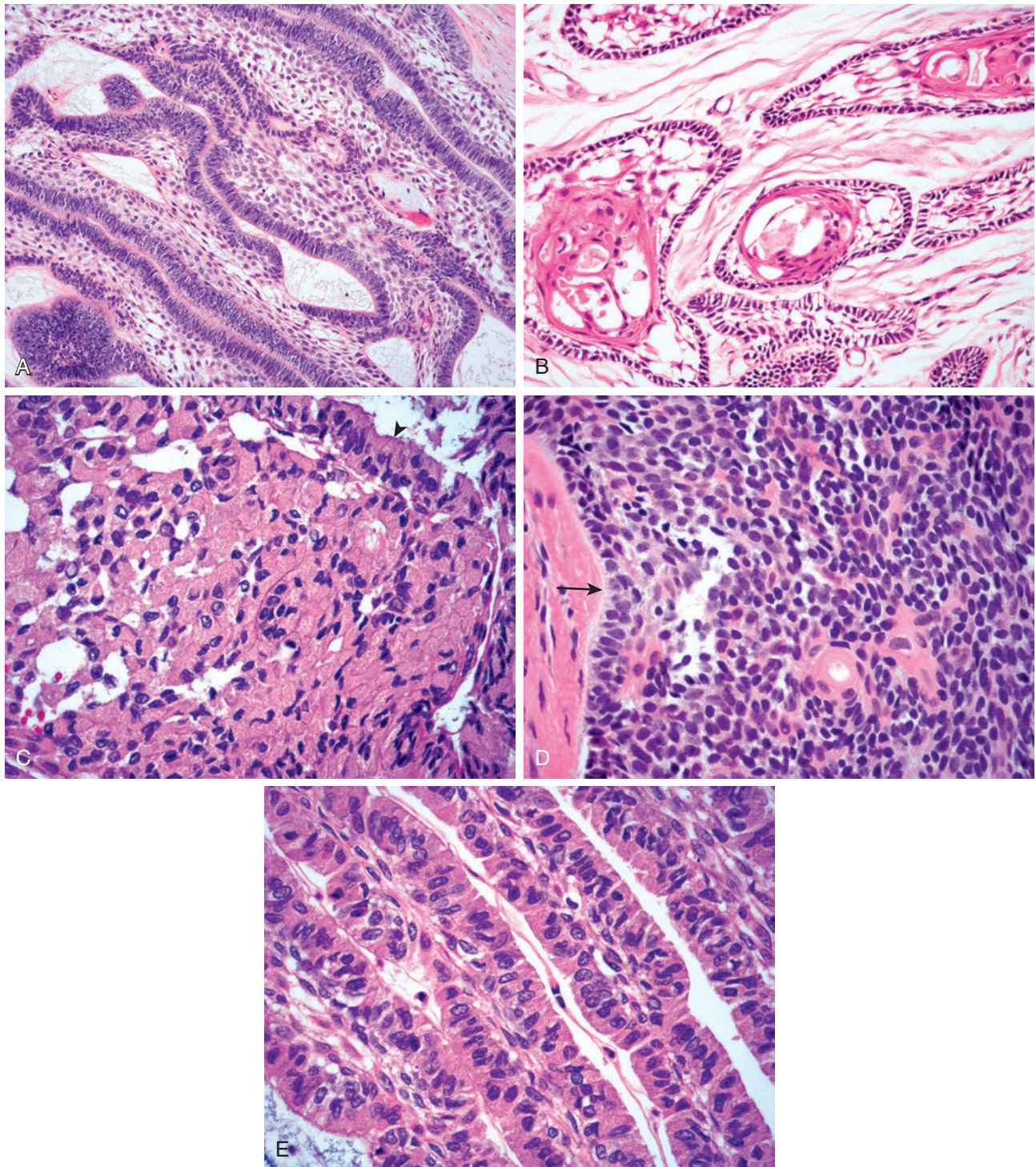


Fig. 6-19. Histology of ameloblastoma.

Histologic variants of ameloblastoma include (A) plexiform, composed of long columns (trabeculae) of columnar epithelial cells with minimal to no evidence of central stellate reticulum although around the columns stellate reticulum is readily identified; (B) acanthomatous, characterized by squamous metaplasia in central areas replacing the stellate reticulum; (C) granular cell, composed of varying cells with prominent granular, eosinophilic-appearing cytoplasm; there is retention of peripheral columnar cells (*arrowhead*). D, Basal cell type is the least common variant and is comprised of small, ovoid, basaloid cells with scant cytoplasm in central areas replacing typical stellate reticulum and retention of peripheral columnar cells with reverse polarity of hyperchromatic nuclei (*arrow*). E, Plexiform and granular cell characterized by trabeculae comprised of granular cells. Any given example of ameloblastoma may include multiple histologic types.

Histology

- Several histologic variants may be seen:
 - Histologic subtypes can be found independently or admixed within the same tumor.
- Follicular (solid and cystic) variant:
 - Most common histologic variant
 - Variably sized epithelial islands composed of central loosely arranged cellular areas identical to stellate reticulum of enamel organ with squamous cells, basal cells, or granular cells surrounded by columnar epithelial cells with clear to vacuolated cytoplasm and hyperchromatic (basaloid) nuclei aligned at the periphery away from the basement membrane referred to as reverse polarity of the nuclei
 - Absence of significant nuclear pleomorphism and increased mitotic activity
 - Microcyst formation commonly present in this histologic subtype
 - Mucocytes may rarely be found.
 - Desmoplastic:
 - Considered a variant of follicular ameloblastoma characterized by presence of a markedly desmoplastic stroma
- Plexiform variant:
 - Second most common histologic variant
 - Composed of long, anastomosing double columns and sheets of cuboidal or columnar epithelial cells with reverse polarity of the peripheral located nuclei with minimal to no evidence of central stellate reticulum
- Acanthomatous variant:
 - Identical to follicular type but characterized by presence of extensive squamous metaplasia in central areas replacing typical stellate reticulum
 - Squamous metaplasia includes keratin pearl formation and individual cell keratinization:
 - Absence of significant nuclear pleomorphism or mitotic activity
 - Retention of peripheral columnar cells with reverse polarity of hyperchromatic nuclei
 - Keratoameloblastoma:
 - Term for ameloblastomas with extensive keratinization of central areas
 - Includes surface parakeratin
 - May show papillary growth (papilliferous keratoameloblastoma)
- Granular cell variant:
 - Composed of varying numbers of cells with prominent granular, eosinophilic-appearing cytoplasm
 - Retention of peripheral columnar cells with reverse polarity of hyperchromatic nuclei

- May show anastomosing trabeculae or cords
- Basal cell variant:
 - Least common variant
 - Composed of small, ovoid, basaloid cells with scant cytoplasm in central areas replacing typical stellate reticulum
 - Retention of peripheral columnar cells with reverse polarity of hyperchromatic nuclei
 - May be histologic type seen in association with peripheral (extraosseous) ameloblastomas
- Additional cell types that can be seen including mucous cells, clear cells, and cells with melanin pigment
- Infiltrative growth may be seen with any histologic variant, including infiltration of bone.
- Special stains including histochemistry and immunohistochemistry are of limited utility in the diagnosis.
- No specific cytogenetic or molecular genetic findings

Differential Diagnosis

- Dentigerous cyst: see earlier in section
- Odontogenic keratocyst: see later in section
- Ameloblastic fibroma
- Squamous odontogenic tumor:
 - Rare benign odontogenic epithelial neoplasm thought to arise from epithelial rests of Malassez of the periodontal membrane
 - Most common in third to fourth decades of life
 - Occur most often in the anterior maxilla or posterior mandible
 - Radiology: well-demarcated radiolucent lesion with sclerotic, osseous border
 - Histologic features include:
 - Irregular-shaped islands of bland-appearing mature squamous epithelium without nuclear pleomorphism, nuclear hyperchromasia, increased mitotic activity, or dyskeratosis
 - Flattened peripheral cells with smoothly contoured connective tissue interface
 - Absence of stellate reticulum and peripheral nuclear palisading with reverse polarity:
 - Assists in differentiating from acanthomatous variant of ameloblastoma
 - Cystic change may be present.
 - Abundant fibrous stroma
 - Epithelial islands may contain spherical eosinophilic hyaline material (reminiscent of Rushton bodies) that stain strongly with PAS
 - Absence of significant cytologic atypia allows for differentiation from intraosseous carcinoma or metastatic squamous cell carcinoma
 - Simple excision (enucleation or curettage) considered preferred treatment and is curative

Treatment and Prognosis

- Complete surgical resection is preferred treatment:
 - For small tumors that are well delineated, conservative but complete excision can be performed.
 - For larger tumors that have spread to adjacent tissues (e.g., bone, other) en bloc resection may be required to include at least 1 cm of normal tissue beyond radiographic margin.
- Surgical curettage not an acceptable form of therapy
- Considered radioresistant; chemotherapy has no proven efficacy.
- Recurrence is not uncommon and may lead to extensive local destruction with facial disfigurement or may pose life-threatening complications as a result of extension into vital structures.
- Metastases are rare and are generally related to long-standing tumors associated with multiple surgical procedures or radiation treatment.
- Prognosis for ameloblastomas depends on tumor size, extent of disease, and location of the tumor:
 - Mandibular ameloblastomas tend to be confined tumors, due to the inherently thick cortical mandibular bone
 - Maxillary ameloblastomas are more likely to demonstrate extension beyond the bone, due to the absence of a thick cortical bone and the intimate association with the sinonasal cavity.
- Malignant ameloblastoma:
 - Represents ameloblastomas with benign features yet metastasize
 - Diagnosis can be rendered only after identification of metastatic tumor:
 - Also referred to by designation metastasizing ameloblastoma
 - Rare occurrence
 - Lung followed by regional lymph nodes represent most common sites for metastases:
 - Other reported metastatic sites include bone, brain, kidney, intestine, and liver.
 - Interval between diagnosis of primary tumor and metastasis can be years
- Ameloblastic carcinoma (Figs. 6-20 and 6-21):
 - Represents rare malignant transformation of a benign ameloblastoma characterized by cytologically malignant epithelial cells with marked nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, increased mitotic activity, necrosis, and lymph-vascular invasion:
 - Predilection for the mandible
 - Presentation may include pain, swelling, trismus, and odynophagia
 - Treated by surgical resection

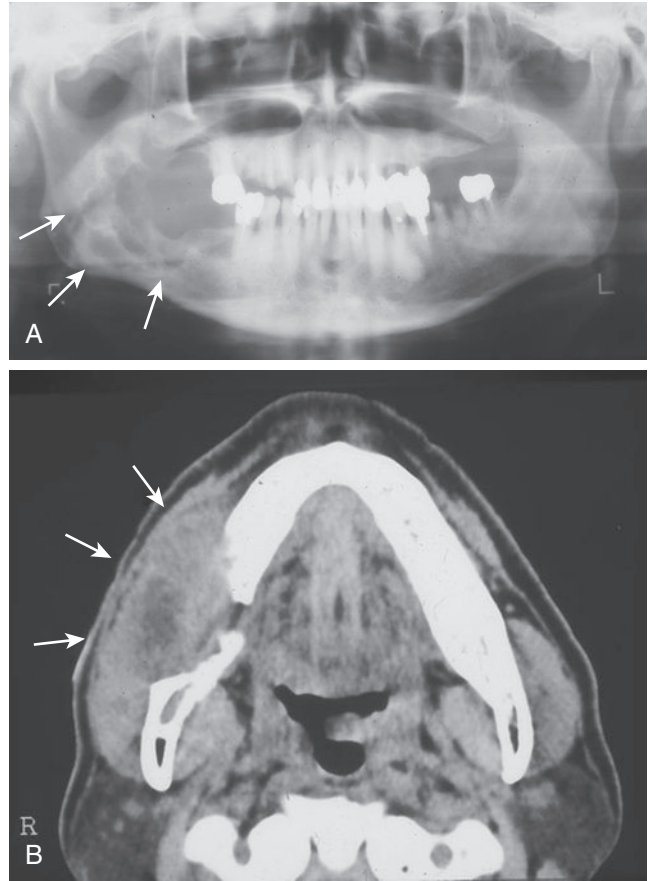


Fig. 6-20. Ameloblastic carcinomas of the mandible in 28-year-old woman.

A, Pantomogram shows a multilocular, expansile lesion in the mandible (arrows). **B**, Axial CT image reveals a multilocular, expansile lesion in the mandible with perforation of bony cortex in right side of the mandible. The mass contains central necrosis and invades masseter muscle, suggesting malignancy (arrows). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-81, p 1520.)

- May metastasize to regional lymph nodes and distantly to lungs, bone, and liver
- Poor prognosis
- Ameloblastic fibrosarcoma (ameloblastic sarcoma) (Fig. 6-22):
 - Rare malignancy in which there is mixed epithelial-mesenchymal odontogenic neoplasm composed of a sarcomatous mesenchymal component arising:
 - De novo
 - From pre-existing odontogenic mixed neoplasm such as an ameloblastic fibroodontoma or ameloblastic fibroma
 - Histology includes foci of ameloblastoma most often in a follicular pattern surrounded

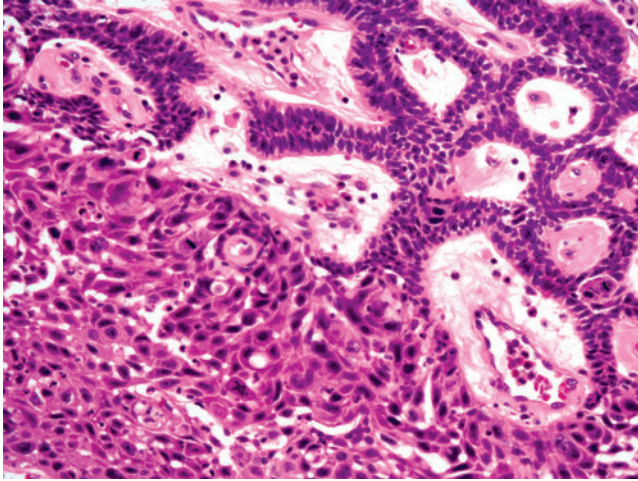


Fig. 6-21. Ameloblastic carcinoma.

Ameloblastic carcinoma includes the presence of histologically identifiable (benign) ameloblastoma (*top right*) transitioning to cytologically malignant area with features of squamous cell carcinoma characterized by presence of individual cell keratinization and intercellular bridges with nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, and increased mitotic activity.

by sarcomatous proliferation with fascicular to herringbone pattern composed of malignant spindle-shaped cells with marked nuclear pleomorphism, increased mitotic activity including atypical mitoses and necrosis

- Biomarker analysis showed alterations of p53 and c-KIT genes restricted to the sarcomatous component
- Treatment follows that for other sarcomas, including radical extirpation and chemotherapy.

Ameloblastoma, Unicystic Type

(Figs. 6-23 and 6-24)

Definition: Variant of conventional ameloblastoma in which there is a single, often large unilocular cyst lined by ameloblastomatous epithelium.

- May develop de novo
- May develop in a preexisting odontogenic cyst

Clinical

- From 5% to 15% of all ameloblastomas are of the unicystic type
- No gender predilection; tends to occur at a younger age than solid/multicystic ameloblastoma primarily in the second to third decades of life
- Greater than 90% involve the mandible, usually the posterior portion of the mandible.
- May be asymptomatic or present as a painless swelling of affected area

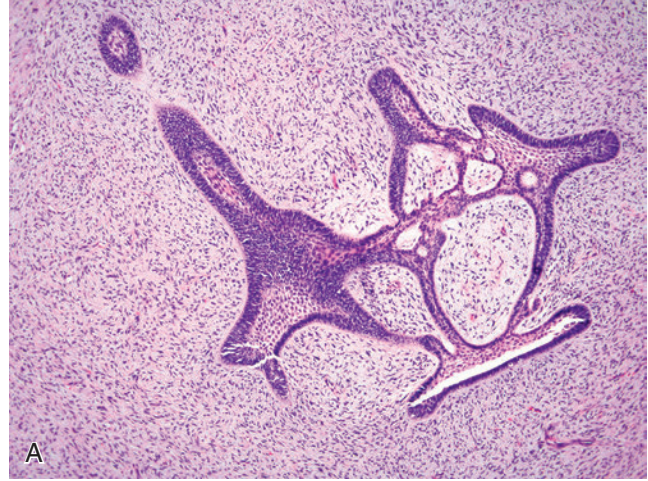


Fig. 6-22. Ameloblastic sarcoma.

The histology includes foci of ameloblastoma, follicular pattern, surrounded by sarcomatous proliferation composed of malignant spindle-shaped cells with nuclear pleomorphism, increased mitotic activity.

- Often associated with an impacted tooth, making it indistinguishable from a dentigerous cyst
- Radiology:
 - Well-delineated unilocular radiolucency
 - Occasionally may show demarcated, perilesional corticated rim
 - Radiolucency often associated with an unerupted tooth, making it indistinguishable from a dentigerous (follicular) cyst

Pathology

Gross

- Indistinguishable from other gnathic cysts

Histology

- Histology subdivided into luminal, intraluminal, and mural types

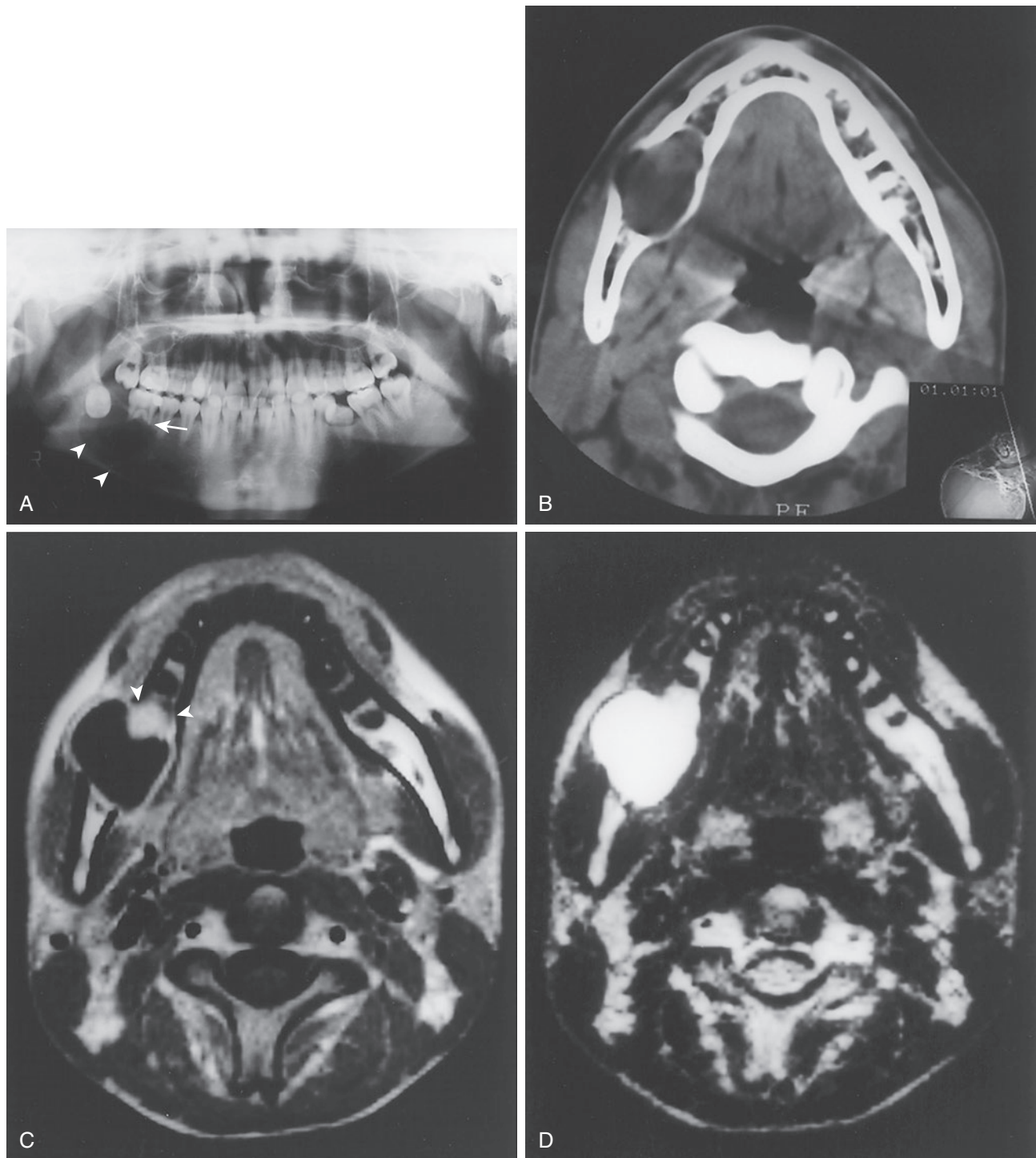


Fig. 6-23. Ameloblastoma, unicystic type.

A, Panoramic radiograph shows a large, unilocular, expansile lesion with an unerupted tooth in the right side of the mandible (*arrowheads*). There is root resorption of adjacent teeth (*arrow*). A cystic lesion is suspected. **B**, Axial CT shows an expansile unilocular lesion, with bulging of the bony cortex without perforation. **C**, Enhanced axial MR image shows a papillary projection (*arrowheads*) along the walls of the unilocular lesion. **D**, Axial T2-weighted MR image reveals the lesion to be of high signal intensity. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-27, p 1488.)

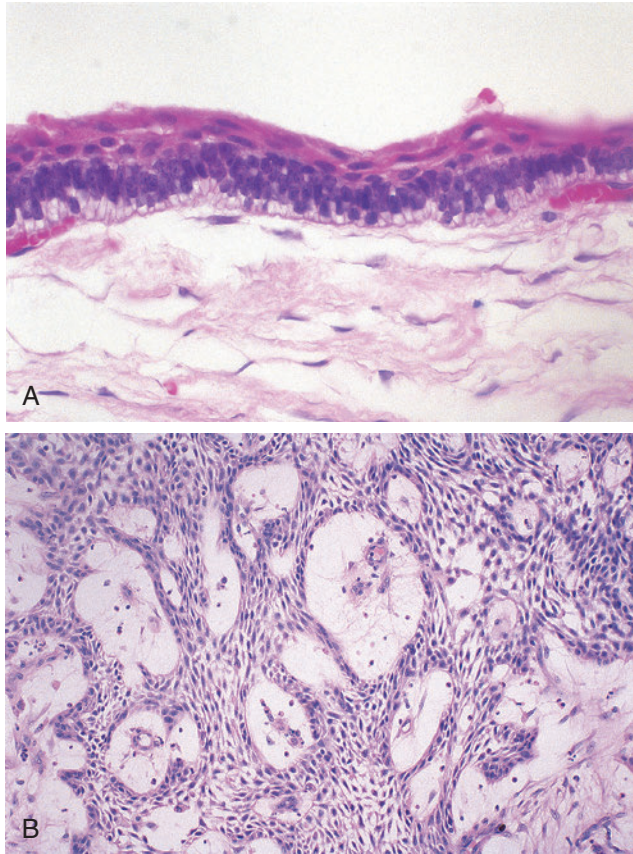


Fig. 6-24. Ameloblastoma, unicystic type.

A, Unicystic luminal type in which the epithelial lining shows palisaded cuboidal and columnar basal cells with reverse polarization. **B**, Intraluminal plexiform unicystic type (plexiform unicystic ameloblastoma) composed of interlacing strands (plexiform) of solid and squamoid-appearing ameloblastoma epithelium lacking reverse polarization.

Luminal Type (Intraepithelial Type)

- Cystic lesion composed of a fibrous tissue wall with the cyst lined by ameloblastomatous epithelium characterized by palisaded cuboidal to columnar basal cells with hyperchromatic nuclei, nuclear polarization, and subepithelial hyalinization

Intraluminal Type

- Similar to luminal type but with one or more nodules of ameloblastomatous epithelium projecting into the lumen
- In examples showing presence of a delicate connective tissue stroma in which interlacing strands of ameloblastomas epithelium are embedded the designation plexiform unicystic ameloblastoma is used:
 - Does not always have palisading columnar cells, nuclear hyperchromasia, and reverse polarization

- Central areas are predominantly solid and squamoid and not loose, resembling stellate reticulum.

Mural Type

- Nests or islands of typical ameloblastomatous epithelium (follicular or plexiform pattern) penetrate or infiltrate the connective tissue cyst wall.

Differential Diagnosis

- Dentigerous cyst

Treatment and Prognosis

- Luminal and intraluminal unicystic ameloblastomas can be treated by curettage or enucleation:
 - Given the presumptive clinical diagnosis of dentigerous cyst, curettage, or enucleation is often performed and only after histologic evaluation is the correct diagnosis rendered.
 - Recurrence rates after curettage or enucleation are low.
- For mural unicystic ameloblastomas, partial or complete jaw resection is recommended given the tendency of this lesion to penetrate bone, resulting in recurrent tumor if inadequately managed.
- Recurrence rates tend to be lower than those for intraosseous ameloblastoma, especially relative to luminal and intraluminal lesions:
 - Approximately 6% without mural involvement
 - Approximately 37% with mural involvement

Ameloblastoma, Desmoplastic Type (Figs. 6-25 and 6-26)

Definition: Ameloblastoma characterized by predominant fibrous connective tissue with irregularly distributed odontogenic epithelium.

Clinical

- From 3% to 13% of all ameloblastomas are of the desmoplastic type.
- No gender predilection, although some reports cite a female predilection; tends to occur over a wide age range from the third to seventh decades of life.
- Predilection for the anterior segment of the mandible and maxilla
- May be asymptomatic or present as a painless swelling of affected area
- Radiology:
 - Unilocular or multilocular combined radiolucent-radio-opaque lesion with poorly demarcated borders
 - Radiologic features may be suggestive of a fibro-osseous lesion.

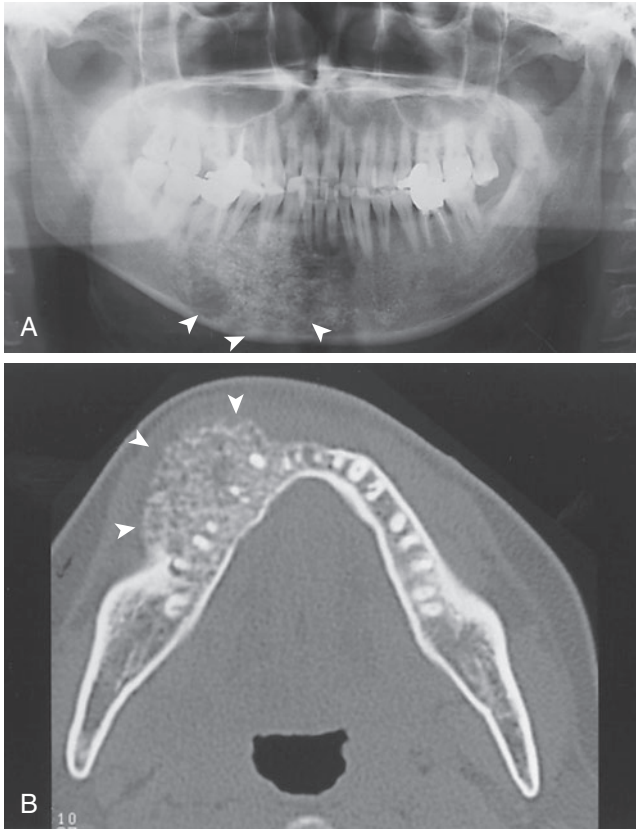


Fig. 6-25. Ameloblastoma, desmoplastic type, in the mandible.

A, Panoramic radiograph shows a diffuse, mixed radiolucent–radiopaque lesion in the mandible (arrowheads). **B**, Axial CT shows a definite buccal expansile radiolucent–radiopaque lesion (arrowheads). (Courtesy Dr. T. Kurabayashi, Dept. of Dental Radiology, Tokyo Medical and Dental University, Tokyo. From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-29, p 1490.)

Pathology

Histology

- Stromal desmoplasia predominates in the form of fibrous connective tissue with abundant collagen of moderate cellularity.
- Follicle-like islands of odontogenic epithelium are irregularly distributed in the collagenized stroma:
 - Typically lack peripheral nuclear polarization
 - Hypercellular central area composed of spindle-shaped cells; also may include squamous cells
 - Microcysts lined by flattened spindle-shaped cells may be seen in centers of the odontogenic epithelial islands; microcysts may occasionally contain eosinophilic material.
- Metaplastic osteoid may be seen and on occasion may be prominent.

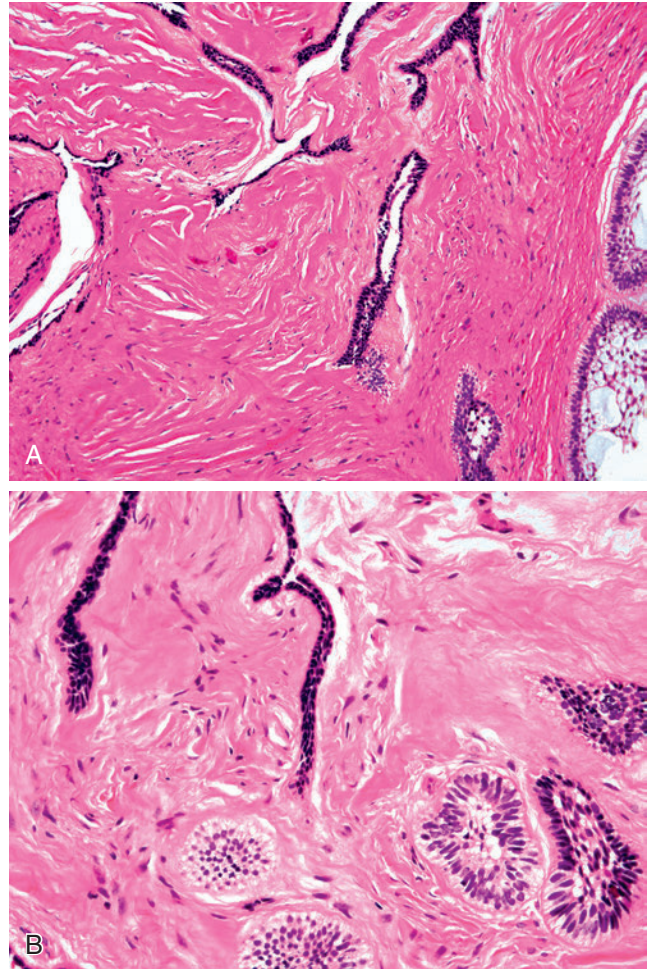


Fig. 6-26. Ameloblastoma, desmoplastic type.

Stromal desmoplasia predominates in the form of collagenized fibroconnective tissue in which there is identifiable irregularly distributed nests, strands, and islands of odontogenic epithelium, some lacking peripheral nuclear palisading and stellate reticulum polarization but other islands showing characteristic peripheral palisading nuclei with reverse polarity and central stellate reticulum.

- Absence of a capsule
- Invasion into adjacent bone can be identified.
- Hybrid lesions refer to the admixture in a given lesion of desmoplastic and classic follicular or plexiform ameloblastomas.
- Immunohistochemistry:
 - Collagen type IV immunoreactivity adjacent to tumor islands, a feature not seen in conventional ameloblastoma:
 - Presence of collagen type IV is indicative of de novo synthesis of extracellular matrix proteins
 - Expression of TGF- β , a feature not seen in conventional ameloblastoma

Differential Diagnosis

- Squamous odontogenic tumor (see above)

Treatment and Prognosis

- Similar treatment as solid/multicystic ameloblastoma, including complete resection of the tumor to include at least 1 cm of normal tissue beyond radiographic margin
- Recurrence rates difficult to determine, owing to limited information in the literature

Ameloblastoma, Peripheral Type

Definition: Extraosseous counterpart to intraosseous ameloblastoma.

Synonyms: Ameloblastoma of mucosal or gingival origin; soft tissue ameloblastoma

Clinical

- Represent less than 10% of all ameloblastomas
- More common in men than in women; occurs over a wide age range but most common in the fifth to seventh decades of life
- Involves gingival or alveolar mucosa of the mandible more often than the maxilla:
 - Mandibular involvement is most common in the canine-premolar region.
 - Maxilla involvement is most common in the tuberosity area.
 - May rarely occur in extragingival sites
- Presentation is painless mass or swelling
- Radiology:
 - Absence of intraosseous radiographic abnormality given its mucosal or soft tissue localization
- Proposed histogenesis is from odontogenic epithelial remnants in the gingival lamina propria or from the basal cell layer of gingival epithelium.

Pathology

Gross

- Sessile exophytic, soft to firm mass with smooth, pebbly, or papillary surface measuring from 0.3 to 6 cm in greatest dimension

Histology

- Histologically similar to intraosseous solid/multicystic ameloblastoma but localized to submucosa without osseous involvement.
- Absence of invasive/destructive growth

Differential Diagnosis

- Peripheral odontogenic fibroma
- Peripheral squamous odontogenic tumor
- Craniopharyngioma:
 - Histologic similarities exist between ameloblastoma and craniopharyngioma and rare occurrence of a (peripheral) ameloblastoma in the

nasopharynx, and rare occurrence of craniopharyngioma in infrasellar (e.g., nasopharyngeal) location may result in differential diagnostic difficulties.

- See Section 3, Pharynx, for complete discussion and illustrations.

Treatment and Prognosis

- Conservative surgical resection is the preferred treatment.
- Low recurrence rate
- Rare examples of malignant peripheral ameloblastomas reported

Odontogenic Keratocyst (OKC) or Keratocystic Odontogenic Tumor (KCOT) (Figs. 6-27 and 6-28)

Definition: Distinctive intraosseous, uni- or multicystic tumor of odontogenic epithelial origin with specific clinical behavior and histopathologic features, including potentially aggressive (infiltrative) growth and association with nevoid basal cell carcinoma syndrome.

Synonyms: Odontogenic keratocystoma; primordial cyst

- 2005 World Health Classification of odontogenic lesions:
 - Defines OKC as a neoplasm and recommends the use of the designation KCOT reflective of its neoplastic nature
 - Neoplastic nature supported by molecular evidence (see below)
 - Given the time-honored use of OKC, this designation is used in this section.



Fig. 6-27. Odontogenic keratocyst: a well-defined uniloculated cyst.

(From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 4-249A, p 380.)

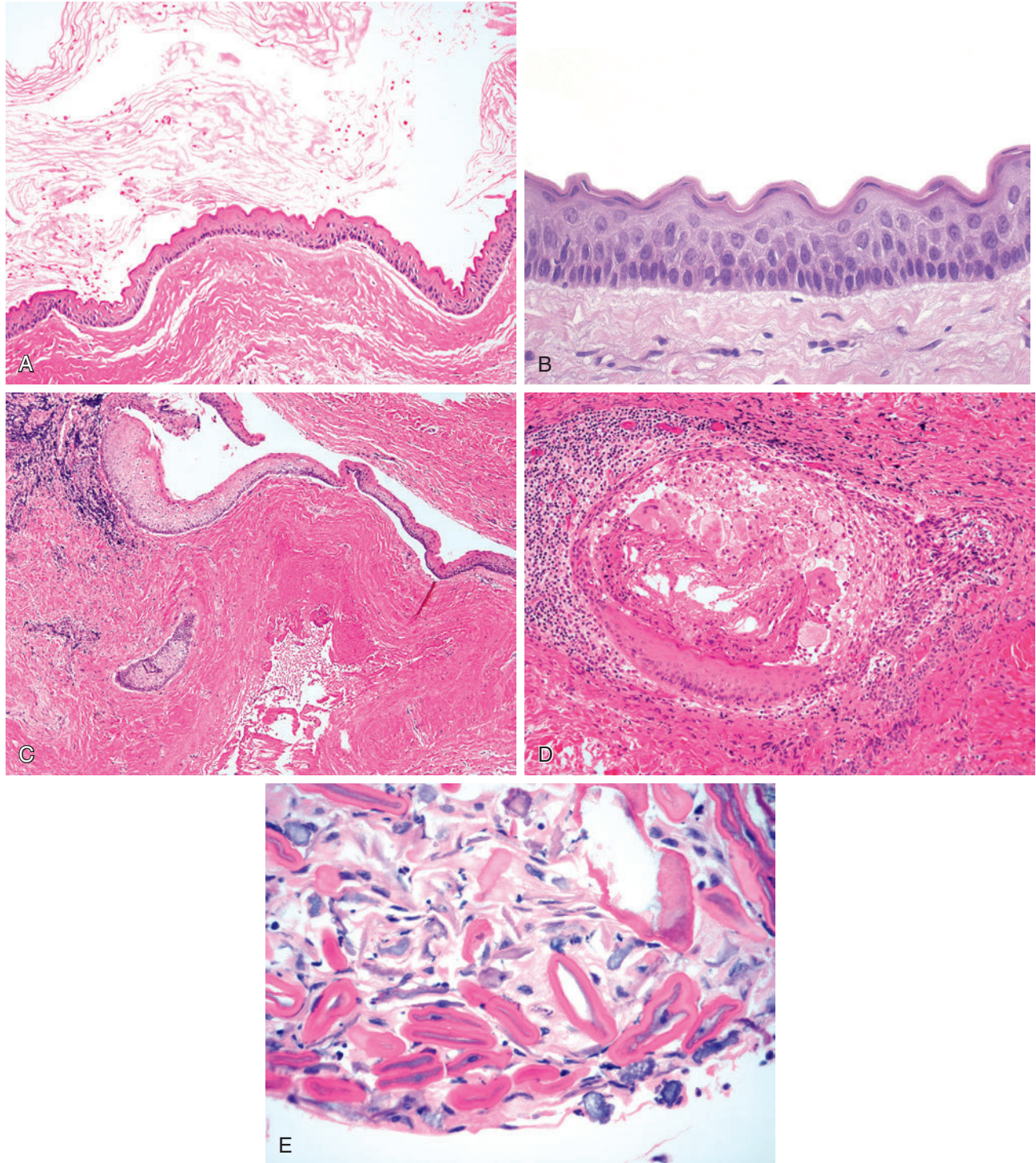


Fig. 6-28. Odontogenic keratocyst.

A and **B**, Odontogenic keratocyst composed of relatively flat-appearing stratified squamous epithelium of 5 to 10 cell layers with surface keratinization including the presence of nuclei (parakeratosis), absence of rete ridges, basal epithelial cells with hyperchromatic nuclei, and nuclear palisading and characteristic corrugated (undulating or wavy) appearance. In **A** there is desquamated keratin (keratinaceous debris) within the cyst lumen as well as areas in which the epithelium appears separated from the connective tissue representing a common feature in odontogenic keratocysts. **C**, In the presence of inflammation (*upper left*) the characteristic features of the epithelial layer may be absent, although away from the inflammation the characteristic surface epithelium is present, including separation of the epithelium from the connective tissue; a satellite cyst is present within the cyst wall. **D**, Higher magnification of a satellite cyst. **E**, Epithelial hyaline bodies (Rushton bodies) can be seen characterized by hyalinized, eosinophilic, angulated, linear, or curved foci within the epithelium.

NOTE: Classification schemes for OKC have identified separate lesion types based on differences in biologic behavior and histomorphology, as well as associated syndromes into central (intraosseous) and peripheral (mucosal) with further subclassification based on the type of keratin layer, including:

- Central or intraosseous OKC:
 - Parakeratotic OKC
 - Orthokeratotic OKC
 - Combined (paraorthokeratotic) OKC
- Peripheral or mucosal OKC
- Clinical and histopathologic spectrum of OKC as defined above is limited to the central or intraosseous parakeratotic OKC, which is discussed here.

Clinical

- Represents more than 80% of odontogenic keratocysts and up to approximately 20% of odontogenic cysts
- Tends to be more common in men than in women; occurs over a wide age range but is most common in the second to third decades of life
- Affects the mandible more often than the maxilla (2:1):
 - In the mandible the most common location is the posterior aspect, specifically the third molar and ramus area
- May be solitary or multiple:
 - If multiple then possibly associated with nevoid basal cell carcinoma syndrome (see below)
- Approximately 50% of patients are asymptomatic.
- Associated symptoms include:
 - Swelling or (intraosseous) drainage of the involved site
 - Pain in the area over the angle of the mandible or preauricular region
 - Discomfort, abscess formation, fistulas, cellulitis, trismus, displacement of teeth, and neurologic involvement
 - Presence of neurologic symptoms depends on the location of the cyst.
 - Neurologic involvement may include paresthesia of the face, teeth, and/or mandible.
 - Expansion of the cyst may result in functional compromise of nearby structures (e.g., excretory duct of parotid gland).
 - Origin from the maxilla may result in nasal obstruction, involvement of the maxillary sinus.
- Laboratory studies:
 - Fluid content from the cyst is low in protein and shows keratocyst antigen.
 - Keratocyst antigen:
 - Soluble polypeptide
 - Present in keratocysts but absent in nonkeratinizing cysts
 - Identical antigenically with lactoferrin
- Radiology:
 - Radiographic features are highly suggestive of the diagnosis but not diagnostic.
 - Well-defined or demarcated, round or ovoid unilocular radiolucency with smooth to corticated margins:
 - >80% are unilocular
 - Periphery may have an ill-defined border with little or no periosteal reaction or cortical sclerosis
 - May be single or multiple
 - Large lesions may appear multilocular.
 - Adjacent tooth may be displaced.
 - An unerupted or impacted tooth may be part of the lesion in up to 40% of cases:
 - In such instances the radiologic appearance may suggest a diagnosis of dentigerous cyst
 - Resorption of roots of teeth adjacent to OKC is uncommon and, if present, may be more suggestive of dentigerous or radicular cyst.
- OKC are thought to originate from odontogenic epithelium and may be of two potential sources:
 - Dental lamina or its remnants
 - Extension of basal cells from the overlying oral epithelium
- Nevoid basal cell carcinoma syndrome:
 - Also referred to as Gorlin syndrome or Gorlin-Goltz syndrome
 - Autosomal dominant inherited disorder with high penetrance
 - Protein patched homolog 1 is a protein that is a member of the Patched family and in humans is encoded by *PTCH1* gene.
 - Caused by mutations in *PTCH* gene, a tumor suppressor gene mapped to chromosome 9q22.3-q31
 - Differences between OKC associated with the nevoid basal cell carcinoma syndrome from non-syndromic associated lesions include:
 - More common in females
 - Occurrence in the first decade of life
 - Greater tendency to be multiple cystic lesions
 - Preference to occur in the maxillary molar region
 - Major components of the syndrome include:
 - Multiple basal cell carcinomas:
 - Begin to appear at puberty or second and third decades of life
 - Most common on mid-face but often appear on skin not exposed to the sun
 - Histology similar to basal cell carcinoma not associated with the nevoid basal cell carcinoma syndrome
 - Multiple OKCs of the jaws
 - Skeletal anomalies are common, including rib and vertebral anomalies:

- Splaying and bifid ribs are most common, with fusion and partial absence being less common
- May be bilateral
- Other skeletal anomalies that can be seen with increased frequency include kyphoscoliosis, spina bifida occulta, and shortened metacarpals.
- Intracranial calcification (lamellar calcification of falx cerebri)
- Plantar and palmar pits:
 - Represent localized retardation of basal epithelial cell maturation
 - May give rise (along base) to basal cell carcinomas
- Characteristic facies with increased cranial circumference and frontal and temporoparietal bossing
- Numerous other abnormalities occur with varying frequency, including a variety of neoplasms:
 - Fibromas (ovarian, cardiac), medulloblastoma, meningioma, fetal rhabdomyoma

Pathology

Gross

- Cystic lesion with a thin, smooth lining, which is usually collapsed and folded and filled with straw-colored fluid and/or thick, cheesy-like material; infected cysts are filled with pus.

Histology

- Lining epithelium:
 - Composed of relatively flat-appearing stratified squamous epithelium of 5 to 10 cell layers with surface keratinization including the presence of nuclei (parakeratosis)
 - Absence of rete ridges
 - Characteristically shows a corrugated (undulating or wavy) appearance
 - Includes basal epithelial cells with hyperchromatic nuclei and nuclear palisading
 - Common feature is separation of the epithelial lining from underlying connective tissue
- Desquamated keratin (keratinaceous debris) can be found in the cyst lumens.
- Mitotic figures can be identified in particular within the suprabasilar layers.
- An inflammatory cell component is typically absent to mild:
 - In the presence of intense inflammation, characteristic features of the epithelial layers as described above may be absent.
 - Rete ridges may be present.
- Satellite cysts, including epithelial rests or small microcysts, may be present within the cyst wall.

- Variable epithelial dysplastic changes can be present but transformation to squamous cell carcinoma is considered rare.
- Ameloblastomatous transformation may be identified:
 - More common in lesions associated with the nevoid basal cell carcinoma syndrome
- Additional findings that may be present include:
 - Mineralization/dystrophic calcification of fibrous connective tissue cyst wall
 - Cholesterol accumulation in the form of cholesterol clefts
 - Epithelial hyaline bodies (Rushton bodies):
 - Hyalinized, eosinophilic, angulated, linear, or curved foci within epithelium
 - Melanin pigment and melanocytes
 - Respiratory type epithelium, mucocytes, and sebaceous glands
- Lesions associated with the nevoid basal cell carcinoma syndrome tend to show:
 - More satellite cysts
 - Solid islands of epithelial proliferation
 - Rests of odontogenic epithelium within the fibrous capsule
 - More commonly have foci of calcifications
- Immunohistochemistry:
 - High proliferating cell nuclear antigen (PCNA) and Ki67
 - Increase p53 positivity
 - p63 immunoreactivity (nuclear) present in most of the cystic epithelium except for the parakeratin
- Cytogenetics and molecular genetics:
 - Majority harbors chromosomal abnormalities (loss of heterozygosity), supporting supposition that OKCs are neoplastic
 - Harbor allelic loss at some of the same loci identified in squamous cell carcinoma, possibly explaining the rare occurrence of squamous cell carcinoma arising in OKC
 - Nevoid basal cell carcinoma syndrome is caused by mutations in *PTCH* gene, a tumor suppressor gene mapped to chromosome 9q22.3-q31.
 - Increasing evidence that the *PTCH* gene plays a role in the development of sporadic (not associated with nevoid basal cell carcinoma syndrome) lesions
 - Syndromic and nonsyndromic lesions show allelic loss of 9q22.
 - p53 and cyclin D1 overexpression more commonly seen in lesions associated with the nevoid basal cell carcinoma syndrome as compared with lesions not associated with this syndrome
 - HPV type 16 reported in a single case

Differential Diagnosis

- Dentigerous cyst
- Radicular cyst
- Orthokeratinized odontogenic cyst:
 - Clinically and histomorphologically different from OKC
 - Not associated with aggressive behavior
 - Not associated with nevoid basal cell carcinoma syndrome
 - Much less common than OKC
 - More common in men than women; tend to occur in young adults
 - Most commonly occur in the mandible, posterior areas; less common in the maxilla:
 - Most often involve unerupted mandibular third molar
 - Histologically, cyst lining composed of a relatively thin layer of noncorrugated stratified squamous epithelium lacking palisading basal layer and showing an orthokeratotic layer of varying thickness with prominent keratohyaline granules below the orthokeratotic surface:
 - In contrast to parakeratosis, orthokeratosis lacks the presence of nuclei within the keratinized surface.
 - Express lower levels of Ki67 and p53 as compared with OKC
 - Usually treated by enucleation and curettage
 - Recurrences are uncommon (approximately 2% recur).
- Ameloblastoma:
 - Overlapping features, including similar ages of occurrence, tendency to predilect to the posterior mandible, uni- and multilocular appearances, and tendency to recur, may present difficulties in diagnosis.
 - Light microscopic features are significantly different, allowing for distinguishing these tumor types.

Treatment and Prognosis

- Preferred treatment is complete surgical excision of the lesion in one piece:
 - Complete excision in one piece may prove difficult given the friable nature of the cyst wall.
 - Extent of surgery (i.e., conservative versus aggressive approach) predicated on size of the lesion, location of the lesion, presence or absence of extension into adjacent structures
- Potential to be locally destructive with invasion of adjacent soft tissues, as well as bone
- Tend to recur:
 - Reported frequency of recurrence varies from approximately 5% to greater than 60%.

- Recurrence may be a function of inadequate surgical removal of the entire cyst to include the cyst lining.
- Recurrence is more common in association with mandibular lesions, especially those located in the posterior body and ascending ramus.
- Multiple recurrences are not unusual.
- Recurrence usually occurs within 5 years of the initial diagnosis; however, recurrent lesions may occur years (10 or more years) after the initial resection:
 - For this reason long-term follow-up, including periodic radiologic imaging, advocated
- Other than the tendency to recur, the overall prognosis is very good.
- Occasional examples may not be controllable by surgery but behave in a progressive manner with destructive growth, including extension to the skull base.
- Rare examples associated with malignant transformation (squamous cell carcinoma)

Adenomatoid Odontogenic Tumor (AOT) (Figs. 6-29 and 6-30)

Definition: Benign epithelial odontogenic neoplasm, usually cystic, characterized by presence of whorled nodules of spindle cells, microcyst or duct-like spaces, and indolent behavior (i.e., slow growth).

Clinical

- Uncommon, representing from approximately 2% to 7% of all odontogenic tumors
- More common in females than in males; most (two thirds) occur in second decade; uncommon occurrence in individuals over 30 years of age
- Often asymptomatic, discovered during course in radiographic workup in individuals having problems with tooth eruption:
 - Larger lesions may cause painless expansion of bone.
- Two thirds of cases occur in maxilla and two thirds occur associated with crown of impacted tooth (follicular type), especially maxillary canines:
 - Intraosseous location unassociated with a tooth (extrafollicular type) may occur.
 - Peripheral (extraosseous) location occurs but is rare.
- Radiology:
 - Appear as unilocular radiolucency with well-circumscribed borders
 - Scattered fine radiopacities may be seen within radiolucent area:
 - Dependent on amount of mineralized tissue within the tumor
 - Described as “snowflakes”

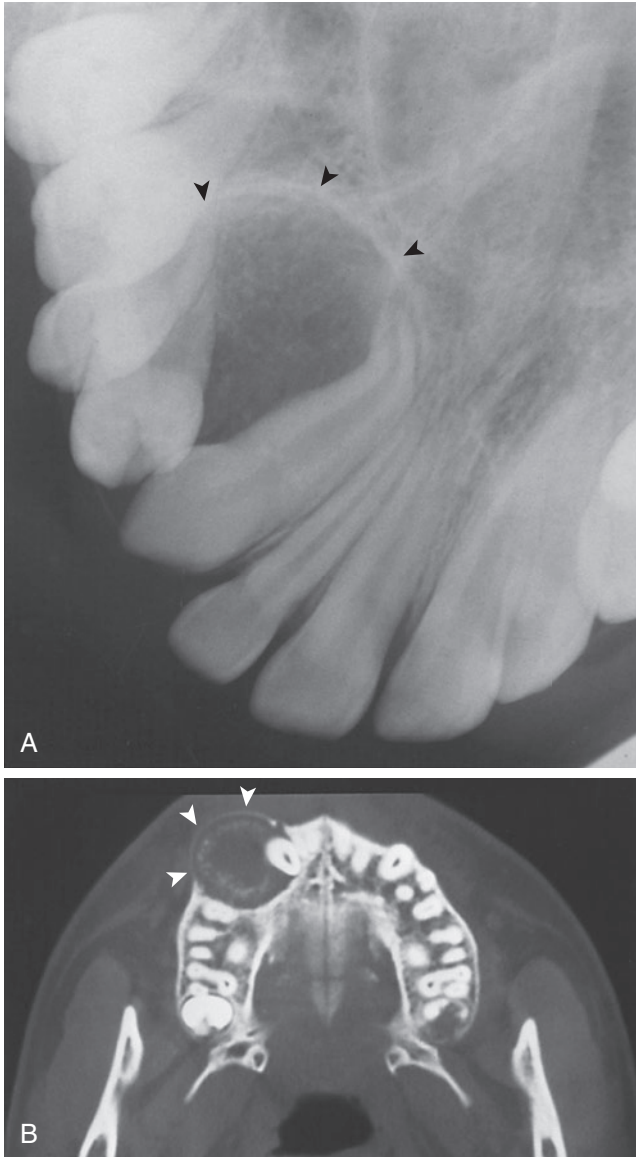


Fig. 6-29. Adenomatoid odontogenic tumor.

A, Occlusal view shows a well-defined radiolucent lesion with curved margins, tooth displacement, and small internal calcifications in the maxilla (*arrowheads*). **B,** Axial CT shows the well-defined rounded lesion with the incorporated canine and tiny calcifications (*arrowheads*).
(From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-48, p 1501.)

- Origin unknown but most likely development is from residues of dental lamina and proliferation of odontogenic epithelium adjacent to reduced enamel epithelium of unerupted teeth

Pathology

Gross

- Well-circumscribed, usually encapsulated, often appearing cystic
- Majority measure from 1 to 3 cm

Histology

- Encapsulated proliferation of spindle-shaped as well as polygonal epithelial cells arranged in solid nodules, whorls and trabeculae, cords and strands in loose fibrovascular stroma:
 - Reticular growth may be seen.
 - Often with clear-appearing cytoplasm
- Cystic spaces referred to as duct-like found in varying numbers are lined by cuboidal to palisaded columnar cells:
 - Represents a characteristic features of this tumor:
 - Diastase-resistant, PAS-positive intraluminal eosinophilic material often seen
 - Some cystic structures show invagination of part of the wall, resulting in horseshoe-shaped structure with two layers of columnar cells separated by a zone of diastase-resistant, PAS-positive material.
 - Mitotic figures can be seen.
- Within nodules rosettes may be seen surrounding small eosinophilic amorphous diastase-resistant, PAS-positive material.
- Additional findings may include:
 - Extracellular calcified material often with concentric laminated rings or annular appearance may be seen adjacent to spindle-shaped and/or columnar cells
 - Eosinophilic, hyalinized dentinoid material often with entrapped epithelium seen in many cases, which may in part be calcified (dystrophic calcification)
 - Melanin pigment
- A common finding in limited areas of most cases are foci with histologic similarity to calcifying epithelial odontogenic tumor (CEOT).
- Histochemistry:
 - Congo red staining may show focal presence of apple green birefringence indicative of amyloid
- Immunohistochemistry:
 - Epithelial cells immunoreactive for variety of cytokeratins, including CK5, 8, 14, 17, 19
 - Low proliferation indices by Ki67 staining

Treatment and Prognosis

- Conservative but complete surgical excision is curative.
- Recurrence rates of approximately 2% reported

Calcifying Epithelial Odontogenic Tumor (CEOT) (Figs. 6-31 and 6-32)

Definition: Benign slow-growing but locally invasive odontogenic neoplasm characterized by sheets and islands of eosinophilic hyperchromatic pleomorphic cells with foci of mineralization and eosinophilic amorphous material that stains with amyloid markers.

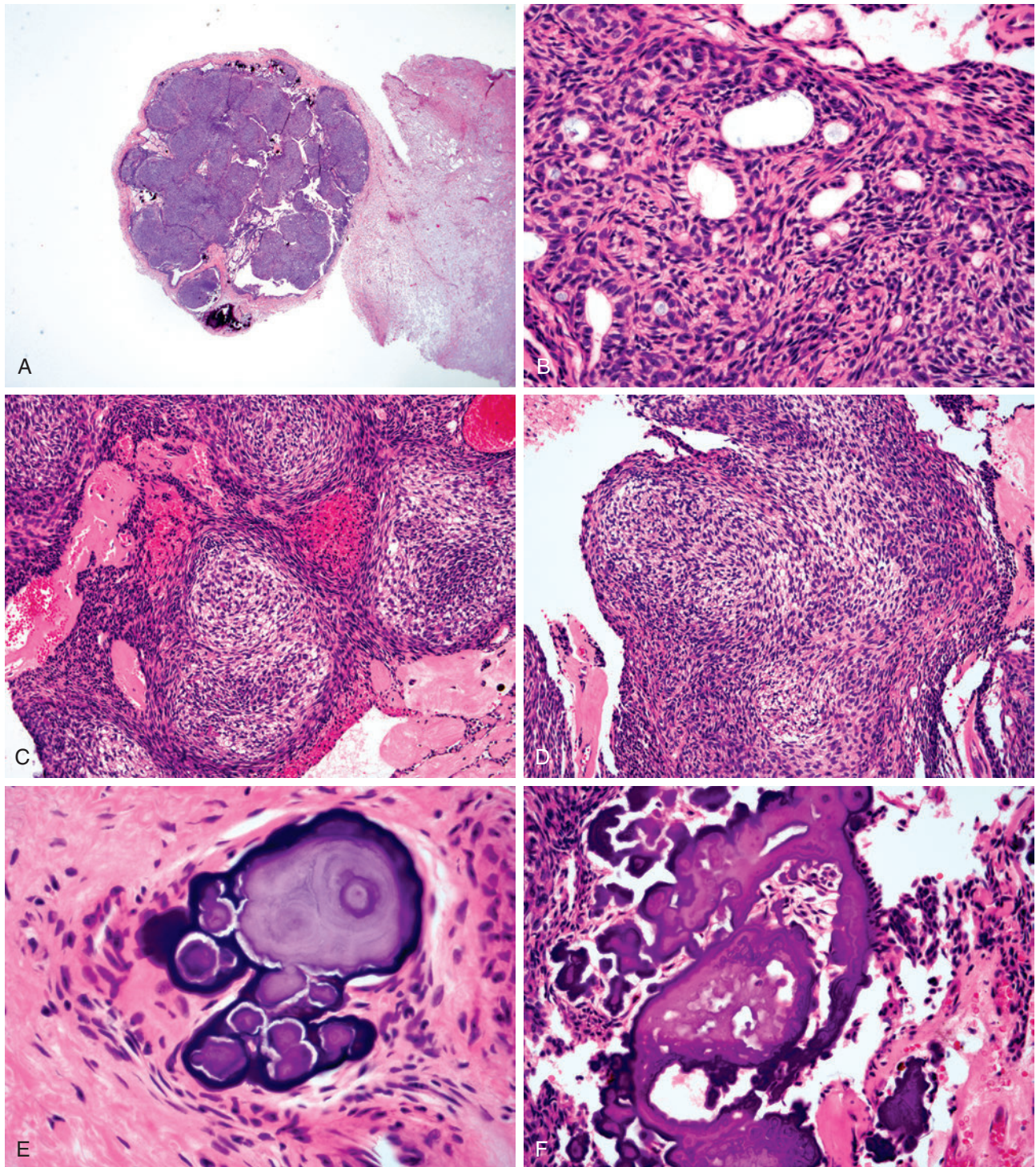


Fig. 6-30. Adenomatoid odontogenic tumor.

A, Intracystic circumscribed to encapsulated cellular proliferation with nodular growth and sharp demarcation from the adjacent connective tissue. **B,** Gland-like or duct-like spaces lined by cuboidal to palisaded columnar cells represent a characteristic features. **C** and **D,** Solid nodules of spindle-shaped cells with whorled or swirling appearance without identifiable duct-like spaces. **E,** Extracellular calcified material with concentric laminated rings or annular appearance may be seen. **F,** Dystrophic calcification appearing as eosinophilic, hyalinized dentinoid material often with entrapped epithelium can be seen in many cases.



Fig. 6-31. Calcifying epithelial odontogenic tumor (Pindborg tumor).

Axial CT (bone window setting) shows marked expansion of the right mandible with loss of bone in the lateral cortex. Multiple calcific densities are noted within the lesion. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-30, p 1490.)

Synonyms: Pindborg tumor; calcifying odontogenic tumor

Clinical

- Rare tumor accounting for less than 2% of all odontogenic tumors
- No gender predilection; most common in the third to fifth decades of life
- May be intraosseous or extraosseous
 - Intraosseous:
 - Represents majority of cases
 - Occurs more often in the mandible than maxilla (2:1)
 - Usually occurs in molar-premolar region
 - 60% associated with unerupted tooth
 - Extraosseous:
 - 5% to 6% of cases are extraosseous.
 - Predilects to anterior segment of jaws
- Presentation is usually that of a slowly enlarging expansile painless lesion within posterior portion of affected jaw
- Approximately 60% associated with unerupted tooth, most often mandibular third molar
- Radiology:
 - Most appear as mixed radiolucent-radiopaque lesions but may show wide variation in appearance:
 - Well circumscribed to poorly demarcated
 - Unilocular or multilocular

- Radiolucent to combined radiolucent-radiopaque with multilocular appearance
- No known cause

Pathology

Gross

- Firm lesion that on cut section is solid with various amounts of calcification
- Minute cystic spaces may be present but prominent cystic change not present although rare cystic variant reported

Histology

Intraosseous CEOT

- Unencapsulated lesion with:
 - Irregular sheets and islands consisting of polyhedral epithelial cells with abundant eosinophilic cytoplasm, round to polygonal nuclei with hyperchromasia and pleomorphism, sharply defined cell borders, and well-developed intercellular bridges
- Other cell types seen in CEOT may include:
 - Cells with clear-appearing cytoplasm (clear cell variant of CEOT):
 - Clear cells contain glycogen (intracytoplasmic diastase-sensitive, PAS-positive).
 - May be dominant cell type raising consideration of an alternative diagnosis such as clear cell odontogenic carcinoma
 - Langerhans cells (Langerhans cell variant of CEOT):
 - These cells are immunoreactive for S100 protein and CD1a
 - Langerhans cells may be seen in “conventional” CEOT but occur in significantly increased numbers in so-called Langerhans cell variant of CEOT
 - Treatment and prognosis similar to conventional CEOT
- Mitotic figures may be seen but generally are few in number.
- Within sheets of lesional cells are various amounts of eosinophilic homogeneous material:
 - Mostly extracellular but may be intracellular swelling cells with eccentric displacement of disintegrated nuclei and loss of cell integrity
 - With increasing calcification, spherules with basophilic concentric laminations are formed.
 - May be present extensively in connective tissue away from tumor islands
 - Stain with Congo red (apple green birefringence) indicative of amyloid
- In minority of cases, foci with histologic features of adenomatoid odontogenic tumor may be present

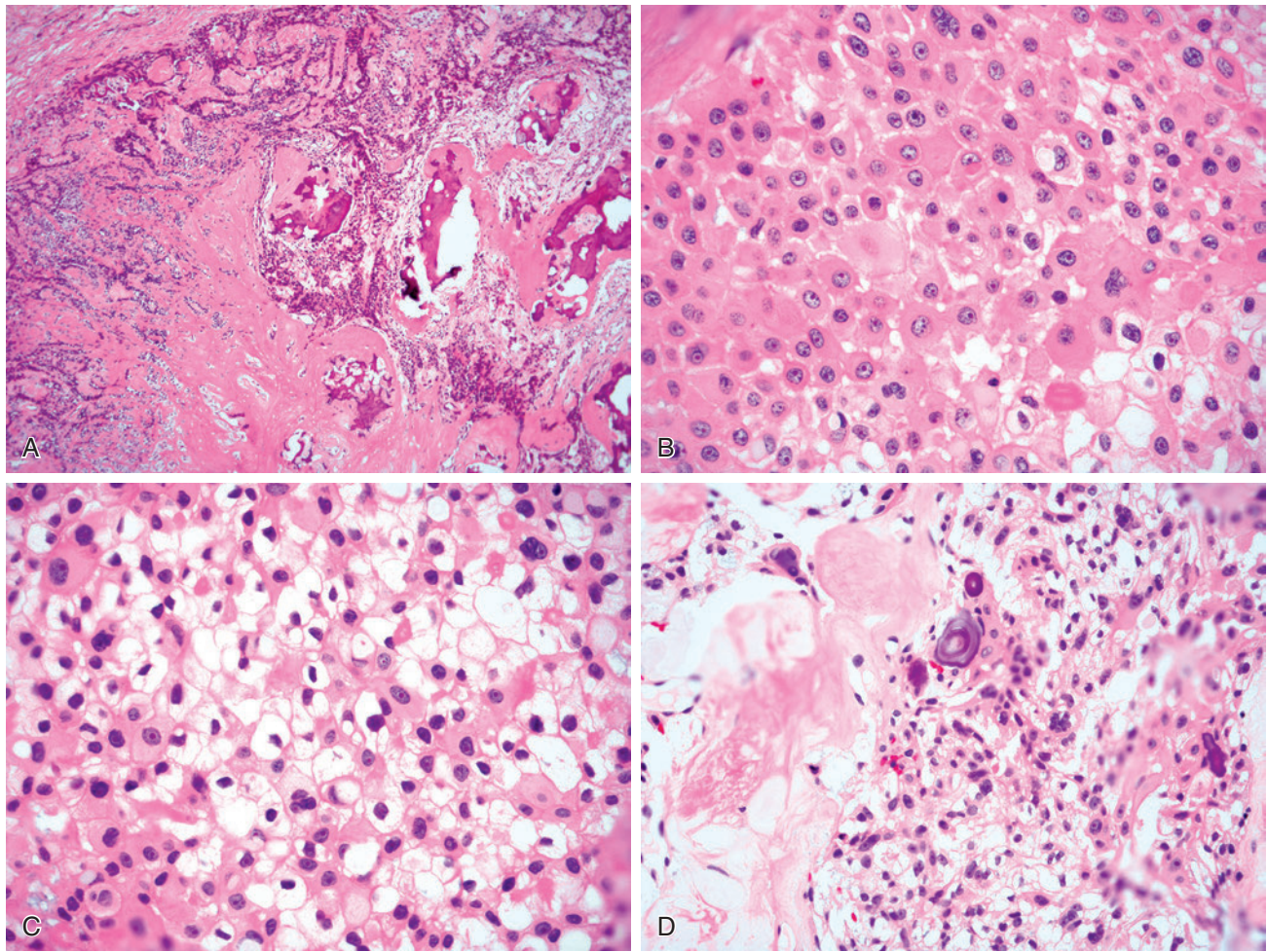


Fig. 6-32. Calcifying epithelial odontogenic tumor.

A, Unencapsulated lesion composed of irregular sheets and islands of tumor with associated calcifications and acellular hyalinized material. **B,** Tumor is composed of polyhedral epithelial cells with abundant eosinophilic cytoplasm, round to polygonal nuclei with hyperchromasia and pleomorphism, sharply defined cell borders, and well developed intercellular bridges. **C,** Cells with clear appearing cytoplasm may be present and may be the dominant cell type representing the clear cell variant of CEOT. **D,** Extracellular eosinophilic homogeneous material that showed apple green birefringence by Congo red staining (not shown) and spherules with basophilic concentric laminations (psammoma bodies) may be identified. (Slide courtesy Mary Richardson, MD, DDS.)

- Immunohistochemistry:
 - Reactive for cytokeratins, EMA, p63, vimentin
 - Staining for purported myoepithelial-related markers including calponin and GFAP reported
 - Negative for S100 protein and smooth muscle actin

Extraosseous CEOT

- Histologically similar to intraosseous CEOT but:
 - Tumor cells tend to form strands and islands rather than large sheets.
 - Amount of calcified material may be minimal or absent.

Treatment and Prognosis

- Conservative surgical resection is preferred treatment.
- Recurrence rates range from 10% to 14%:
 - Long-term follow-up is required, in particular when conservative surgery is performed.
- Malignant calcifying odontogenic tumor:
 - Rare tumor
 - Histologically characterized by prominent nuclear pleomorphism, increased mitotic activity, increased proliferation rate, and lymph-vascular invasion.
 - Loss of p53 transcriptional activity

Calcifying Cystic Odontogenic Tumor (CCOT) (Figs. 6.33-6.34)

Definition: Benign cystic neoplasm of odontogenic origin characterized by ameloblastoma-like epithelium with eosinophilic ghost cells and calcifications.

Synonyms: Gorlin tumor, Gorlin cyst, Calcifying odontogenic cyst, odontogenic ghost cell tumor, dentinogenic ghost cell tumor

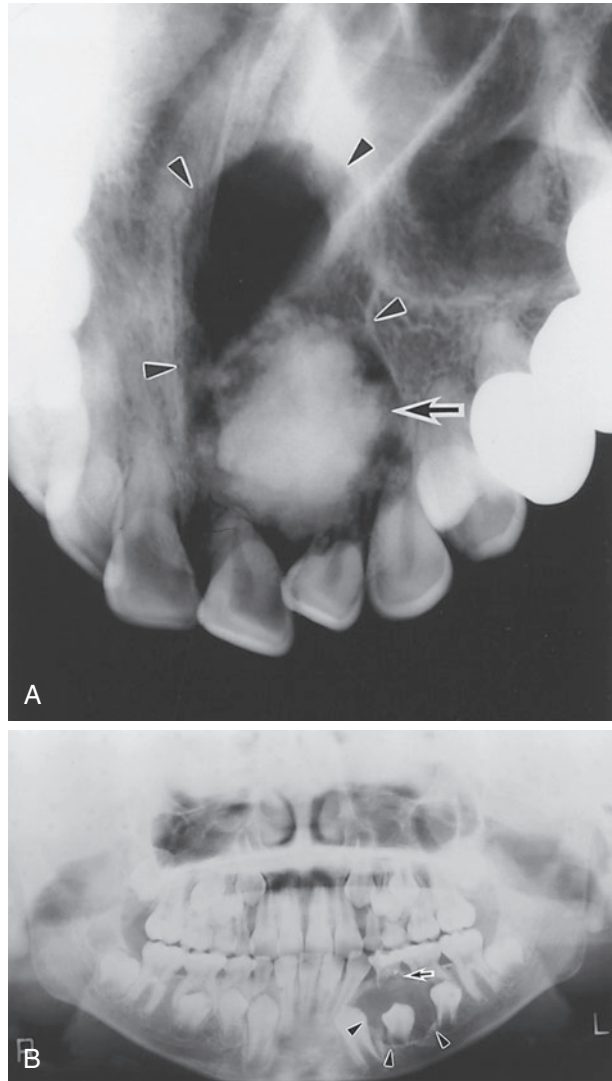


Fig. 6-33. Calcifying cystic odontogenic tumor.

A, Occlusal radiograph shows a unilocular lesion (arrowheads) with odontoma (arrow) in the right side of the maxilla. Calcified tissue can be observed adjacent to the odontoma. **B,** Pantomogram shows a pericoronal calcifying odontogenic cyst (arrowheads) with tiny calcifications. Root resorption can be observed at the left side of the milk tooth (arrow). (From Som & Curtin: *Head and Neck Imaging*, ed 5. Philadelphia: Elsevier, Figures 25-36 and 25-37.)

- World Health Organization classifies CCOT as a benign odontogenic neoplasm
- Various classification schemes suggested for CCOT including:
 - Benign cyst versus neoplasm
 - Cystic versus solid
 - Central (intraosseous) versus peripheral (extraosseous)
 - Odontogenic neoplastic variants
- CCOT may be associated with a variety of odontogenic neoplasms (hybrid tumors) referred to as neoplastic associated variants including:
 - Odontoma (most common)
 - Ameloblastoma
 - Solid/multicystic
 - Unicystic
 - Adenomatoid odontogenic tumor
 - Ameloblastic fibroma
 - Ameloblastic fibro-odontoma
 - Odonto-ameloblastoma
 - Odontogenic-fibromyxoma

Clinical

- Rare tumor accounting for less than 2% of all odontogenic tumors
- No gender predilection; wide age range from first to tenth decade of life, with peak incidence in second and third decades:
 - Lesions in young adults often associated with odontomas
- Usually asymptomatic unless secondarily inflamed
- Circumscribed, smooth surface mass measuring up to 4 cm in greatest dimension
- May be intraosseous or extraosseous
 - **Intraosseous:**
 - Equal distribution between maxilla and mandible
 - Most found in incisor-cuspid area (anterior portion of jaws)
 - Less commonly involve posterior portion of jaws
 - Present as painless swelling
 - **Extraosseous:**
 - Most found in incisor-cuspid area (anterior portion of jaws)
 - Appear as circumscribed, elevated, smooth surface mass
- Radiology:
 - Cystic unilocular or multilocular radiolucency with discrete well-defined margins containing scattered calcifications that may produce a “salt and pepper like” appearance
 - Displacement of teeth or root resorption occasionally seen

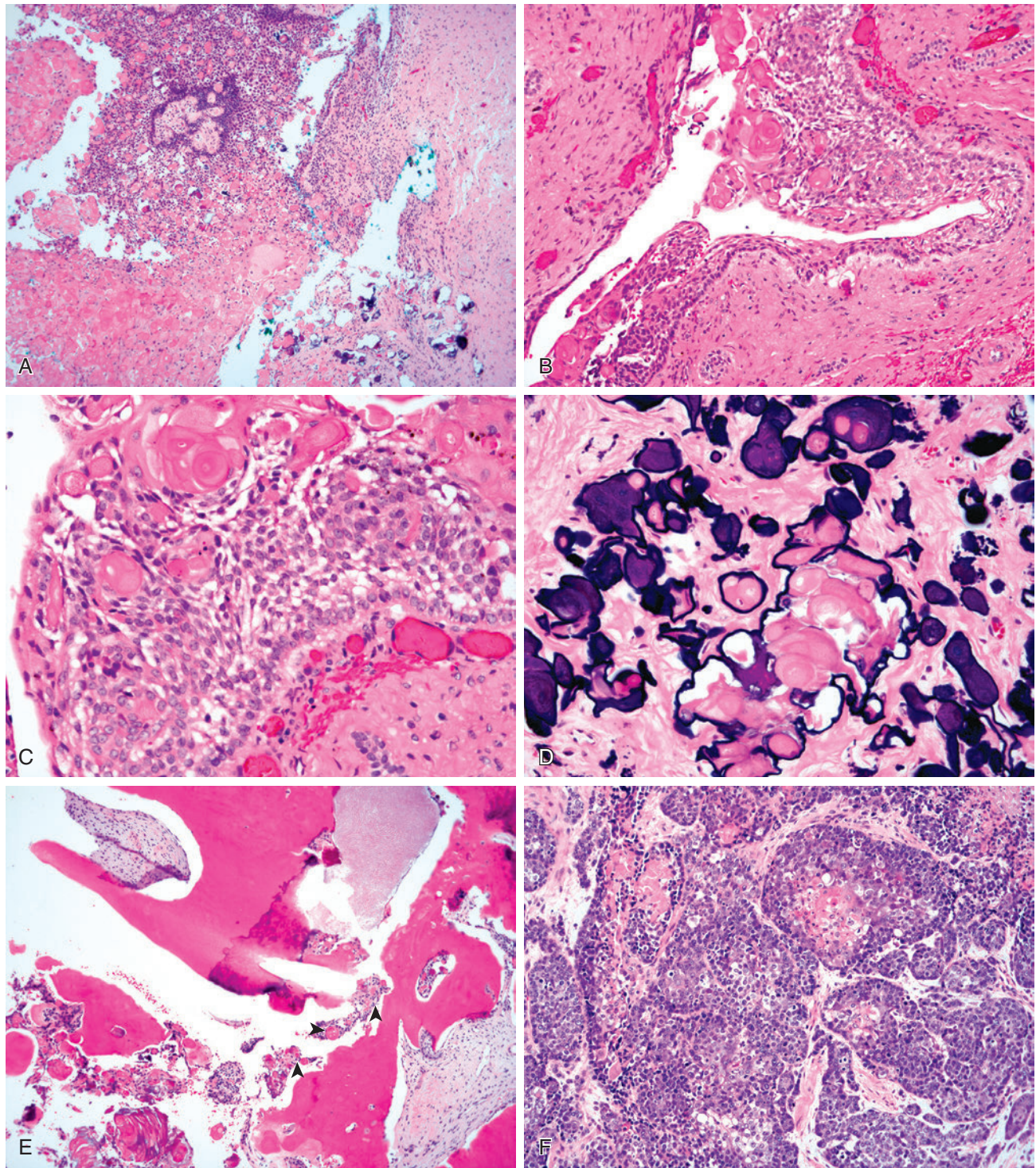


Fig. 6-34. Calcifying cystic odontogenic tumor.

A, Cystic odontogenic epithelial proliferation with ghost cells and calcifications. **B** and **C**, Loosely arranged epithelium of variable thickness with stellate cells, cuboidal to columnar-appearing basal cells with nuclear palisading and numerous eosinophilic ghost cells characterized by the loss of nuclei with preservation of cell outline. **D**, Ghost cells with dystrophic mineralization (calcification) surrounded by dentinoid. **E**, CCOTs may be associated with other odontogenic neoplasms (hybrid tumors), the most common being odontoma, as seen in this image characterized by the presence of enamel matrix, cementum, and pulp (*top*). Foci of CCOT including ghost cells are present adjacent to the odontoma (*arrowheads*). **F** and **G**, Ghost cell odontogenic carcinoma characterized by a solid proliferation of hyperchromatic and pleomorphic epithelial cells with increased mitotic activity and associated/admixed islands of ghost cells. This tumor occurred in a 10-year-old who had malignant transformation of a CCOT.

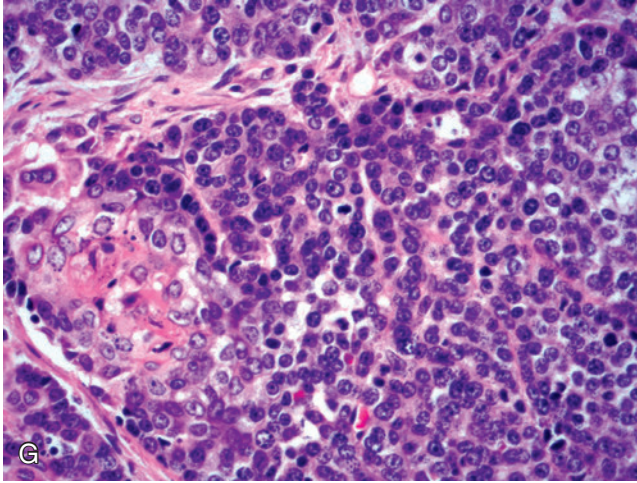


Fig. 6-34, cont'd

- Associated unerupted tooth seen in approximately one third of cases
- May be associated with odontoma, latter appearing as opaque component
- Radiologic appearance similar to that of adenomatoid odontogenic tumor and calcifying epithelial odontogenic tumor
- Extraosseous lesions may show saucerization and may occasionally displace adjacent teeth
- No known etiology

Pathology

Histology (for both intraosseous and extraosseous CCOT)

- Cystic, multicystic, or solid cellular proliferation comprised of an epithelial lining that includes:
 - Loosely arranged epithelium of 4 to 10 cells in thickness resembling stellate reticulum (stellate cells) of ameloblastoma
 - Basal cells that may be cuboidal or columnar with nuclear palisading resembling ameloblasts but histologic findings reaching criteria of ameloblastoma not typically identified
 - Eosinophilic material representing so-called **ghost cells** characterized by loss of nuclei with preservation of cell outline
 - May fuse to form large sheets of amorphous, acellular material
 - Similar to ghost cells seen in pilomatixoma (calcifying epithelioma of Malherbe) and craniopharyngioma
 - Mechanisms involved in formation of ghost cells are unknown

- Dystrophic mineralization (calcification) within ghost cells commonly present
- Foci of eosinophilic matrix material representing dysplastic dentin (dentinoid) or cementum may be present adjacent to epithelial component:
 - May result from inductive effect on adjacent mesenchymal tissue
- Solid variant comprised of haphazard arrangement of strands and cords of columnar and stellate epithelial cells and ghost cells
- Sheets of epithelial cells with clear appearing cytoplasm separated by thin fibrous connective tissue stroma may be identified:
 - Clear cells contain glycogen (diastase-sensitive, PAS-positive)
- Other findings may include presence of:
 - Cholesterol granuloma formation
 - Melanin pigment
- Approximately 20% associated with odontomas:
 - Usually unicystic
 - Combined features of CCOT and odontoma, latter characterized by:
 - Enamel matrix, dentin, and pulp
- Immunohistochemistry:
 - LEF-1, a nuclear transcription factor of Wnt pathway regulating multipotent skin stem cell differentiation:
 - Reported positive in 64% of CCOTs analyzed (7/11)
 - Strong diffuse staining also found in salivary gland basal cell adenoma (63%; 5/8) and basal cell adenocarcinoma (69%; 11/16)
 - β -Catenin, a transcriptional coactivator that interacts with LEF-1:
 - Nuclear staining reported in 83% of CCOTs analyzed (9/11)
 - Nuclear β -catenin also found in salivary gland basal cell adenoma (50%; 4/8) and basal cell adenocarcinoma (43%; 6/14)
 - Coexpression of LEF-1 and nuclear β -catenin found in all LEF-1-positive CCOTs
 - Findings indicate possible diagnostic utility of LEF-1 and β -Catenin in CCOT and in salivary gland tumors

Treatment and Prognosis

- Simple enucleation for unilocular lesions and enucleation with bony curettage for multilocular lesion considered adequate treatment
- Recurrent tumor:
 - May uncommonly occur with intraosseous lesions
 - Not reported in extraosseous lesions
- Follow-up including radiographic imaging recommended

- When associated with other tumor types (e.g., ameloblastoma) treatment and prognosis follow that of more aggressive tumor type
- May rarely undergo malignant transformation to ghost cell odontogenic carcinoma characterized by:
 - Solid proliferation of hyperchromatic and pleomorphic epithelial cells with abnormal mitoses and associated/admixed islands of ghost cells
 - Require wide local excision with tumor-free margins
 - May recur or metastasize resulting in patient death.

Odontogenic Myxoma

(Figs. 6-35 and 6-36)

Definition: Benign but locally invasive intraosseous neoplasm recapitulating mesenchymal portion of tooth-forming unit (i.e., dental papillae) characterized by presence of abundant myxoid or mucoid extracellular matrix with or without fibrous stroma and associated hypocellular component, including bland-appearing spindle-shaped to stellate to round-appearing cells.

Synonym: Odontogenic fibromyxoma

Clinical

- Considered an uncommon neoplasm
- No gender predilection; may occur over a wide age range from very young (first decade of life) to older individuals (eighth decade and older) but considered most common in second and third decades of life
- Most often occur in posterior tooth-bearing areas of mandible and maxilla:
 - More often identified in mandible than maxilla
- Small lesions are asymptomatic, but as lesions enlarge there is progressive swelling with bony expansion.
- Radiologic imaging findings vary and may include:
 - Small unilocular radiolucent lesion between roots of teeth
 - Large multilocular radiolucency
 - Borders vary from well defined with sclerotic margins to poorly defined with diffuse margins.
 - Often associated with root absorption and perforation of cortex
 - Variably described as soap bubble, honeycomb, tennis racket, or ground glass appearance
- Cause is unknown

Pathology

Gross

- On cut section surface appears homogeneous and translucent and gelatinous

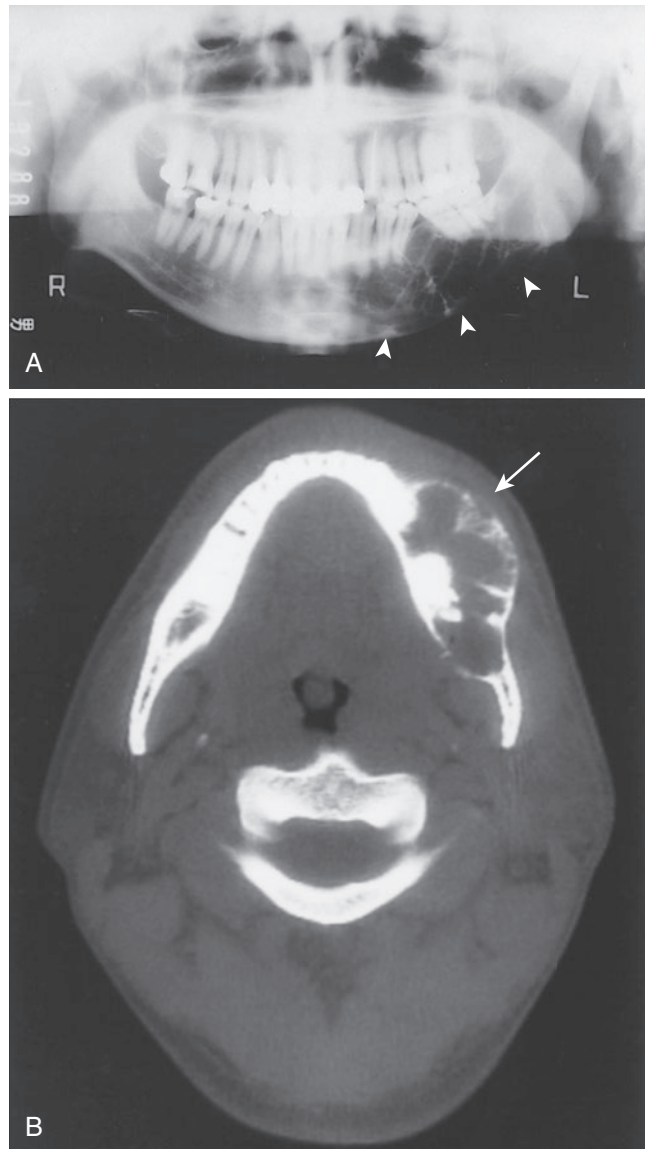


Fig. 6-35. Myxoma of the mandible.

A, Pantomogram shows an ill-defined lesion with straight septa and tooth displacement (*arrowheads*). **B**, Axial CT (bone window setting) shows buccal expansion of the lesion with straight septa (*arrow*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 25-50, p 1502.)

Histology

- Unencapsulated, usually hypocellular proliferation composed of spindle-shaped to stellate to round-appearing cells embedded in myxoid stroma:
 - Areas of increased cellularity may be present.
 - Absence of significant nuclear pleomorphism and increased mitotic activity:
 - Binucleate cells and mitotic figures can be seen.

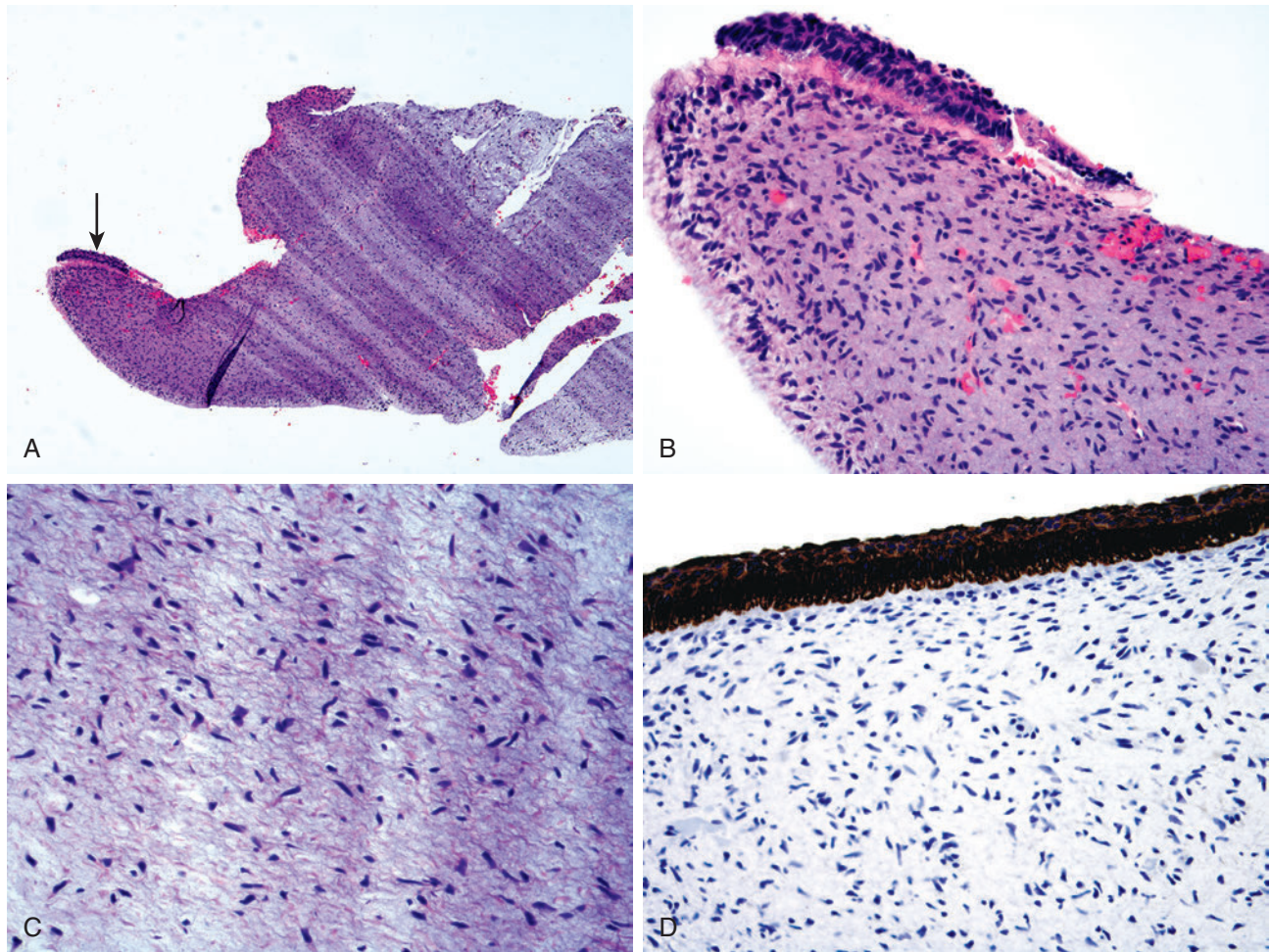


Fig. 6-36. Odontogenic myxoma.

A, Polypoid unencapsulated spindle-shaped proliferation embedded in myxoid stroma; odontogenic epithelium is focally present (*arrow*). **B** and **C**, Variably cellular proliferation composed of spindle-shaped to stellate to round-appearing cells lacking significant nuclear pleomorphism or increased mitotic activity as well as absence of complex curvilinear or plexiform vascular pattern that can be seen in sarcomas. In **B** odontogenic epithelium composed of columnar-appearing cells is seen, although such epithelium is only found in a small percentage of cases and is unnecessary in the diagnosis. **D**, The odontogenic epithelium is cytokeratin (AE1/AE3) positive.

- Variable amount of fibrous or collagenized stroma may be present in any case:
 - Based on the amount of fibrous stroma a designation of odontogenic fibromyxoma may be used.
- Nests or islands of odontogenic epithelium may or may not be present:
 - Rarely present (<10% of cases)
 - Not a requirement for diagnosis
- Nondescript vascularity lacking complex curvilinear or plexiform vascular pattern that can be seen in sarcomas
- Immunohistochemistry:
 - Spindle cells:
 - May be reactive for actins (smooth muscle and muscle specific)
 - Cytokeratins, S100 protein negative
 - If odontogenic epithelium is present will be reactive for cytokeratins (AE1/AE3, CK5, 7, 14, 19)
- Cytogenetics and molecular genetics:
 - Absence of guanine nucleotide-binding protein/ α -subunit (GNAS) mutation that is present in fibrous dysplasia

Differential Diagnosis

- Dental follicle (see Fig. 5-4):
 - Readily differentiated on basis of clinical and radiologic findings

- Dental follicle confined to crown of unerupted tooth and a few millimeters around it
- Dental follicle more collagenized than myxomas and may contain reduced enamel epithelium with numerous islands of odontogenic epithelium
- Dental papilla (see Fig. 5-5):
 - Represents formative dental pulp
 - May be separated from developing tooth during surgery and included in surgical specimen
 - Histologically distinguished from odontogenic myxoma by presence of odontoblasts close to surface and narrow cell-free zone beneath odontoblasts
- Odontogenic fibroma (Fig. 6-37):
 - Rare benign mesenchymal odontogenic neoplasm composed of fibrous, myxoid, and collagenized tissue with or without odontogenic epithelium
 - Divided into central and peripheral:
 - Central odontogenic fibroma (COF): originates in bone
 - Peripheral odontogenic fibroma: originates outside of bone (extragnathic) occurring in gingiva or attached alveolar ridge mucosa (in edentulous areas)
- Central odontogenic fibroma can be divided into two histologic variants, including:
 - Epithelial-poor type:
 - Noninfiltrating connective tissue lesion resembling dental follicle
 - Minimally cellular with dispersed collagen fibers
 - Fibromyxoid background
 - Scattered remnants of inactive-appearing odontogenic epithelium appear as small irregular islands and cords
 - Calcifications may be present.
 - Epithelial-rich-type:
 - Cellular fibroblastic connective tissue admixed with less cellular vascularized areas
 - Islands or strands of inactive-appearing odontogenic epithelium integral component and often conspicuous but may be sparse
 - Calcified material considered to be metaplastically produced dysplastic cementum or osteoid or dentin present
- Additional histologic variants described including:
 - Ameloblastomatoid
 - COF with numerous giant cells
 - COF with numerous granular cell
- Sinonasal myxoma/fibromyxoma; see Section 1, Sinonasal Tract

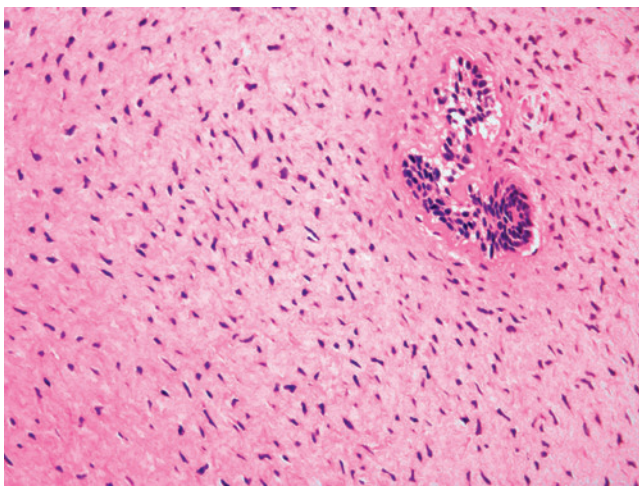


Fig. 6-37. Odontogenic fibroma.

Inactive-appearing odontogenic epithelium irregular-shaped island is present within a background of fibroconnective tissue.

Treatment and Prognosis

- Conservative surgery by enucleation and curettage can be performed for small lesions (smaller than 3 cm).
- Segmental resection with immediate reconstruction preferred for larger tumors
- Recurrence rates are high, ranging from 10% to 33% with an average of 25%:
 - Depends on extent of surgery
 - Long-term follow-up is required, in particular when conservative surgery is performed.
- Malignant transformation (odontogenic myxofibrosarcoma) exceedingly rare

BENIGN TERATOMA

Definition: Tumor composed of a variety of mature tissues derived from two or three germ layers and foreign to the site of occurrence.

- See Section 5, Neck, for complete discussion.

MALIGNANT TUMORS

POTENTIALLY MALIGNANT DISORDERS

Definition: Clinical presentations that may have a potential to become cancer conveying the concept of a multi-step process of cancer development, but unlikely, on a priori grounds, that there is uniformity in the way individual patients or tissues behave

- Use of term potentially malignant disorder conveys:
 - Not all lesions and conditions described under this term transform to cancer.
 - There is a group of morphologic alterations, among which some may have an increased potential for malignant transformation.
 - Potentially malignant disorders of oral mucosa are also indicators of risk of likely future malignancies elsewhere in (clinically normal-appearing) oral mucosa and not only site-specific predictors.

Synonyms: Pre-cancer, precursor lesions, epithelial precursor lesions; premalignant lesions; intraepithelial neoplasia

- Oral potentially malignant disorders include (but may not be limited to):
 - Oral leukoplakia (including proliferative verrucous leukoplakia)
 - Oral erythroplakia
 - Actinic keratosis (cheilitis)
 - Oral submucous fibrosis (see previous chapter)
 - Palatal lesions in reverse smokers:
 - Specific to populations who smoke with the lighted end of the cigar, cigarette, or cheroot inside the mouth, resulting in red, white, or mixed lesions of the palate
 - All changes related to this habit are noted on palate.
 - Lichen planus:
 - Considerable controversy as to its potentially malignant nature
 - See previous chapter
 - Oral discoid lupus erythematosus (DLE):
 - Conflicting data in literature regarding whether oral DLE is a potentially malignant disorder
 - Hereditary disorders that may have an increased risk of malignancy in the mouth include:
 - Dyskeratosis congenital
 - Epidermolysis bullosa
- This section focuses on only oral leukoplakia, proliferative verrucous leukoplakia, oral erythroplakia, and actinic cheilitis.

Oral Leukoplakia (OL)

(Figs. 6-38 through 6-40)

Definition: Clinical term for a white mucosal lesion (plaque or patch) that cannot be rubbed or scraped off and that is not recognized (clinically or pathologically) as any other disease.

◦ *Leuko* means white and *plakia* means patch.

Synonyms: Keratosis; hyperkeratosis

Clinical Features

- Estimated prevalence of oral leukoplakia, worldwide, is approximately 2%:
 - Incidence increases with age
- More common in men than in women; most common in the fifth through seventh decades of life:
 - Uncommon in younger age groups (less than 30 years of age).
- Occurs most commonly on the vermilion border of the lower lip, buccal mucosa, and gingiva; less common locations include the tongue (lateral and ventral), palate (hard and soft), and floor of mouth
- Clinical diagnosis of leukoplakia is not necessarily an indicator and does not necessarily correlate with histopathologic confirmation of an underlying dysplasia:
 - Precancerous potential of leukoplakia is well established, is more often predicated on the facts that keratosis is associated with an increased risk of malignant transformation as compared with nonkeratotic oral lesions and that keratosis is present in a significant percentage (greater than one third of cases) of oral carcinomas.
 - Of all oral leukoplakias from 9% to 37% represent dysplasia, carcinoma in situ, or invasive carcinoma at time of biopsy.
 - Overall risk of dysplasia transforming to invasive carcinoma is estimated to be approximately 16% to 36%.
 - There is a correlation between the site of leukoplakia and the incidence of an associated dysplasia:
 - Greatest frequency of epithelial dysplasia is found in leukoplakic lesions of the floor of mouth, tongue (lateral and ventral), and vermilion border of the lip
- Cause:
 - Includes tobacco use, trauma, microorganisms, ultraviolet radiation:
 - Arguably, most common cause of oral leukoplakia is due to tobacco, a finding supported by the fact that:



Fig. 6-38. Clinical appearance of oral leukoplakia.

Oral leukoplakia including (A) homogeneous leukoplakia appearing as thin, white confluent flat area involving the right ventral tongue and floor of mouth; (B) relatively small, thin, flat, and well-demarcated patch of homogeneous leukoplakia of the ventral tongue; (C) nonhomogeneous leukoplakia appearing as a thick, white lesion with increased surface irregularities of the ventral tongue; (D) nonhomogeneous leukoplakia appearing as a thick, white plaque with fissures.

(From Woo S: *Oral pathology*, Philadelphia, 2012, Elsevier, Fig. 11-1.)

- Smokers are more prone to have leukoplakia than nonsmokers.
- Heavy smokers have larger and more numerous leukoplakic lesions than nonsmokers.
- Cessation of tobacco use often results within 1 year in the disappearance or reduction in the size of leukoplakic lesions.
- Also may be caused by chronic irritation due to friction (frictional keratosis) and chemicals (chemical keratosis):
 - Frictional keratosis is a common finding in areas where chronic (persistent or recurring) mild irritation occurs.
 - Causes include ill-fitting dental prosthetics, chronic cheek biting or lip biting, exuberant toothbrushing, as well as the use of smokeless tobacco.
 - Chronic exposure to chemical compounds may result in leukoplakia, including those found in smokeless tobacco, medications (e.g., aspirin), and spices (e.g., peppermint, cinnamon).
- Nicotinic stomatitis is another form of chemically or thermally induced leukoplakia, representing a generalized whiteness of the palate in people who smoke cigars and pipes:
 - Fact that these changes are more likely a result of heat rather than chemicals is a reason that this type of leukoplakia has limited to no malignant potential
- Leukoplakic lesion associated with irritation is reversible after elimination of the irritant; further, this type of lesion is not considered to have malignant potential.
- Microorganisms that may be associated with oral leukoplakia include *Candida albicans* and *Treponema pallidum*, the causative agent for syphilis:
 - *Candida* infestation of the squamous epithelial layers may result in a leukoplakic or

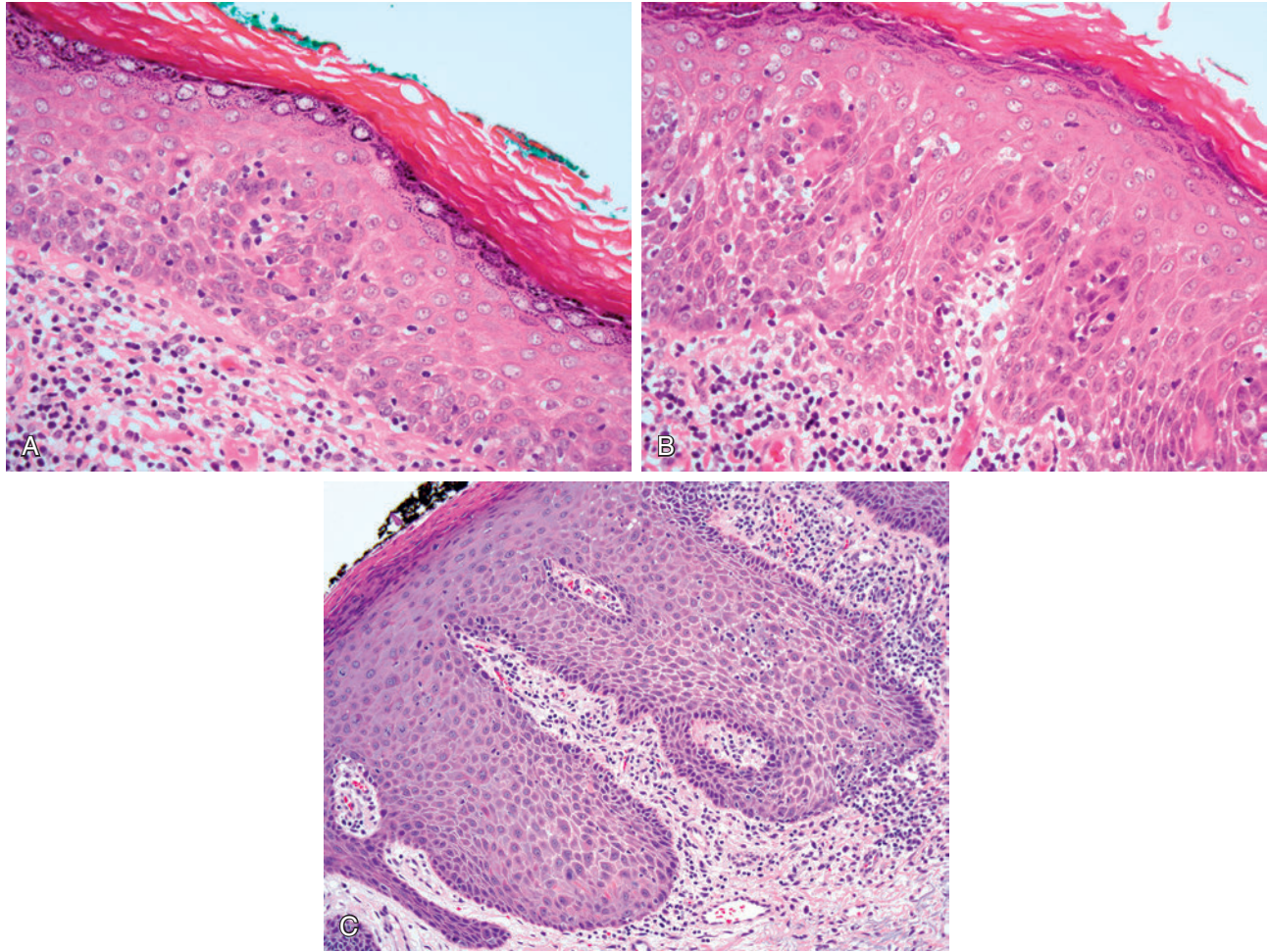


Fig. 6-39. Histology of (oral) leukoplakia.

The histologic features corresponding to a clinical leukoplakic lesion may include a wide spectrum of changes falling within the general category of keratosis with or without dysplasia. The following examples all represent varying degrees of (hyper)keratosis without dysplasia and progressive changes in the architectural features. **A**, Flat epithelium with orthokeratosis and absence of dysplasia. **B**, Orthokeratotic squamous epithelium with hypergranulosis and slightly elongated and downwardly extending rete ridges without dysplasia. **C**, Parakeratotic squamous epithelium with greater degree of elongated and downwardly extending rete ridges without dysplasia. The presence of inflammation in the submucosa does not affect the diagnosis, treatment, or prognosis.

- erythroplakic lesion (candidal leukoplakia); antifungal therapy usually results in diminishing or disappearance of the lesion.
- *Candida albicans* can be present in the oral cavity of up to 50% of the normal population.
- Tobacco smoking is considered to represent a predisposing factor in oral *Candida* infection.
- Whether candidal infestation represents secondary colonization or is the cause of leukoplakia is debatable, but the clinical leukoplakic lesion and the histopathologic keratosis with concurrent epithelial changes associated with

Candida infection may simulate the appearance of a squamous cell carcinoma.

- Conflicting findings related to possible role of human papillomavirus infection
- Ultraviolet radiation may cause leukoplakia of the lower lip referred to as actinic cheilosis (see later).

Pathology

Gross

- Leukoplakic lesions vary in appearance from:
 - Thin, white to gray plaque that may appear wrinkled, flat, or translucent (so-called thin or early leukoplakia)

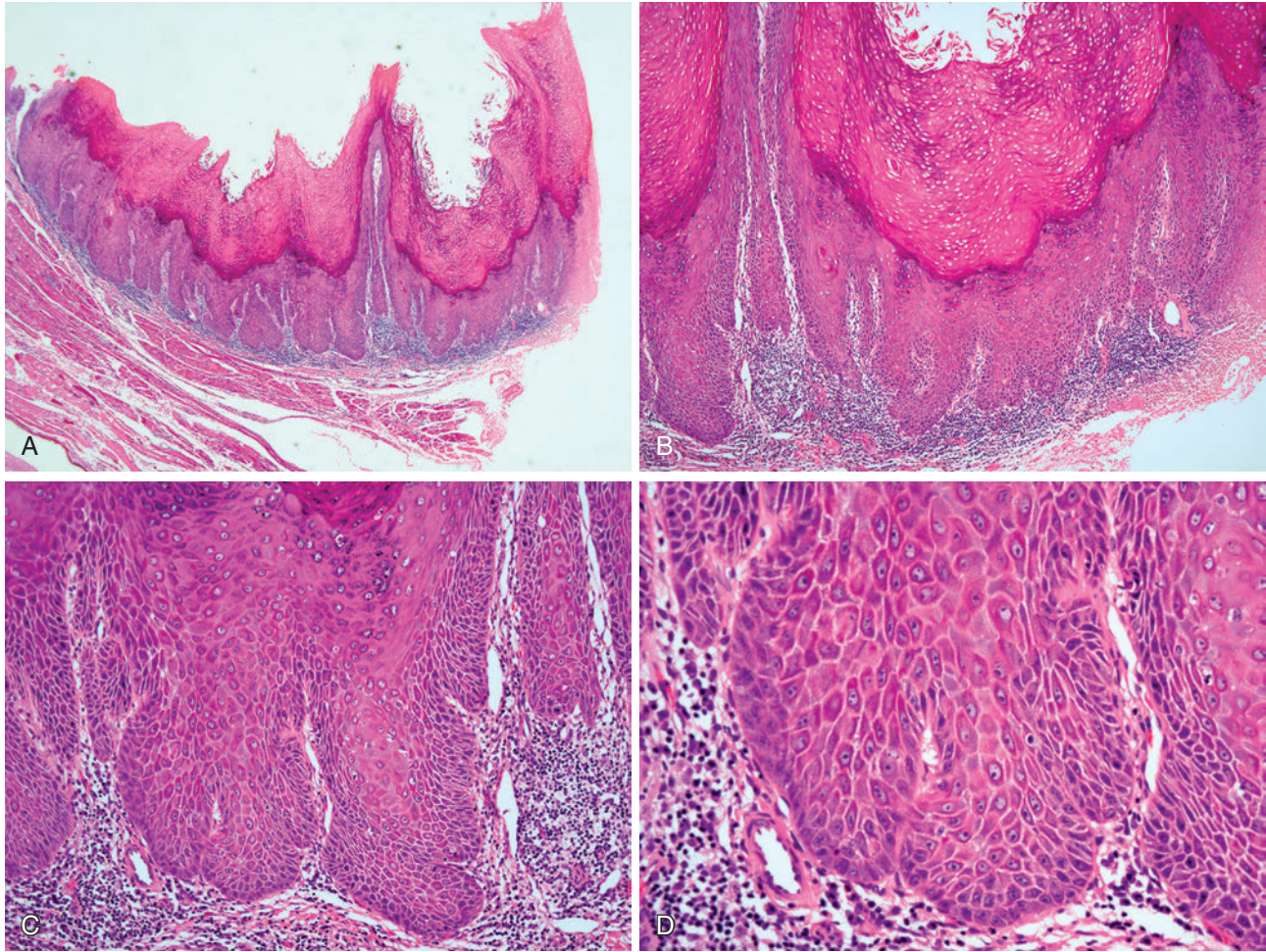


Fig. 6-40. Verruoid (hyper)keratosis without dysplasia.

A and B, Low magnification shows prominent verruoid (hyper)keratosis with associated irregular epithelial hyperplasias including elongated and downwardly extending rete ridges. **C and D,** At higher magnifications, the epithelial cells lack dysplastic changes. These overall features could be those of proliferative verrucous leukoplakia (PVL) or even verrucous carcinoma, but in contrast to these other lesions after excision there were no recurrences and/or progression of the lesion. Nevertheless, purely on the basis of the histologic findings differentiation between verruoid hyperplasia, PVL, and verrucous carcinoma is not possible. In this setting, complete excision is recommended with close clinical follow-up. If such a lesion recurs, persists, or progresses, then it is likely to represent PVL or verrucous carcinoma.

- Thicker lesion with a distinct white appearance, leathery consistency, and deeper mucosal fissures (so-called thick or homogeneous leukoplakia)
- Thick, white lesion with increased surface irregularities (so-called granular, nodular, or nonhomogeneous leukoplakia)

Histology

NOTE: Leukoplakia (as well as erythroplakia and speckled leukoplakia) are clinical and not histopathologic terms; these clinical designations should not be used in the microscopic diagnosis.

- Histology of leukoplakic lesions includes hyperkeratosis representing thickened keratin layer on the

surface epithelium with a thickened spinous layer (acanthosis) that may in turn be associated with:

- Parakeratosis (loss of the granular layer with the presence of nuclei in the thickened keratin layer)
- Orthokeratosis (retention of the granular layer with an absence of nuclei in the thickened keratin layer)
- Variable mixed chronic inflammatory cell infiltrate is present in the submucosa.
- Majority of leukoplakic lesions are devoid of epithelial dysplasia or have dysplastic changes limited to the basal zone; however, the full spectrum of epithelial dysplasia ranging from mild, moderate, and severe dysplasia may be present:

- Diagnosis of dysplasia is primarily predicated on cytomorphologic changes but also incorporate architectural changes (see Section 5, Larynx).
- Histochemistry:
 - In presence of a neutrophilic infiltrate of the surface epithelium a fungal infection should be considered.
 - To this end, special stains for microorganisms (e.g., Gomori methenamine silver, periodic acid Schiff) should be performed.
 - Presence of fungal forms (hyphae, spores) within the depth of the surface epithelium would be indicative of fungal infestation; the latter as previously noted may be associated and perhaps is the cause of clinical leukoplakic lesions.
 - Histologically, there may only be hyperkeratosis and irregular epithelial hyperplasia without dysplasia, but, in conjunction with the microorganisms, there may be a concomitant significant dysplasia and/or carcinoma.
 - In fungal colonization microorganisms are limited to the keratin layer or the very superficial epithelium.
- Immunohistochemistry:
 - Literature is replete with studies evaluating the utility of various antibodies in the diagnosis of dysplastic epithelial lesions and in potential use in predicting malignant transformation, but there are no individual markers that consistently or reliably predict malignant transformation.
- Cytogenetics and molecular genetics:
 - In spite of tremendous progress in field of molecular biology, there is as yet no single marker or set of markers that reliably allows for predicting the malignant transformation of OL in an individual patient.
 - DNA ploidy and loss of heterozygosity (LOH) have been extensively evaluated:
 - DNA ploidy:
 - High predictive value of aneuploidy in dysplastic leukoplakic and erythroplakic lesions (and to some extent nondysplastic leukoplakic lesions) in identification of progression to carcinoma
 - No correlation between the degree of dysplasia and DNA ploidy
 - LOH:
 - LOH on chromosomes 9p21 and 3p14 have greater probability of progression to squamous cell carcinoma.

Differential Diagnosis

- Reactive hyperplasia
- Pseudoepitheliomatous hyperplasia
- Infectious (i.e., fungal) disease
- Squamous cell carcinoma

Treatment and Prognosis

- Treatment of a leukoplakic lesion is predicated on the histopathologic findings associated with this lesion; as such, biopsy of a leukoplakia is required:
 - Owing to the fact that leukoplakic lesions often have a markedly thickened keratin layer, clinicians should bear in mind that a biopsy of the lesion should be deep enough to include the epithelial-to-stromal interface.
 - Any biopsy falling short of including this interface may be insufficient for histopathologic review and diagnosis.
 - Multiple biopsies may be required, especially if the leukoplakia is large or extensive.
- In the presence of an adequate sample (i.e., to include the epithelial-to-stromal interface) a histologic diagnosis of:
 - Hyperkeratosis without dysplasia or with mild dysplasia does not require additional treatment but should necessitate vigilant follow-up (e.g., at 6-month intervals).
 - Hyperkeratosis with moderate or severe dysplasia (i.e., high-grade intraepithelial dysplasia) necessitates additional treatment, including complete removal of the lesion by surgical excision, electrocautery, cryosurgery, laser ablation:
 - Vigilant follow-up in these patients is also needed.
 - In addition, if a patient is known to use tobacco products, all efforts to eliminate the use of tobacco are recommended.
- Annual malignant transformation ranges from 2% to 3%.
- At present, no reliable clinicopathologic or molecular predicting factors of malignant transformation
- Risk factors that may be associated with increased potential to malignant transformation of oral leukoplakia but are not absolute indicators include:
 - Long duration of leukoplakia
 - Homogeneous thick leukoplakia:
 - May undergo malignant transformation from 1% to 7% of cases
 - In presence of surface granularity or verruciform appearance the risk of potential to malignant transformation rises from 4% to 15%
 - Thin leukoplakia seldom becomes malignant.
 - Female gender
 - Occurrence in the absence of smoking history (smokeless or cigarette/cigar use)
 - Localization on the tongue or floor of mouth
 - Size ≥ 4 cm showed to be predicting factor of malignant transformation in oral leukoplakia
 - Presence of epithelial dysplasia:
 - Often dependent on the extent of dysplasia with the incidence of hyperkeratosis with mild

dysplasia progressing to more severe dysplasia or carcinoma being low and the incidence of hyperkeratosis with moderate or severe dysplasia progressing to carcinoma significantly higher than that of mild dysplasia.

Proliferative Verrucous Leukoplakia (PVL) (Fig. 6-41)

Definition: Aggressive irreversible form of oral leukoplakia with a tendency to recur, often with multifocal oral involvement, and to undergo malignant transformation to either verrucous carcinoma or conventional squamous cell carcinoma.

- Diagnosis is determined clinicopathologically and usually made in retrospect.
- A recent proposal for a diagnosis of PVL required:

- Involvement of more than two oral cavity subsites
- Total added size of leukoplakic areas of at least 3 cm
- Well-documented period of at least 5 years of disease evolution being characterized by spreading and occurrence of one or more recurrences in a previously treated area

Synonym: Verrucous hyperplasia

Clinical Features

- Uncommon lesion
- More common in women than men (4:1); most common in elderly women over 60 years of age with mean age in eighth decade of life
- Typically occurs in the setting of a long history (decades) of oral leukoplakia

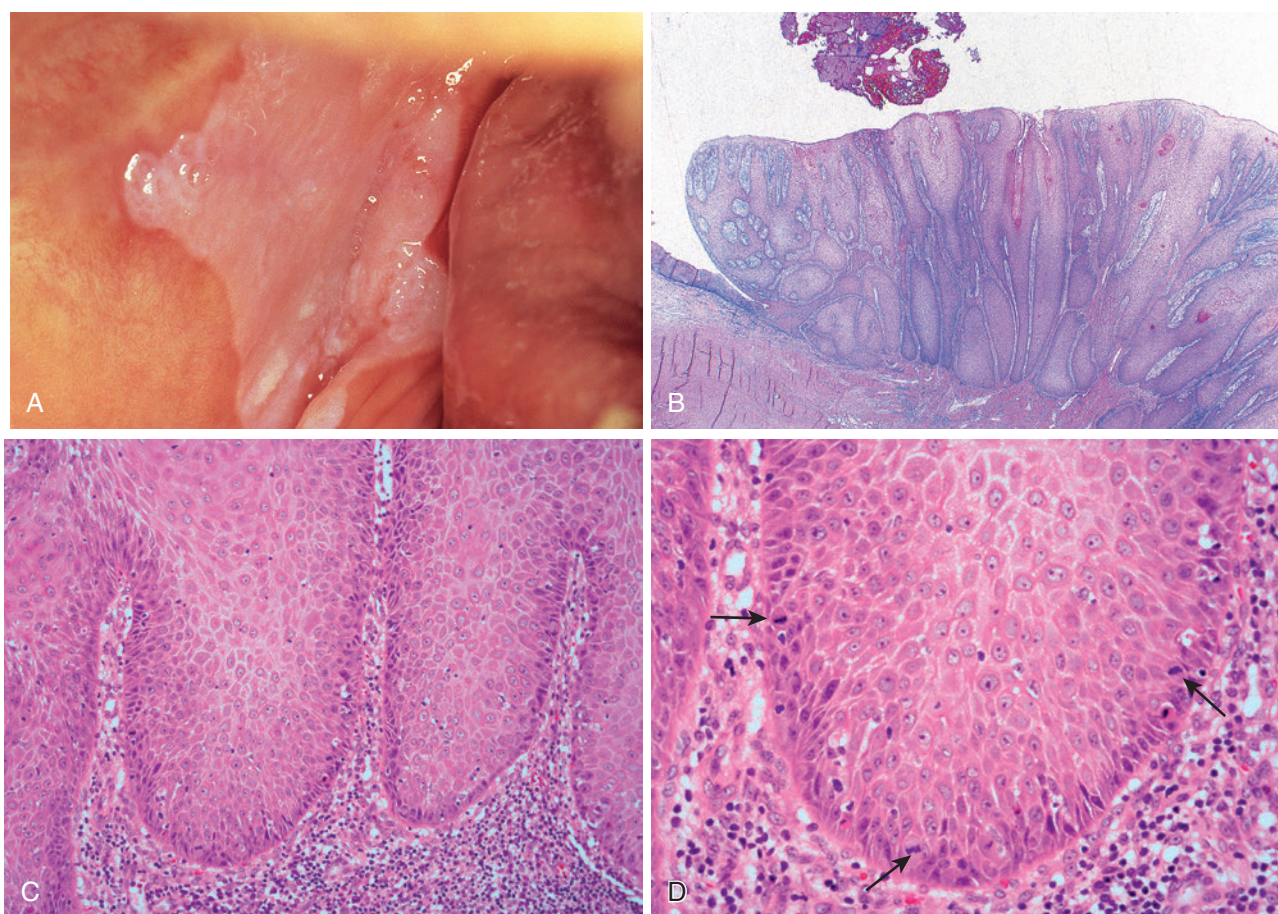


Fig. 6-41. Proliferative verrucous leukoplakia.

A, Older white female with persistent and progressive leukoplakic lesion of the oral cavity for many years presented with large confluent white patch of her buccal mucosa. **B**, Verrucoid squamous epithelial proliferation markedly elongated rete ridges, but the epithelial proliferation remains superficial (without submucosal invasion) and does not extend deeper than the adjacent normal epithelium seen along the extreme left side of the image. **C** and **D**, At higher magnification, the epithelial cells lack dysplastic changes; scattered mitotic figures are present (arrows) in the basal zone epithelium. The histologic diagnosis of PVL is problematic and typically requires clinicopathologic correlation and usually is made retrospectively after persistent, recurrent, and progressive leukoplakic intraoral lesions.

- Most common on buccal mucosa or oral tongue but also may involve gingiva, alveolar mucosa, floor of mouth, palate, and lip
- Risk factors:
 - No known risk factors associated with PVL including use of smokeless tobacco, smoked tobacco, alcohol, areca nut use
 - A history of tobacco use is present in a high percentage of patients (greater than 50%), but a significant minority of patients have no history of tobacco use.
 - Human papillomavirus (HPV) PVL has been reported, but etiologic significance of HPV in development of PVL remains unproven.

Pathology

NOTE: Diagnosis of PVL in its early stages is virtually impossible due to the innocuous appearance of the lesions and overlapping clinical and pathologic features with other types of leukoplakic lesions.

Gross

- Clinically, the lesion is a flat, thickened keratosis with the histologic appearance of a nondysplastic keratosis.
- With progression of disease, the lesions become multiple, multifocal, and confluent, with an exophytic and/or warty (verruroid) appearance; it is in the latter clinical form that squamous cancer (verrucous carcinoma or conventional squamous cell carcinoma) is seen.

Histology

- Composed of hyperplastic squamous epithelium with regularly spaced, verrucous epithelial projections, and associated hyperkeratosis
- Sharply defined lesion with hyperplastic epithelium remaining superficial (without submucosal invasion) and does not extend deeper than that of the adjacent epithelium:
 - Above feature contrasts with the downward growth into the underlying submucosal com-

partment by the bulbous rete ridges in verrucous carcinoma

- Lichenoid inflammatory infiltrate is uncommon.
- Any given lesion may show a combination of verrucous hyperplasia, verrucous carcinoma, and conventional well-differentiated squamous cell carcinoma.
- To exclude the presence of submucosal invasion, complete excision of the lesion allowing for histologic examination of the entire lesion is most appropriate:
 - Adequate sampling is imperative; otherwise, there will be diagnostic and differential diagnostic problems on incisional biopsy material.
- Cytogenetics and molecular genetics:
 - Loss of heterozygosity at chromosome 9p loci:
 - Represent a similar finding found for dysplastic premalignant lesions of oral cavity
 - p53 gene mutations not identified, although variable p53 expression reported
 - Homozygous deletion of exon 1β of p14 gene reported:
 - Similar findings identified in squamous cell carcinoma, affirming aggressive nature of PVL
 - Larger prospective, multicenter studies including sequentially acquired lesions with comparative analysis are needed to better determine molecular, genetic, and epigenetic alterations associated with PVL.

Differential Diagnosis (Table 6-2)

- Reactive (nonspecific) verrucoid hyperplasia and verrucous hyperkeratosis
- Oral leukoplakia
- Verrucous carcinoma

Treatment and Prognosis

- Surgical management is preferred treatment:
 - Generally unsuccessful owing to inherent geographic spread and progressive nature of PVL
 - Disease-free survival rates after surgery are low due to recurrence and multifocal involvement.

TABLE 6-2 Proliferative Verrucoid Leukoplakia (PVL): Differential Diagnosis

	PVL	COL	VC
Gender	F > M (4:1)	M > F (2:1)	M ≫ F
Age	>60; mean 8th decade	Younger ages	Elderly
Most common sites	Oral cavity, tongue	Anywhere in oral cavity	Buccal mucosa, larynx
Risk factor(s)	Unknown	Tobacco, others	Tobacco
Presence of dysplasia	Rare	Low (5% to 15%)	No
Progression to malignancy	High*	Low (1% to 2%)	Yes

COL, Conventional oral leukoplakia; VC, verrucous carcinoma.

*To verrucous carcinoma and/or conventional squamous cell carcinoma.

- Nonsurgical treatments include:
 - Radiotherapy, topical agents, cryotherapy, and phototherapy not shown to be effective in controlling disease.
- Therapeutic goal may be one of control rather than cure, maintaining surveillance to detect invasive cancer early requiring wide excision
 - Radiotherapy should be reserved for invasive carcinoma with aggressive features.
- Early recurrence is common, usually accompanied by greater extension and an increase of epithelial changes including dysplasia
- Malignant transformation to verrucous carcinoma and/or conventional squamous cell carcinoma is almost always the outcome.
 - Given that PVL is associated with VC in a high percentage of cases, some authors believe that PVL should be considered as a premalignant condition or an early biologic form of VC and treated accordingly.
- Such a consideration would obviate the confusion, both clinically and pathologically, that surrounds the use of the term verrucous hyperplasia in describing these oral cavity lesions.
- Prognosis considered poor:
 - In one study of 30 patients followed from 1 to 20 years:
 - 13 of 30 (43%) of patients died of or with their disease (persistent or recurrent)
 - 14 of 30 (20%) were alive with disease
 - 3 of 30 (10%) were alive without PVL

Oral Erythroplakia (Fig. 6-42)

Definition: Clinical term for a red mucosal lesion (plaque or patch) that cannot be rubbed or scraped off and that is not recognized (clinically or pathologically) as any other disease:

- Erythroplakia represents the red equivalent of leukoplakia.

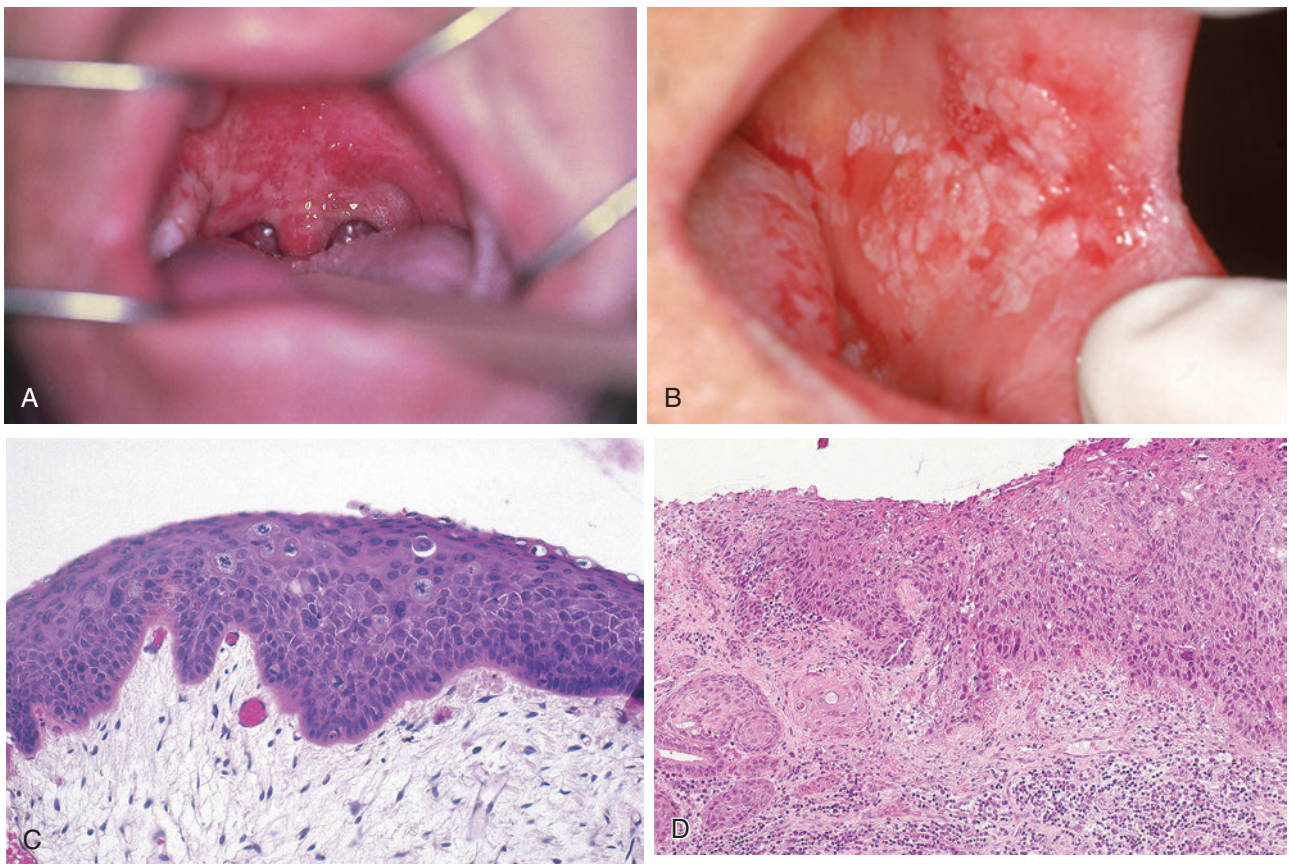


Fig. 6-42. Oral erythroplakic lesions.

A, Diffuse erythroplasia of the palate and uvula. **B**, Irregular-appearing erythroleukoplakic lesion of the left buccal mucosa. The corresponding histologic findings often include a significant dysplastic lesion including **(C)** high-grade intraepithelial dysplasia and **(D)** invasive squamous cell carcinoma (arrows).

- Red areas associated with leukoplakic lesions are referred to as erythroleukoplakia, speckled leukoplakia, or speckled mucosa:
 - More common than purely red (erythroplakic) lesion

Clinical

- Less common lesion than leukoplakia with prevalence between 0.02% and 0.83%
- No distinct gender predilection; most common in patients older than the fifth decade of life:
 - Uncommon in younger age groups (less than 30 years of age)
- May be asymptomatic, appearing as a solitary red mucosal, sharply demarcated, flat lesion with smooth or granular surface:
 - Similar to clinical presentation for early (asymptomatic) oral squamous cell carcinoma
 - Solitary lesion helpful in clinically distinguishing erythroplakia from erosive lichen planus, lupus erythematosus, and erythematous candidiasis, because these lesions occur almost always in a bilateral, more or less symmetric pattern.
- Occurs most commonly on floor of the mouth, tongue (lateral and ventral), soft palate, tonsillar region, and retromolar region:
 - Dorsal tongue rarely involved
- In contrast to leukoplakia, presence of erythroplakia may correlate to an underlying significant dysplasia (i.e., moderate to severe dysplasia) or to carcinoma:
 - Not all red erythroplakic lesions herald dysplasia/carcinoma, because many red oral mucosal lesions may be inflammatory.
- Cause:
 - Tobacco and alcohol important factors

Pathology

Gross

- Well-circumscribed erythematous, velvety, or granular plaque

Histology

- Squamous epithelial proliferation characterized by:
 - Absence of surface keratinization
 - Commonly shows moderate to severe (i.e., high-grade) dysplasia ranges:
 - Majority of clinical erythroplakic lesions have histologic changes of severe dysplasia
 - Severe dysplasia/carcinoma in situ present in 40% of cases
 - Invasive carcinoma present in >50% of cases
 - Absence of keratinization coupled with presence of epithelial dysplasia would allow classification as nonkeratinizing (“classical”) dysplasia.

- Epithelial alterations varying from atrophic to hyperplastic with submucosal nonspecific inflammation and dilated capillaries
- Cytogenetics and molecular genetics:
 - No individual markers that consistently or reliably predict malignant transformation
 - DNA ploidy and loss of heterozygosity (LOH) have been extensively evaluated:
 - DNA ploidy:
 - High predictive value of aneuploidy in dysplastic leukoplakic and erythroplakic lesions (and to some extent nondysplastic leukoplakic lesions) in identification of progression to carcinoma
 - No correlation between the degree of dysplasia and DNA ploidy
 - LOH:
 - LOH on chromosomes 9p21 and 3p14 have greater probability of progression to squamous cell carcinoma.

Differential Diagnosis

- Inflammatory lesions
- Atrophic oral lichen planus

Treatment and Prognosis

- In general, erythroplakia must be treated because of its high risk of malignant transformation.
- Surgery, either by cold knife or by laser excision, is recommended treatment.
- No data from the literature about the recurrence rate after excision of erythroplakias, but recurrence and multifocal oral mucosal involvement occur frequently and vigilant follow-up in these patients is required
- Progression to malignant transformation ranges from 18% to 47% with an average of approximately 28%.

Actinic Cheilitis (Fig. 6-43)

Definition: Premalignant lesion of the vermilion border of the lip, especially the lower lip due to long-term exposure to the ultraviolet radiation of sunlight.

Synonyms: Solar cheilosis; solar cheilitis; farmer’s lip; sailor’s lip

Clinical Features

- More common in men than in women and does not typically occur in patients younger than the fifth decade of life
- Occurs almost exclusively in Caucasians, especially those with fair skin
- Closely correlated with total cumulative exposure to sunlight with increased prevalence in those who

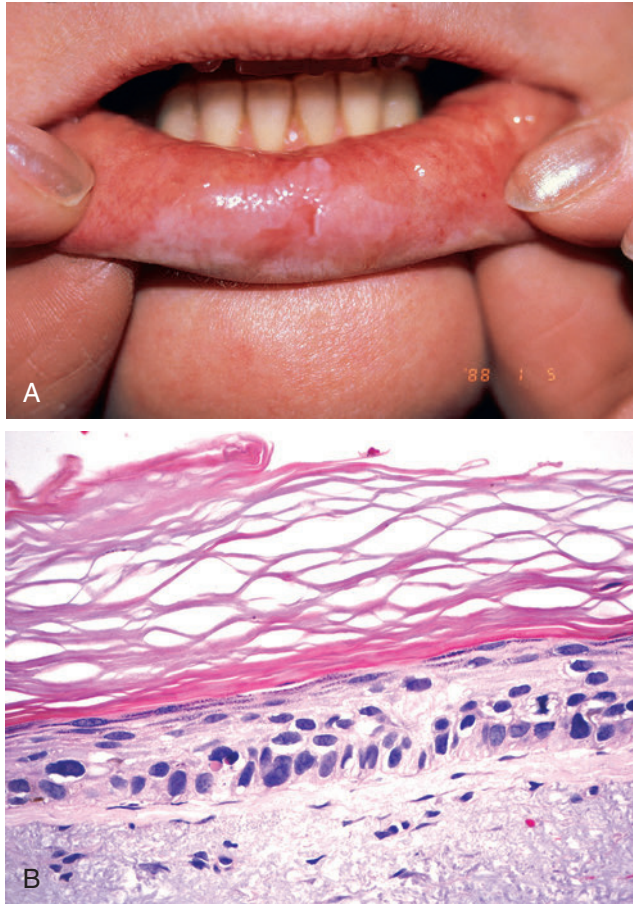


Fig. 6-43. Actinic cheilitis.

A, Leukoplakic lesion of the lower lip with loss of the distinct demarcation between the lower lip vermilion border and the skin of the lip. **B**, Corresponding histologic findings include hyperkeratosis with orthokeratosis, atrophy of the surface (squamous) epithelium with loss of rete ridges, intraepithelial high-grade dysplasia, and solar (actinic) elastosis of the submucosa.

work out of doors, such as farmers, sailors, beach workers

- Because the lesions develop slowly, patients are usually not aware of changes.
- Lower lip vermilion is the most common site of occurrence.
- Early changes include local puffiness and atrophy, characterized by a smooth and blotchy-appearing, pale to erythematous area:
 - Normally distinct demarcation between the lower lip vermilion border and the skin of the lip becomes indistinct or blurred.
- With progression the lesion becomes rough and scaly and may thicken, becoming leukoplakic; lesions may ulcerate especially secondary to trauma:

- Ulceration is usually painless and may last for several months.
- Overall appearance simulates a squamous cell carcinoma; however, in contrast to carcinoma, the lesions of actinic cheilitis do not become indurated.
- Overall process is similar to that of the cutaneous actinic keratosis.

Pathology

Histology

- Similar to cutaneous actinic keratosis, including:
 - Hyperkeratosis with parakeratosis and/or orthokeratosis
 - Surface (squamous) epithelial atrophy, including loss of rete ridges
 - Epithelial dysplasia ranging from mild to severe invariably present
 - Subjacent stroma with solar damage (solar or actinic elastosis) characterized by the presence of acellular, basophilic change due to breakdown of collagen secondary to ultraviolet light damage

Differential Diagnosis

- Erosive lichen planus
- Lupus erythematosus of the lip mucosa

Treatment and Prognosis

- Irreversible process; nevertheless in the majority of cases surgical intervention is not immediately indicated.
- Treatment includes limiting exposure of the area to the damaging effect of sunlight by the use of lip balm and/or sunscreen.
- Those cases in which the clinical findings are worrisome for carcinoma may require biopsy to exclude a diagnosis of squamous cell carcinoma.
- In those circumstances in which progressive (more severe) epithelial dysplasia may be present, lip mucosal stripping (i.e., vermillionectomy) may be required:
 - Vermilionectomy remains the standard for efficacy.
- Up to 10% of cases undergo malignant transformation to well-differentiated squamous cell carcinoma:
 - Malignant transformation often takes years, typically does not occur in patients under 60 years of age, and develops so slowly that there are minimal morbidity (e.g., metastases) and negligible mortality due to disease.
 - In the presence of squamous cell carcinoma more extensive surgical intervention is required.
 - Metastatic squamous cell carcinoma arising from actinic cheilitis may occur.

Keratinizing and Nonkeratinizing Dysplasia

Definition: Alteration in a malignant direction in the appearance of epithelial cells with an increased likelihood to progress to squamous cell carcinoma.

Synonyms: Keratosis with atypia; atypia; mild dysplasia; moderate dysplasia; severe dysplasia; squamous intraepithelial lesion (SIL); squamous intraepithelial neoplasia (SIN); laryngeal intraepithelial lesion (LIN); laryngeal intraepithelial lesion (LIL); simple hyperplasia; basal/parabasal hyperplasia; atypical hyperplasia

- Causes include:
 - Tobacco use:
 - Most common associated risk factor
 - Up to 90% of patients with oral leukoplakia use tobacco products (smokeless tobacco; cigarettes, pipe)
 - Excess alcohol use:
 - Alcohol potentiates the effect of tobacco smoking.
 - Risk of developing dysplastic lesions increases with duration of smoking with or without alcohol use
 - Chronic infections, including fungal infection:
 - *Candida albicans* is ubiquitous in the oral cavity in normal populations.
 - Tobacco smoking can be a predisposing factor for oral candidal infection.
 - Whether fungi cause dysplasia or are secondary colonizers in the presence of dysplasia remains uncertain.
 - Role of human papillomavirus (HPV) in the oral cavity intraepithelial dysplastic lesions remains unproven.
 - High-risk HPV uncommon finding in head and neck squamous cell carcinoma from patients who have history of tobacco or alcohol use
- See Section 5, Larynx and Trachea, for a more complete discussion and illustrations.

HEAD AND NECK CARCINOMA

General Considerations

- Majority of head and neck cancers arise from the surface mucosa and are squamous cell carcinomas
- Worldwide incidence of head and neck cancer exceeds half a million cases, annually ranking it the fifth most common cancer worldwide.
- In the United States, 52,000 people develop head and neck cancer annually and 11,500 die from disease.
- Head and neck squamous cell carcinoma (HNSCC):
 - Second only to lung cancer as most common smoking-related cancer
 - Treatment often results in substantial morbidity.

- Mutational cause is diverse with few targetable mutations.
- Risk factors associated with HNSCC:
 - Primary risk factors include tobacco use and alcohol consumption
 - Tobacco and alcohol have synergistic effect on the risk of developing HNSCC.
 - Betel nut chewing, widespread in regions of Asia, is an independent risk factor for development of HNSCC.
 - Oncogenic viruses:
 - HPV associated with oropharyngeal carcinomas (see Section 3, Pharynx)
 - EBV associated with nasopharyngeal carcinomas (see Section 3, Pharynx)
 - HIV-infected patients have increased relative risk of 2- to 3-fold to develop HNSCC.
 - Conventional keratinizing squamous cell carcinoma of oral cavity and variants thereof not known to be associated with any oncogenic viruses
 - Genetic alterations may contribute to increase in risk of HNSCC.
- Genetics of HNSCC:
 - Hallmarks of cancer necessary for a malignant tumor to develop include:
 - Acquisition of sustained proliferative signaling
 - Evasion of growth suppressor signals
 - Resistance to cell death (evasion of apoptosis)
 - Replicative immortality (immortalization)
 - Induction of angiogenesis
 - Activation of tissue invasion and metastasis
 - Dereglulation of cellular energy metabolism
 - Evasion of immune destruction
 - Additional enabling characteristics include:
 - Genome instability and mutation
 - Tumor-promoting inflammation
 - Molecular mechanisms underlying malignant change in upper aerodigestive tract include genetic and epigenetic causes:
 - Common genetic alterations in HNSCC include:
 - Deletions, translocation, isochromosomes, and less frequently amplifications
 - Losses of genomic material more frequent than gains and affect:
 - 3p, 9p, 21q, 5q, 13q, 18q, and 8p
 - ◻ Loss of heterozygosity at 3p14 early genetic alteration
 - ◻ Loss of heterozygosity at 9p21 occurs early in progression of HNSCC
 - ◻ Loss of heterozygosity chromosome region 17p13 is a late genetic alteration
 - Tumor suppressor genes or oncogenes associated with chromosomal alterations include:
 - Loss of 3p associated involves *FHIT* and *RASSF1A*

- Loss of 9p21 associated with *CDKN2A*
- Loss of 17p13 associated with *TP53*
- Gains of genomic material associated with HNSCC include:
 - Gain in 3q, among the most frequent gain and includes *TP63* (an epithelial development gene) and *PIK3CA*
 - Gain in 7p includes *EGFR*
 - Gain in 8q includes *MYC* oncogene
 - Gain in 11q13 includes *CCDN1*
- Genetic progression model for HNSCC has been proposed, including:
 - Loss of 9p leading to inactivation of *CDKN2A*, an early event found in 70% of HNSCC, frequently followed by loss of 3p (*FHIT*, *RASSF1*) and 17p (*TP53*) in transition to dysplasia
- Recent molecular evaluation of mutational landscape of HNSCC using whole exome-sequencing technology and gene copy number analyses showed:
 - Tumors from patients with a history of tobacco use had more mutations than tumors from patients who did not use tobacco.
 - Tumors that were negative for human papillomavirus (HPV) had more mutations than did HPV-positive tumors.
 - Most frequent somatic mutations found in *TP53*, *CDKN2A*, *PIK3CA*, *HRAS*, *FBXW7*, and *NOTCH1*
 - Nearly 40% of 28 mutations identified in *NOTCH1* were predicted to truncate the gene product, suggesting that *NOTCH1* may function as a tumor suppressor gene rather than an oncogene in HNSCC.
 - Two new genes, *CEBPA* and *FES*, were recently identified, extending the spectrum of HNSCC mutations.
 - Significant proportion of mutated genes are involved epidermal development and squamous differentiation
- Cancer epigenetics: study of epigenetic modifications to genome of cancer cells not involving a change in the nucleotide sequence:
 - Mechanisms of epigenetic silencing of tumor suppressor genes and activation of oncogenes include:
 - DNA methylation
 - Histone modifications
 - Dysregulation of DNA binding proteins
 - Epigenetic changes in HNSCC include inactivation of individual tumor suppressor genes, including:
 - *CDKN2A*, *CDH1*, *DAPK1*, *RASSF1*, *RAR-β*, *DCC*, *MGMT*, *NDRG2*, *DLEC1*
 - More recently, integrated molecular analysis based on methylation binding domain sequencing, 450K methylation arrays, whole exome sequencing, and whole genome gene expression arrays in primary head and neck squamous cell carcinoma (HNSCC) tumors:
 - Uncovered 186 downregulated genes harboring cancer-specific promoter methylation, including *PAX1* and *PAX5*
 - Identified 10 key tumor suppressor genes including *GABRB3*, *HOXC12*, *PARP15*, *SLCO4C1*, *CDKN2A*, *PAX1*, *PIK3AP1*, *HOXC6*, *PLCB1*, and *ZIC4*) inactivated by promoter methylation and/or somatic mutation.
 - Among the novel tumor suppressor genes discovered with dual mechanisms of inactivation, a high frequency of genomic and epigenomic alterations in the paired box (PAX) gene family of transcription factors, which selectively affect canonical NOTCH and TP53 pathways to determine cell fate, cell survival, and genome maintenance
 - Such findings highlight the importance of assessing tumor suppressor genes at genomic and epigenomic levels to identify key pathways in HNSCC, deregulated by simultaneous promoter methylation and somatic mutations.
- “Field cancerization” (Fig. 6-44):
 - Multiple, independent carcinogenic events occur in separate cells due to exposure of the “preconditioned epithelium” or “condemned mucosa” to a carcinogenic agent
 - Field of preconditioned epithelium or “condemned mucosa” (i.e., mucosa rendered more susceptible to tumor formation) becomes activated or breaks down into cancer, producing multiple separate carcinomas rather than from a single cell that becomes malignant.
 - Subsequent studies confirmed the “field cancerization” phenomenon, in which significant dysplastic changes affect a wide epithelial mucosal field in patients at high risk for developing cancer (e.g., heavy smokers and drinkers) with identification of similar genetic alterations in matched dysplastic and malignant lesions in oral cavity.
 - Concept of “field cancerization” and “condemned mucosa” explain the greater risk to the head and neck cancer patient for development of a second primary malignancy, which in turn plays a significant role in the tendency for these tumors to recur or persist despite therapeutic intervention, with adverse impact on survival.
 - Frequent development of synchronous or metachronous second or multiple primary cancers in

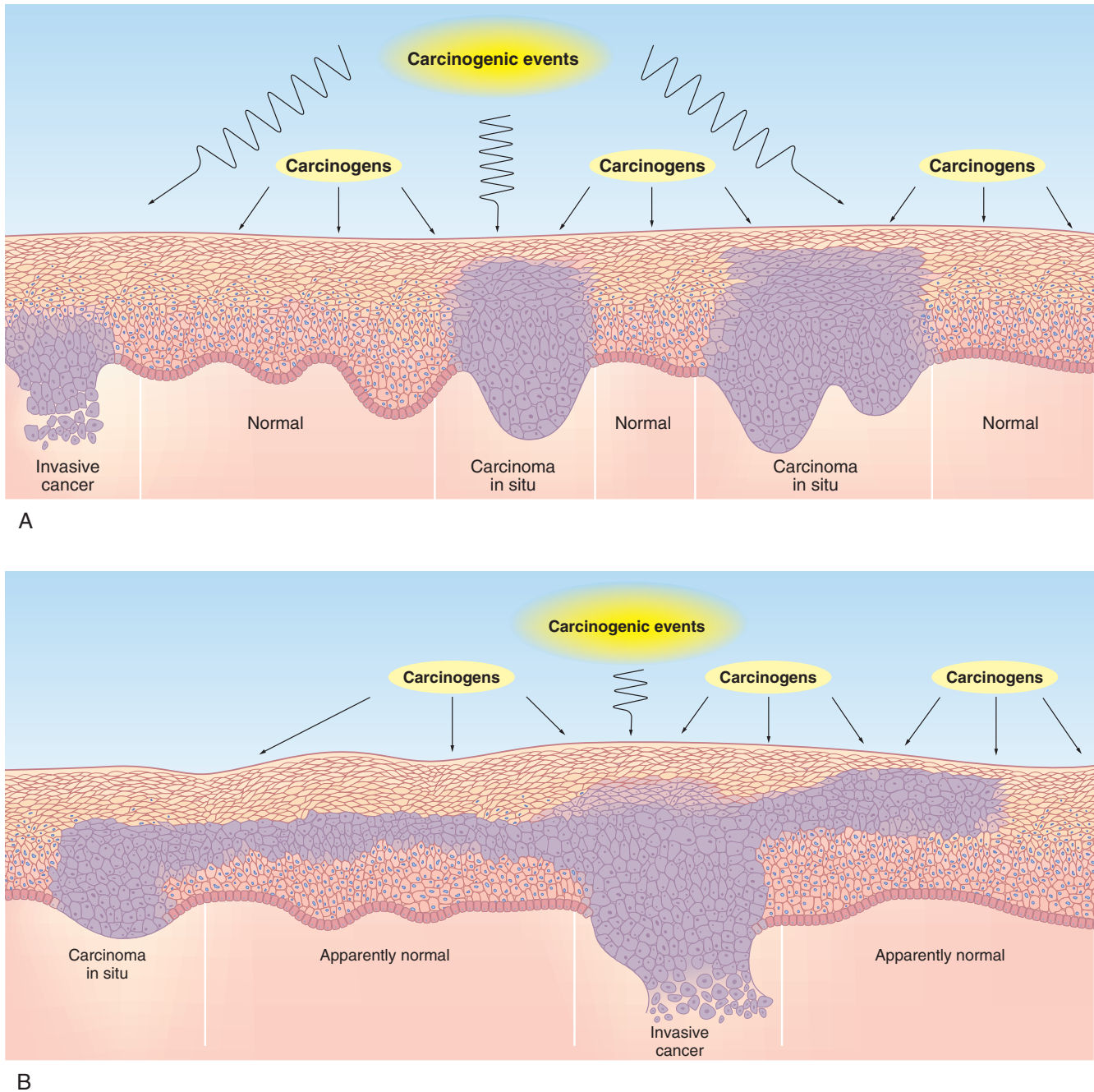


Fig. 6-44. Field cancerization.

A, Depiction of the initial hypothesis that multiple carcinogenetic events occur in separate cells leading to the development of independent cancerous foci. **B,** Alternative hypothesis confirmed in several studies shows that a single focus of carcinoma develops and spreads laterally without disruption of the adjacent apparently normal mucosa.

the head and neck and/or lung support concept of field cancerization:

- Second tumor may be clonally similar to or distinct from the primary tumor.
- Alternative hypothesis suggested that a single focus of tumor develops and spreads laterally by

arborization without disrupting adjacent normal mucosa:

- Synchronous but separate carcinomas (primary floor of mouth and piriform sinus lying 6 to 7 cm apart) and metachronous carcinomas (recurrences of these tumors after

radiotherapy) in a single patient evaluated to determine whether the tumors were of common or independent clonal origin

- Histologically, the two tumors shared a similar morphology, including invasive moderate to poorly differentiated keratinizing squamous cell carcinomas.
- All four tumors found to be of monoclonal origin, suggesting that in some patients second primary cancers may arise at distant sites because of the lateral spread of malignant clones
- Lateral spread presupposes the multiple factors required for active neoplastic cell motility with penetration of extracellular matrices.
- Other studies using X chromosome inactivation and LOH analysis in multiple HNSCC from female patients show high probability that second primary tumors were progeny of the same clone, supporting the idea that many second primary tumors represent extensions of the initial tumor clone.
- Use of molecular markers has validated concept of field cancerization:
 - Oral epithelium evaluated for use as surrogate tissue for assessing tobacco-induced molecular alterations in lungs by studying methylation status of CDKN2A and FHIT in oral and bronchial brush specimens from smokers enrolled in chemoprevention trial showed:
 - Dose-response relationship between number of sites methylated in lung and presence of oral methylation observed for CDKN2A
 - Other studies have shown concomitant methylation of three or more genes in sputum associated with greater than sixfold increase in risk for lung cancer.
 - Global gene expression changes have been reported in response to cigarette smoke throughout respiratory tract, including bronchus, nose, and mouth.
- Mutagen sensitivity:
 - Although exposure to a carcinogen is critical to the potential development of a head and neck malignancy, host-specific factors also influence cancer risk by modulating the susceptibility to carcinogenetic agents.
 - Individual response to the mutagenic activity of exogenous agents resulting in defective DNA repair mechanisms, referred to as mutagen sensitivity, is a complex phenomenon involving multiple genetic factors.
 - Mutagen sensitivity has been reported to be a significant risk factor for HNSCC, and the interaction between cigarette smoking and mutagen sensitivity has been shown to have a multiplicative effect.
 - Clinical follow-up of the mutagen-sensitive head and neck cancer patient has shown these patients to be at greater risk to develop a second primary malignancy as compared with a control group of head and neck cancer patients who were less mutagen sensitive.
 - Prospective studies of head and neck cancer patients have shown that mutagen sensitivity was a significant predictor of risk for developing a second primary malignancy and can then be used as a “marker” for second primary malignancies.
 - Second primary malignancy:
 - In spite of recent advances in the therapeutic management of the head and neck cancer patient, overall survival of these patients has not substantially improved.
 - Prime reason for absence of improved overall survival of the head and neck cancer patient is their increased risk of developing a second primary malignancy.
 - As compared with standard population, head and neck cancer patient is at greater risk (10 to 30 times) of developing a second primary malignancy, with the frequency varying from less than 5% to as high as 36%, with many studies in the 15% to 25% range.
 - Criteria used in defining multiple primary carcinomas include that:
 - Tumors be separate and distinct (at least 2 cm apart) without any dysplasia in the intervening mucosa and that the second primary tumor does not represent a metastasis or recurrent tumor
 - Diagnosis of a second primary tumor such as in the lung includes the presence of a solitary lesion that is histologically distinct from primary tumor
 - Second primary malignancies occurring within a 6-month period from the discovery of primary cancer are termed synchronous cancer, whereas second primary malignancy that occurs after the 6-month period from the discovery of the first tumor are referred to as metachronous cancer.
 - Most second malignancies develop in other upper aerodigestive tract mucosal sites:
 - Non-head and neck sites in which second malignancies develop include the lungs, esophagus, and bowel.
 - Most often, histology of second primary malignant neoplasm is a squamous carcinoma, but other histologic types such as adenocarcinomas may occur.

- Some of the more recently defined high-grade variants of squamous cell carcinoma (e.g., basaloid squamous cell carcinoma) are notorious for the presence of multiple concurrent primary tumors in mucosal sites of the head and neck at the time of initial presentation; factors that may play a significant role in development of a second malignancy include the site of the original primary cancer, age of the patient, size of the primary tumor, status of regional lymph nodes, and use of tobacco and alcohol:
 - Head and neck second malignancies are more likely to develop when the primary cancer is in the oral cavity, hypopharynx, or oropharynx than if the index tumor is of laryngeal origin.
 - Patients who developed their tumors prior to 60 years of age may be at greater risk of developing a second primary malignancy.
 - Patients with lower stage index tumors (T1 and T2) and patients who had no nodal metastasis (N0) at the presentation of their index tumor were more likely to develop a second malignancy than patients with higher stage index tumors and patients who did have nodal metastasis at the presentation of their index tumor.
 - Patients with index tumors of the head and neck who smoke tobacco (greater than 20 pack-years) and consume alcohol were at significant increased risk of developing a second malignancy than head and neck cancer patients who did not.
 - Microsatellite instability and smoking after treatment of the index tumor correlate with increased risk of multiple malignancies.
 - During the HPV era, second primary malignancy risk associated with oropharyngeal SCC has declined to lowest risk level of any subsite.
- Survival rates after the second cancer are influenced by the site of the second malignancy and persistent use and abuse of tobacco and alcohol:
 - Second malignancies of the lung and esophagus portend a significantly worse prognosis than second malignancies of other head and neck sites, with 5-year survival rates from the diagnosis of the second malignancy of 2% (for lung) and 3% (for esophagus) versus 20% for second head and neck malignancies.
 - Continued use of tobacco and alcohol also adversely affected survival rates, with 5-year survival rates of 5% for smokers versus 20% for nonsmokers, and 6% for drinkers versus 27% for nondrinkers.
 - Despite a modicum of increased overall survival in some groups, the development of a second malignancy is almost always fatal.
- Site of the second malignancy differs for different index tumors:
 - Development of a second primary head and neck or esophageal malignancy is more prevalent after oral cavity and pharyngeal index tumors.
 - Development of a second primary tumor of the lung is most common after a laryngeal index tumor.
- Shared mucosal susceptibility between index tumor and second malignancy is suggested as accounting for phenomenon of second primary malignancies:
 - A common “digestive tract axis” is shared between oral cavity, pharynx, and the esophagus, whereas the larynx and lung share a common “respiratory tract axis.”
 - Shared mucosal susceptibility is variation on “field cancerization” concept (see previous), highlighting importance of carcinogen activation of an entire exposed mucosa
 - Normal mucosa surrounding preinvasive and microinvasive HNSCCs share common genetic aberrations with tumor supporting the concept that second primary tumors represent extensions of initial tumor clone.
- Increased glutathione S-transferase (GST) expression, a carcinogen-detoxifying enzyme, may represent a possible “marker” for development of secondary malignancies in the head and neck cancer patient:
 - In patients with primary oral squamous cell carcinoma who developed a second primary head and neck malignancy, there is increased expression of GST in the normal tissues in direct vicinity of the index tumor in comparison with matched controls.
 - Increased GST is believed to have predictive value for the development of a second primary tumor.
 - More recently, findings suggest that copy number variant (CNV) and promoter genetic variants in glutathione S-transferase Mu class 1 (GSTM1) and promoter haplotype are better predictors of recurrence/second primary tumors of head and neck cancer than just measuring the presence/absence of GSTM1.
- Genetic variants in the PI3K/PTEN/AKT/mTOR pathway could serve as biomarkers to identify which patients are at high risk of recurrence/second primary tumor while also predicting response to 13-cRA chemoprevention for HNSCC patients.
- A critical issue for the otolaryngologist in the evaluation and planned treatment of the head and neck cancer patient is to be aware of the

possibility that the patient has or will develop a second primary malignancy:

- Diagnosis of a primary head and neck cancer should initiate panendoscopic evaluation of the entire upper aerodigestive tract, as well as the lower aerodigestive tract and esophagus to exclude the possibility of a synchronous second primary cancer, with vigilant follow-up care given the possibility of developing a metachronous cancer.
 - Results of these findings may ultimately affect the diagnostic approach, treatment protocol, and prognostic impact for that patient.
 - Development of a second primary malignancy is in all likelihood a multifactorial process combining genetic and environmental risks.
 - Development of a second primary cancer may potentially be predictive on the basis of sophisticated molecular biologic assessment (e.g., DNA microarrays).
 - Prognostic indicators in HNSCC include:
 - Status of surgical resection margins:
 - Arguably, single most important parameter in determining local recurrence in HNSCC presence of residual carcinoma at surgical resection margins
 - Margin status and local recurrence are site dependent and assist in explaining why surgeons are more apt to accept nearer margins for laryngeal carcinoma (free margins up to 2 mm) but require wider margins (5 to 10 mm) for carcinomas of extralaryngeal mucosal sites.
 - Larynx perhaps is an outlier in regard to positive margins and local recurrence:
 - As compared to extralaryngeal mucosal sites, patients with primary laryngeal squamous cell carcinoma with positive surgical margins have a significantly lower incidence of local recurrence.
 - Factors that may contribute to the lower incidence of local recurrences in laryngeal squamous cell carcinoma with positive margins supporting organ sparing (conservative) laryngectomy may include:
 - ◻ These patients have early stage carcinoma associated with a more favorable prognosis.
 - ◻ Submucosa of the glottic region has (quantitatively) less lymph-vascular spaces, thereby decreasing the incidence of spread and lowering the incidence of locoregional failure.
 - Among the extralaryngeal sites with significant recurrence rates after negative surgical margin determination include the oral cavity and pharynx:
 - A factor that contributes to the recurrence rates of pharyngeal and oral cavity carcinomas in the face of negative surgical margins is the tendency for submucosal spread by these carcinomas.
 - Intraoral sites with negative margins but significant recurrence rates include the palate, tonsil, buccal mucosa, tongue, gingiva, floor of mouth, and lip.
 - Absence of positive margins does not guarantee local control of disease nor is it a reliable guide to the biologic behavior of a tumor.
 - In general, the lower the clinical stage and/or pathologic class the better the ability to achieve local control and the overall better survival rates.
 - Factors that may affect whether a margin is positive or negative and in prognosis (control of disease) include:
 - Clinical stage:
 - ◻ Patients with positive margins more often have stage III and IV operable tumors, have a significantly higher rate of local failure, distant failure
- Resection margin status alone is not an independent predictor of local recurrence nor should resection margin status alone be used as the sole variable in deciding whether adjunctive radiation therapy is required; rather the need to give adjunctive radiation is suggested to be based on the following parameters:
 - Clinical stage:
 - Patients with positive margins more often have stage III and IV operable tumors, have a significantly higher rate of local failure, distant failure
 - Tumor dimensions:
 - Tumor size and extent of invasion determine clinical and pathologic T stage for HNSCC:
 - ◻ T stage has traditionally been considered an important risk factor for presence of concomitant nodal metastasis, local recurrence, and poor survival.
 - Malignancy grading and risk stratification:
 - Histologic risk assessment that includes score based on worst pattern of invasion. Patterns of invasion include:
 - ◻ Grade I = invasion in broad pushing front
 - ◻ Grade II = invasion in “finger-like” broad pushing pattern or separate large tumor islands
 - ◻ Grade III = invasive tumor islands of tumor at periphery greater than 15 cells/island
 - ◻ Grade IV = invasive tumor islands of tumor at periphery smaller than 15 cells/island or

strands of tumor cells in single cell filing pattern regardless of island size

- Grade V = satellites of dispersed tumor infiltrates of any size with 1 mm or greater distance of intervening normal (nonfibrotic) tissue at the tumor-host interface
- Histologic assessment results in stratification of patients into low-risk, intermediate-risk, and high-risk categories that define recommendations for adjuvant radiotherapy (Table 6-3):
 - Carcinomas invading with grade 3 or 4 patterns are associated with an increase in

nodal and distant metastasis and a significant decrease in survival.

- Grade 3 and 4 invasive patterns tend to be larger tumors (higher T stage).

NOTE: In practice, the histologic assessment of the patterns of invasion is not considered a standard of practice, and most pathologists do not render such an evaluation on intraoperative consultation or even in permanent sections.

- Perineural invasion (PNI) (Fig. 6-45):
 - Presence of PNI represents an important predictor of poor prognosis.
 - Presence of PNI associated with higher risk of metastasis to regional lymph nodes

TABLE 6-3 Risk Assessment for Oral Squamous Cell Carcinoma

Histologic Variable	0	1	3
Perineural invasion	None	Small nerves	Large nerves
Lymphocytic response	Continuous band	Large patches	Little to none
Worst pattern of invasion at interface*	1, 2, or 3	4	5
Risk Score†	Risk for LR	Overall Survival Probability	Adjuvant Treatment with RT
0	Low	Good	No benefit
1 or 2	Intermediate	Intermediate	No benefit
3 to 9	High	Poor	Beneficial regardless of 5-mm margins

Adapted from Brandwein-Gensler M et al: Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival, *Am J Surg Pathol* 29:167-178, 2005.

*Patterns of invasion: 1 = invasion in broad pushing front; 2 = invasion in “finger-like” broad pushing pattern or separate large tumor islands; 3 = invasive tumor islands of tumor at periphery greater than 15 cells/island; 4 = invasive tumor islands of tumor at periphery smaller than 15 cells/island or strands of tumor cells in single cell filing pattern regardless of island size; 5 = satellites of dispersed tumor infiltrates of any size with 1 mm or greater distance of intervening normal (nonfibrotic) tissue at the tumor-host interface.

†Sum of all points; *LR*, local recurrence; *RT*, radiotherapy.

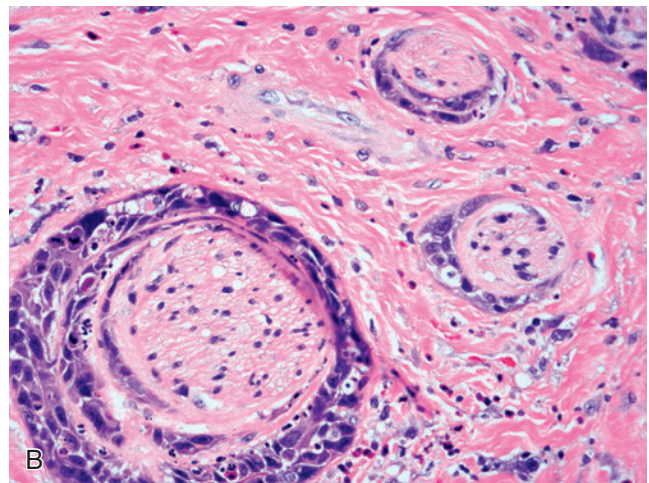
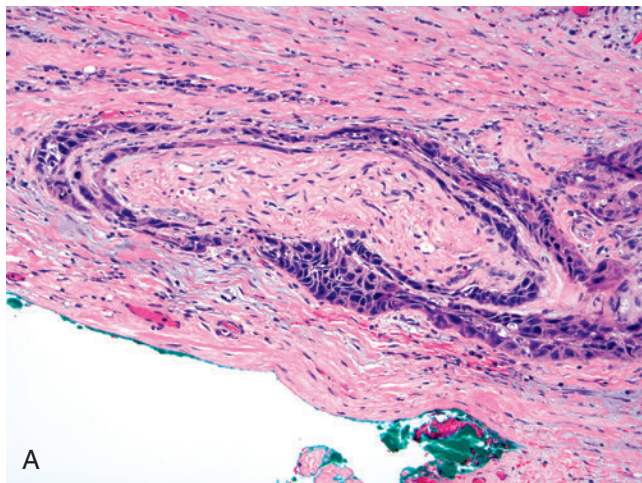


Fig. 6-45. Squamous cell carcinoma with perineural invasion.

Lingual invasive squamous cell carcinoma wrapping around peripheral nerves constitutes perineural invasion, also referred to as neurotropism. In (A) carcinoma lies within a few millimeters of the inked resection margin.

- Following definitive treatment, presence of PNI in primary tumor associated with poor local control, regional control, cause-specific survival, and overall survival
- Associated with increase risk of distant metastasis in some but not all studies
- Relationship between PNI and prognosis appears to be independent of nerve diameter (e.g., large named nerve versus small unnamed nerve).
- Despite importance of PNI, percentage of mucosal HNSCCs positive for PNI ranges from 5% to 52%.
- Lymph-vascular invasion (LVI) (Fig. 6-46):
 - Presence of tumor within lymphatic spaces and/or blood vessels (angioinvasion) does not necessarily indicate that metastatic disease is present or will develop:

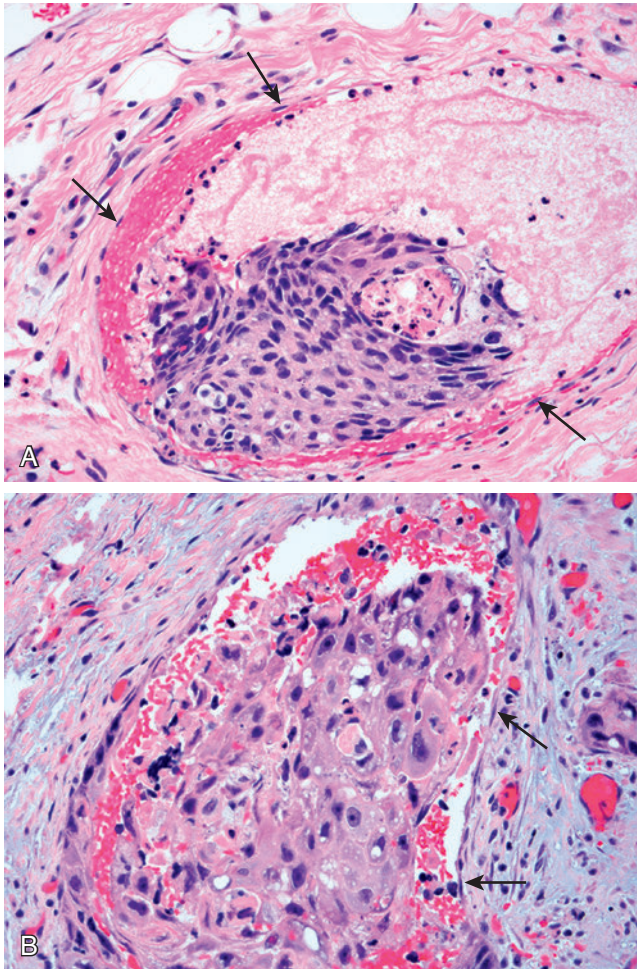


Fig. 6-46. Lymph-vascular invasion.

Buccal invasive squamous cell carcinoma invading into endothelial-lined (arrows) lumens and is adherent to the vessel wall. Such findings constitute lymph-vascular invasion.

- Several studies have demonstrated a statistical correlation between the identification of lymph-vascular space invasion and nodal metastasis.

- Lymph node metastasis (Fig. 6-47):
 - In general, cervical nodal metastasis is considered an adverse prognostic finding.
 - For head and neck metastatic carcinoma to lymph nodes, several factors may have prognostic significance, including the presence of extracapsular extension by the tumor, site of nodal metastasis, number of lymph nodes with

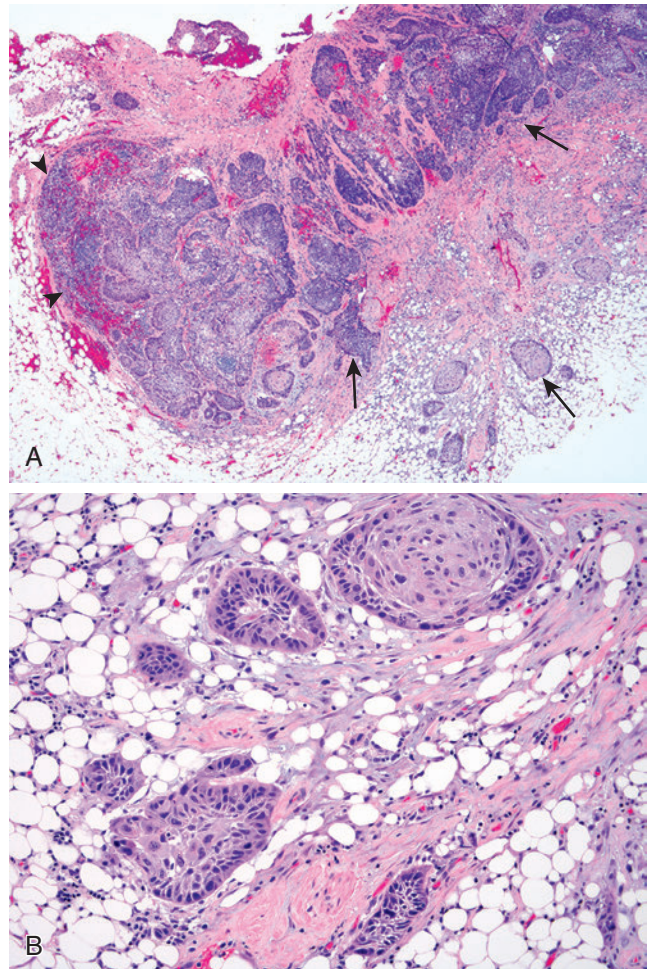


Fig. 6-47. Extranodal extension.

Laryngeal squamous cell carcinoma metastatic to a cervical neck lymph node with extranodal extension. **A**, At low magnification residual lymph node parenchyma (arrowheads) can be seen but most of the node architecture is effaced by the metastatic carcinoma, the latter with extensive invasion into perinodal soft tissues (arrows). **B**, Higher magnification shows the presence of moderately well-differentiated squamous cell carcinoma within perinodal adipose tissue.

metastatic disease, node fixation, and tissue response to metastatic tumor.

- Metastatic carcinoma confined to within the lymph node has survival rates similar to histologically negative lymph nodes.
 - Presence of nodal metastasis with extension of the tumor outside the capsular confines of the lymph node and into perithyroidal soft tissues (extranodal extension [ENE]) is generally considered an adverse finding associated with increased risk of recurrent disease, increased risk of distant metastasis, and reduction in long-term survival by up to 50%.
 - ENE is further subdivided based on whether the extracapsular spread is found microscopically or whether this feature was evident by gross examination:
 - Macroscopic ENE associated with an even greater risk of recurrent disease than by microscopic determination alone
 - Lymph nodes measuring more than 3 cm demonstrate a greater than 75% incidence of ENE.
 - Documentation in the surgical pathology report should include the presence or absence of nodal metastasis and if nodal metastasis is present whether there is or is not extracapsular spread.
 - Presence of ENE is an indicator for adjuvant therapy (radiation or chemotherapy).
 - Presence of lymph node and/or distant metastasis is correlated with increased morbidity and mortality in association with most malignancies, including HNSCC (a notable exception would be thyroid papillary carcinoma, which generally is an indolent tumor even in the presence of nodal metastasis).
 - Site of metastatic disease may affect overall prognosis:
 - Patients with a nodal metastasis to the lower neck area have a worse prognosis than patients in whom the metastatic deposits are limited to upper neck.
 - Abnormal retropharyngeal adenopathy, as determined by radiographic assessment (e.g., CT, MRI, PET), is an adverse predictor of outcome in squamous cell carcinoma of the head and neck:
 - Rates of neck relapse and distant metastasis are significantly higher with retropharyngeal adenopathy.
 - Rates of 5-year relapse-free survival and absolute survival are significantly lower with retropharyngeal adenopathy.
 - Size of largest positive lymph node may serve as clinical predictor of outcome but conflict-
- ing information in the literature affirming and disproving size
- Distant metastasis:
 - Distant metastatic tumor from a head and neck squamous carcinoma carries ominous clinical import, generally heralding the demise of the patient over relatively short periods of time despite all attempts at controlling disease.
 - Distant metastasis by hematogenous spread to visceral sites from a head and neck squamous carcinoma most commonly includes spread to the lungs, liver, and bone.
 - Among the factors that may be associated with distant metastatic tumor are the histologic type of cancer, tumor size, and the status of cervical lymph node involvement.
 - Several of the more recently described high-grade variants of squamous carcinoma, including the basaloid squamous cell carcinoma and adenosquamous carcinoma, often present as large tumors that are deeply invasive, associated with nodal and distant metastasis.
 - Reason for this aggressive behavior at presentation is not completely understood.
 - Increased tumor size (T stage) and cervical node involvement (N stage) have been shown to have a high incidence of distant metastases.
 - In addition to N stage, the number of lymph nodes involved, the number of lymphatic chains involved, and the presence of extranodal extension spread have been shown to be associated with an increased incidence of distant metastasis.
 - When three or more lymph nodes have metastatic disease the distant recurrence-free survival is reduced to 41% as compared with 84% when one lymph node was involved and 57% when two lymph nodes were involved.
 - When two or more lymphatic chains contained metastatic tumor, the distant recurrence-free survival is reduced to 40% as compared with 74% when one lymphatic chain was involved.
 - Nodal status has been viewed as a significant prognostic factor in the presence of distant metastases such that the presence of tumor in cervical lymph nodes represents a positive correlation with the development of distant metastases.
 - Distant metastasis occurs most frequently in patients with residual or recurrent disease in the neck.
 - Skin involvement by HNSCC is uncommon:
 - Usually is an indication of advanced or recurrent disease
 - Has adverse prognostic implications

- Presence of direct cutaneous extension from a mucosal SCC is associated with a mean survival of 7 months, whereas intra-dermal lymphatic spread carried a mean survival of 3 months.
- Involvement of facial skin had an overall better prognosis than when there was involvement of neck skin, with 12-month and 3-month median survival, respectively.
- Invasion of soft tissue structures (Fig. 6-48):
 - Surgical margins of resection may include all soft tissue components, including adipose tissue, skeletal muscle, bone, and neural structures.
 - For laryngeal carcinomas invasion of the cartilaginous framework is considered to represent an adverse prognostic finding:
 - Cartilage invasion is most frequently seen in association with transglottic carcinomas.
 - Invasion of cartilage often occurs in cartilage that has undergone ossification.
 - Hyaline cartilage believed to be resistant to invasive cancer
 - In the larynx, there is preferential invasion of squamous carcinoma into ossified cartilage as compared with nonossified cartilage:
 - However, this is not universally held to be true because there may be extensive invasion of laryngeal squamous carcinoma into nonossified cricoid and thyroid cartilage.
 - An increased incidence of nodal metastasis and mortality is associated with the presence of cartilage invasion.
 - Presence of neurotropism in HNSCC should be considered an adverse finding in head and neck malignancies indicative of the tumor's biologic aggressiveness as determined by an

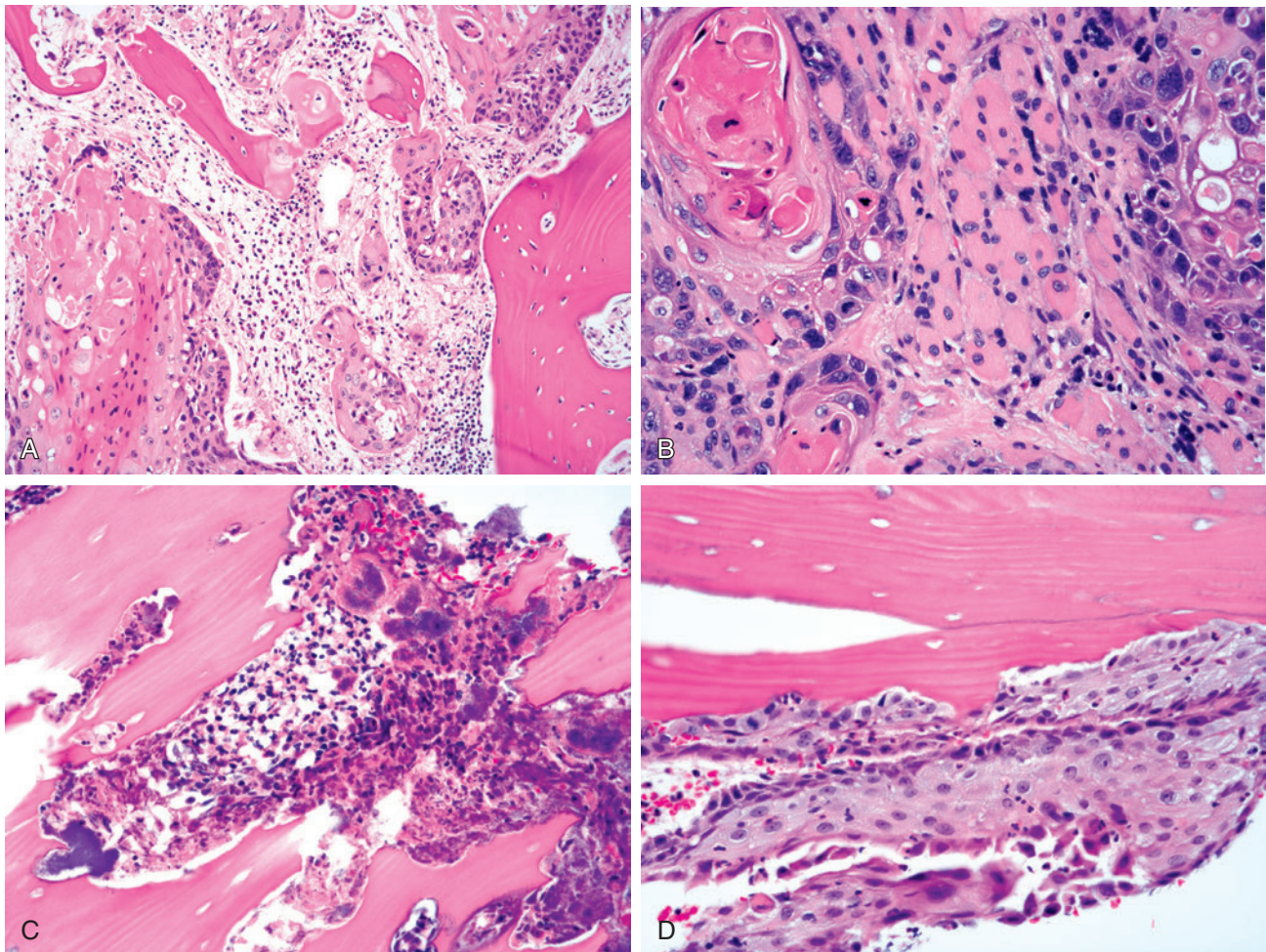


Fig. 6-48. Invasive squamous cell carcinoma.

Floor-of-mouth invasive squamous cell carcinoma showing (A) osseous invasion and (B) invasion into skeletal muscle. C, Infected osteoradionecrosis includes necrotic bone and associated neutrophilic infiltrate containing bacterial colonies consistent with *Actinomyces* species. D, Squamous epithelium resulting from fistula from oral cavity mucosa is directly applied to bone comprised of bland-appearing squamous cells lacking cytomorphic features of carcinoma.

- increased incidence of local recurrence, nodal metastasis, and/or decreased patient survival.
- Extension into soft tissue structures such as fat and muscle or cartilaginous and osseous invasion by HNSCC in general is indicative of a higher clinical stage tumor associated with a higher incidence of nodal metastasis.
 - Invasion and destruction of bone by cancer are thought to be performed by osteoclasts mediated by prostaglandins rather than by the direct action of the invasive cancer.
- For oral cavity carcinomas, presence of dentition significantly influences nerve-related spread:
- A fourfold increase in cancer spread related to the inferior alveolar nerve in edentulous, nonirradiated mandibles as opposed to partially dentate, nonirradiated mandibles and nerve involvement is associated with extensive spread of carcinoma in the medullary parts of the bone.
 - Bone, in particular the osseous margins of resection of the mandibular region, pose an especially significant issue in regard to carcinomas of the alveolar ridge, floor of mouth, lower buccal sulcus, and lower retromolar region:
 - Carcinomas of these sites are among those with the highest rate of recurrence.
 - Evaluation of mandibular bone for the presence and extent of involvement is a key determinant in patient management. Methods of evaluating for osseous involvement include preoperative radiologic assessment; gross inspection; frozen section or imprint evaluation of bone from the resected osseous stump; and frozen section of adherent soft tissues.
 - Clinical determination of mandibular involvement is not reliable because one third of histologically proven carcinomatous invasion of the mandible showed no clinical indication of (preoperative) bone involvement.
 - Spread of oral carcinoma to mandible typically occurs by direct invasion rather than by metastasis, lymph-vascular space spread, or via nerves.
 - Spread of carcinoma is nearly always through cancellous bone and its marrow spaces.
 - Size of the carcinoma (T stage) does not appear to influence the incidence of bone involvement but proximity to bone does.
 - Must be differentiated from infected osteoradionecrosis (IORN) with pseudocarcinomatous hyperplasia (PCH) or pseudoepitheliomatous hyperplasia (PEH):
 - Actinomycosis of the jaws is a rare disease described in patients with IORN and bisphosphonate-associated osteonecrosis (BON)
 - Typical scenario for IORN is patient with oral squamous cell carcinoma treated with radiation who develops osteoradionecrosis characterized by:
 - Fragments of necrotic bone intimately associated with bacterial colonies showing findings consistent with *Actinomyces* as well as an associated neutrophilic cell infiltrate
 - Benign squamous epithelium representing PCH or PEH may be present:
 - Given fact that gnathic bone is close to epithelial structures of both gum and periodontium, PCH/PEH may occur strongly associated with occurrence of fistula
 - Mandibular involvement much more common occurrence than involvement of maxilla
 - Critical issue is whether epithelium represents PCH/PEH or invasive carcinoma
 - Histologic features favoring PCH/PEH include:
 - Fragments of squamous epithelium identified in medullary space directly applied to necrotic bone trabeculae predominantly comprised of rather bland appearing cells lacking histologic features of squamous cell carcinoma
 - Often characterized by more mature epithelial layer covering bone trabeculae without intervening stroma, and basal type epithelial layer surrounding a central fibrovascular core
 - No cytomorphic features of malignancy
 - Invasive squamous cell carcinoma tends to include tumoral islands within centromedullary area surrounded by stroma with cytomorphic features of malignancy
 - Host immunologic response:
 - Host response to cancer as seen by the presence of a peritumoral lymphocytic infiltrate (PLI) may portend a better prognosis than those cases in which there is an absence of a significant inflammatory cell response.

- Tumor angiogenesis:
 - Tumor angiogenesis or neovascularization is defined as the ingrowth and development of new capillary vessels, representing an important factor in solid tumor growth.
 - Tumor angiogenesis permits rapid expansion of primary invasive carcinomas (e.g., skin, breast, lung, and prostate), correlating with the presence of metastatic disease and decreased survival rates.
 - Tumor angiogenesis can be measured by immunohistochemical staining of the blood vessels in a tumor and determining its vascularity (microvessel counts).
 - Studies to date for head and neck carcinomas have not been found to be useful prognostic marker in determining the frequency of local recurrence, metastatic disease or survival in head and neck cancer patients; these results sharply contrast with invasive cancers of other organ systems.
- Factors related to patient's general medical condition:
 - Comorbidity:
 - Refers to presence of other diseases, illnesses, or conditions not directly related to index cancer that may influence care of cancer patients, selection of treatment modalities, evaluation of treatment effectiveness
 - Nutritional status:
 - Strong evidence for association between malnutrition and increased risk of postoperative complications
 - Anemia:
 - Commonly occurs in patients with head and neck cancer
 - Due to a number of causes including comorbid illness, intraoperative blood loss, toxicity from chemotherapy and/or radiation therapy, and malignancy-associated anemia of chronic disease
 - Thought to enhance radioresistance via enhancing tumor hypoxia
 - Correlates with inferior local-regional control among patients treated with surgery alone, suggesting anemia may influence outcome independent of its influence on hypoxic resistance
 - Karnofsky performance status (KPS)
 - **Definition:** Attempt to quantify cancer patient's general well-being and activities of daily life and is a measure used:
 - To determine whether cancer patients can receive chemotherapy
 - To determine whether dose adjustment is necessary
 - As a measure for the required intensity of palliative care
 - In oncologic randomized controlled trials as a measure of quality of life
 - Provides uniform, objective assessment of an individual's functional status
 - Reliable independent predictor of survival outcome for patients with solid tumors
 - Required baseline assessment in clinical protocols in head and neck cancers
 - Scale is in 10-point increments from 0 (dead) to 100 (normal, no complaints, no evidence of disease):
 - 100: normal, no complains, no evidence of disease
 - 90: Able to carry on normal activity; minor signs or symptoms of disease
 - 80: Able to carry on normal activity with effort; some signs of symptoms of disease
 - 70: Cares for self; unable to carry on normal activity or do active work
 - 60: Requires occasional assistance but is able to care for most of own needs
 - 50: Requires considerable assistance and frequent medical care
 - 40: Disabled; requires special care and assistance
 - Diagnosis and treatment of depression may also aid in symptom control and improved quality of life.

SQUAMOUS CELL CARCINOMA (SCC) OF THE ORAL CAVITY

General Considerations

- Oral SCC represents approximately 5% of all malignant neoplasms in men and approximately 2% of all malignant neoplasms in women.
- Squamous cell carcinoma (SCC) or variants thereof are the most common malignant neoplasms, accounting for approximately 95% of all malignant neoplasms of the oral cavity.
- More common in men than in women:
 - Male gender predilection is historically related to greater use/abuse of tobacco and alcohol by men; however, with greater use of tobacco and alcohol by women, gender predilection may alter in the next few decades.
- Occurs over a wide age range but most common in the fifth to ninth decades of life; considered unusual prior to 40 years of age:
 - A definitive subset of patients developing squamous cell carcinoma are under 40 years of age:

- May include men and women but approximately 50% are women
- Young women developing lingual carcinoma are noteworthy for an absence of history of tobacco and alcohol use/abuse.
- To date, no definitive known predisposing risk factors but likely related to genetic susceptibility
- Most common sites of occurrence in the oral cavity in descending order of frequency are:
 - Lower lip, tongue, floor of mouth, gingival, palate, tonsil, upper lip, buccal mucosa, uvula
- Causative factors linked to the development of oral squamous carcinoma include:
 - Tobacco and alcohol: combined effect of tobacco and alcohol in development of SCC is well established, is multiplicative, and represents independent risk factors:
 - Tobacco:
 - Tobacco use/abuse includes smoking and chewing (smokeless tobacco).
 - Major cause of oral squamous cell carcinoma
 - Alcohol:
 - Alcohol potentiates tobacco-related carcinogenesis.
 - Oncogenic viruses:
 - Human papillomavirus (HPV) and Epstein-Barr virus (EBV):
 - Found in small percentage of oral squamous cell carcinomas
 - Sunlight (for carcinoma of the lip)
 - Nutritional factors include:
 - Plummer-Vinson syndrome (chronic iron deficiency)
 - Cirrhosis
 - Immunocompromised states:
 - Link of gingival carcinoma to immune-related disorders, including HIV/AIDS patients and host-versus-graft disease after marrow transplants, suggests an etiologic role.
 - Effect may be as a potentiator in conjunction with other risk factors (e.g., oncoviruses)
 - Conditions potentially linked to the development of oral carcinoma include:
 - Syphilis
 - Lichen planus
 - Submucous fibrosis
 - Sideropenic dysphagia
 - Environmental factors include:
 - Exposure to nickel, leather tanning products, formaldehyde
 - Above exposures may not be directly linked to development of squamous carcinoma but greater use of tobacco and alcohol products by workers with the above cited exposures may represent the greater risk factors.
- Other factors include:
 - Trauma and dental irritation
 - Poor oral hygiene
- Common sites in the oral cavity for the development of SCC include:
 - Tongue: lateral and ventral surfaces
 - Floor of mouth
 - Alveolar trigone
 - Buccal mucosa
 - Gingival and edentulous alveolar ridges
- Less common primary sites in the oral cavity for the development of SCC include:
 - Hard palate and dorsal aspect of the tongue:
 - Involvement of these sites most often occurs from extension of the carcinoma from adjacent sites.
- Signs and symptoms of oral SCC vary, depending on size and location of the lesion, and include:
 - Small lesions may be asymptomatic or present with minimal findings and vague symptoms.
 - Leukoplakia, erythroplakia, or speckled leukoplakia (mixed leukoplakic and erythroplakic)
 - Mass lesion; ulceration; pain (local and referred); difficulty swallowing, speaking, chewing, and opening the mouth; bleeding; and weight loss
 - Enlarged neck nodes (appearing as a neck mass) may be present in conjunction with an identifiable intraoral mass or in the absence of an intraoral mass.
 - In advanced cancers there may be:
 - Invasion into adjacent structures such as bone, muscle, and skin and may result in orocutaneous fistulas
 - Cachexia, severe anemia, and bleeding
- Radiology:
 - Radiographic imaging, including CT scan, MRI, and PET scan, supplements the clinical evaluation of oral SCC.
 - Imaging studies assist in the assessment of:
 - Local extent of the primary tumor
 - Regional nodal disease
- Histology:
 - Majority of oral SCC are of the keratinizing (conventional) type
 - Histologic grade includes variations of well-, moderately and poorly differentiated SCC
 - Associated premalignant surface epithelial changes often are identified:
 - Carcinoma in situ (CIS): cellular dysplasia involving the entire thickness of the mucosa without compromise of the basement membrane; the dysplasia may extend into adjacent seromucous glands and is still considered an in situ lesion

- Microinvasive carcinoma: malignant cells that have penetrated the basement membrane and infiltrate into the superficial compartment of the lamina propria
- For a more complete discussion and illustrations, see Section 5, Larynx.
- Variants of conventional SCC may also be identified, including:
 - Verrucous carcinoma
 - Spindle cell squamous carcinoma
 - Basaloid squamous cell carcinoma
 - Adenosquamous carcinoma
 - Lymphoepithelioma-like carcinoma
 - Others
- Treatment:
 - Primary therapy for oral SCC depends on several factors, including those related to the primary tumor, those related to the patient, and those related to the treatment delivery team:
 - Clinical stage:
 - Early stage cancers (stage I, II) include surgery, radiotherapy, or combination.
 - More advanced cancers (stage III, IV) include combinations of surgery, radiation, and chemotherapy.
 - Radiotherapy: the basis of radiation therapy for cancer treatment is due to the ability of ionizing radiation to cause damage to DNA strands, either directly fragmenting the molecule or indirectly creating an area of ionized free radicals in the vicinity of the coiled chromatin, thereby impairing the capacity of cells to repair or regenerate; radiation can essentially be delivered in two ways:
 - Teletherapy: delivery of ionizing radiation from a remote distance
 - Brachytherapy: delivery of ionizing radiation at a site close to (e.g., within a cavity or intracavitary) or within the target organ or tissue (interstitial)
 - Chemotherapy is the use of chemical (anticancer) agents to treat or control disease by destroying cancer cells:
 - Induction chemotherapy is the first stage in treatment where chemotherapy is used to reduce the number of cancer cells.
 - Neoadjuvant chemotherapy is the term used for the administration of chemotherapy prior to surgery and is generally designed to decrease the size of the tumor prior to resection:
 - In general, neoadjuvant chemotherapy can improve the chances for complete surgical resection or decrease the overall surgery needed.

- Chemical agents most commonly used neoadjuvantly include cisplatin and 5-fluorouracil.

Surgical Specimens

- Surgical resection for oral cavity cancers are among the most radical procedures, resulting in extensive cosmetic and functional deformities associated with significant quality of life issues.
- Postoperative rehabilitation of functional status includes speech, swallowing, and breathing.
- Among the variety of surgical procedures used in the treatment of oral cavity cancers include:
 - Glossectomy:
 - Partial or complete surgical removal of the tongue
 - Mandibulectomy:
 - Marginal mandibulectomy
 - Mandible sparing procedure
 - Indicated:
 - To obtain satisfactory three-dimensional margins around the primary tumor
 - When the primary tumor approximates the mandible
 - When minimal cortical erosion or minimal erosion of the alveolar process of the mandible is present
 - Not indicated:
 - In the presence of massive soft tissue disease or of gross invasion into the cancellous part of the mandible
 - In patients with previous irradiated edentulous mandibles
 - Patients with a pipe-stem mandible
 - Segmental mandibulectomy:
 - Required in the presence of gross invasion of the cancellous part of the mandible or invasion of the alveolar canal by perineural spread
 - Required for all primary tumors of the mandible
 - Mandibulotomy or mandibular osteotomy:
 - Mandible-sparing procedure
 - Designed to gain access to the oral cavity or oropharynx for resection of primary tumors not accessible through an open mouth or through the lower lip cheek-flap approach
 - May be approached laterally, in the midline or paramedian
 - Composite resection
 - Resection of part of mandibular alveolar ridge (marginal or segmental mandibulectomy) often along with the floor of mouth and a part of the tongue

- Generally used for advanced squamous cell carcinoma, although occasionally used for osteoradionecrosis after complications of prior irradiation or for other malignancies such as osteosarcoma
- Incidence of developing a second primary tumor in patients with oral carcinoma is significantly increased:
 - Patients with squamous cell carcinoma of the upper aerodigestive tract are at significant increased risk of developing another mucosal squamous cell carcinoma.
 - For a more complete discussion on second primary tumors and field cancerization see previously in this section.
- Prognosis is influenced by a variety of factors, the most important being the clinical stage of the neoplasm:
 - Approximately 75% of intraoral SCC are advanced stage tumors (i.e., stage III, IV) at diagnosis, negatively affecting prognosis.
- TNM staging for oral cavity cancers, including the lip, is detailed in [Table 6-4](#).

NOTE: Staging of oral cavity tumors applies to epithelial neoplasms and not to nonepithelial tumors, including mesenchymal, hematolymphoid, melanocytic, neuroendocrine, osseous, and cartilaginous tumors.

- Owing to differences in the clinicopathologic and prognostic findings, site-specific oral squamous carcinoma is addressed separately.

Squamous Cell Carcinoma (SCC) of the Lip ([Fig. 6-49](#))

- Accounts for approximately 25% to 30% of all oral SCCs
- More common in men than in women; most frequently identified in the fifth through eighth decades of life:
 - Less common occurrence in women may relate to protective effect of lipstick use and less outdoor exposure.
- More common in Caucasians; rare in blacks and dark-skinned individuals
- More than 90% occur on lower lip; less than 10% occur on upper lip.
- Most common site of occurrence is the vermilion border (exposed mucosa between the mucocutaneous junction and the point of contact of the lips) lateral to the midline.
- Clinical presentation varies depending on stage of cancer:
 - Majority of lip SCCs are superficial, representing Tis, T1, and T2 neoplasms.



Fig. 6-49. Squamous cell carcinoma of the lip.

- Early lesions:
 - White, red, or mixed-appearing thickening
 - Non-healing fissure or erosion
- More advanced lesions:
 - Usually ulcerated and indurated lesion
- Carcinomas of the lower lip, unlike those of upper lip, tend to grow slowly.
- Some carcinomas have propensity to involve nerves, causing numbness, pain:
 - Neurotropism may occur even in the presence of favorable findings such as better differentiated cancers and lower clinical stage.
- Cause:
 - Chronic exposure to sunlight most important etiologic factor
 - Also linked to pipe smoking
- Pathology:
 - Conventional well to moderately differentiated keratinizing SCC accounts for the majority of these carcinomas.
 - Other histologic variants of SCC may occur including (but not limited to) spindle cell squamous carcinoma and adenoid SCC.

TABLE 6-4 TNM Classification: Lip and Oral Carcinomas

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	(Lip) Moderately advanced local disease: tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
T4a	(Oral cavity) Moderately advanced local disease: tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscles of tongue, genioglossus, hyoglossus, palatoglossus and styloglossus), maxillary sinus, skin of face
T4b	Very advanced local disease: tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid
Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify tumor as T4	
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Staging Oral Cancers	
Stage 0	TisN0M0
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0 T1N1M0 T2N1M0 T3N1M0
Stage IVA	T4aN0M0 T4aN1M0 T1N2M0 T2N2M0 T3N2M0 T4aN2M0
Stage IVB	AnyTN3M0 T4bAnyNM0
Stage IVC	AntTAnyNM1

- Complete surgical excision and/or radiotherapy are preferred treatments.
- Brachytherapy effective in treatment, with local control rates of >90% for T1-T2 lower lip cancers
- Lymph node metastasis:
 - Regional lymph node metastases occur in only 10%.
 - Elective neck dissection warranted for higher grade carcinomas, larger tumors (T2 or greater and for thicker lesions >1 cm), clinically positive nodes, carcinomas at the oral commissure, and locally recurrent tumors
 - Metastases occur late in the disease course, involving the submental and submandibular lymph nodes are primary echelon drainage pathway:
 - Drainage may go to intraparotid or jugular chain lymph nodes.
- SCCs of lower lip are slow growing but will eventually spread to adjacent structures.
- SCCs of upper lip tend to metastasize to regional lymph nodes (periparotid) relatively early in the course of disease.
- Overall 5-year survival rate is:
 - Lower lip greater than 75%
 - Upper lip 34% to 58%
- Factors influencing prognosis include:
 - Tumor size:
 - Smaller tumors (i.e., T1 and T2) in the absence of clinically detectable nodal metastasis:
 - Cure rates of more than 90%
 - Correlated with early detection
 - Larger tumors (i.e., T3, T4) in the absence of clinically detectable nodal metastasis:
 - Survival rate of 30% to 50%
 - Presence of metastatic disease:
 - Regional nodal metastasis associated with 50% decrease in overall 5-year survival
 - Neurotropism:
 - Presence of perineural or intraneural invasion is associated with decrease survival rates.
 - Other important adverse prognostic findings include:
 - Tumor thickness/depth of invasion
 - Angioinvasion
 - Histologic grade of the tumor:
 - Grade I: 3-year cure rate of 95%
 - Grade II: 3-year cure rate of 46%
 - Grade III: 3-year cure rate of 38%
 - Correlates less well (as compared with tumor size, nodal metastasis) to patient outcome but pattern of invasion correlates with predicting clinical course:
 - Less differentiated carcinomas associated with worse prognosis linked to greater tendency to regional nodal metastasis



Fig. 6-50. Carcinoma of the oral (mobile) tongue.

Squamous cell carcinoma of the lateral tongue.

Squamous Cell Carcinoma of the Oral Tongue (Fig. 6-50)

- Accounts for approximately 25% of all oral carcinomas; excluding the lips, lingual carcinomas compose greater than 50% of all intraoral carcinomas, representing the most common site of oral SCC.
- More common in men than women; most frequently identified in the fifth through ninth decades of life; considered unusual prior to 40 years of age
- A definitive subset of patients with oral tongue SCC are under 40 to 45 years (SCC of oral tongue in young individuals):
 - May include men and women but higher percentage occurs in women
 - Young women developing lingual carcinoma are noteworthy for an absence of history of tobacco and alcohol use/abuse.
 - No definitive known predisposing risk factors but may be linked to genetic susceptibility, immune deficiencies, exposure to effects of tobacco via “passive” smoking, and viruses
 - Whole-exome sequencing and copy number analysis found that SCCs of the oral tongue occurring in young individuals (<45 years) were genomically similar to those of older patients (>45 years), and cause for increasing incidence of SCC of the oral tongue in younger patients remains unknown.
- Most common site of occurrence is the lateral and ventral aspect of the anterior two thirds of the tongue, referred to as the mobile portion of the tongue; less common sites include the dorsal aspect and the tip.
- Most common clinical appearance is that of painless ulcerated or exophytic mass:
 - More commonly appears as an erythroplakic than leukoplakic lesion

- Cause:
 - Tobacco and alcohol represent main etiologic factors.
 - Other factors associated with the development of lingual SCC include:
 - Nutritional deficiency (e.g., Plummer-Vinson syndrome, cirrhosis), trauma and dental irritation, and poor oral hygiene
- Pathology:
 - Conventional well- to moderately differentiated keratinizing squamous carcinoma accounts for the majority of the carcinomas.
 - Other histologic variants of squamous carcinoma including (but not limited to) spindle cell and adenoid squamous carcinoma can occur.
- Complete surgical excision alone or in combination with radiotherapy represents the treatment options:
 - Determination of whether surgery alone or in combination with radiation is used depends on several factors, including:
 - Age of the patient
 - Location of the tumor
 - Extent of disease
 - Surgical risk
 - Local excision with margin control for T1 lesions
 - Partial glossectomy for T2 lesions
 - Subtotal or total glossectomy for more advanced lesions
- Preoperative assessment of bone involvement dictates need for mandibulectomy (marginal or segmental):
 - Marginal mandibulectomy for minimal involvement of mandible
 - Segmental mandibulectomy for clearly demonstrable (clinical and/or radiologic) invasion of the mandible
- Management of the neck may include:
 - For patients with clinically positive cervical lymph nodes (N1) at presentation neck dissection is indicated.
 - For more advanced neck metastasis, neck dissection with or without radiotherapy is recommended.
 - Patients with early stage disease with a thickness of <2 mm and/or N0 necks, question of neck dissection is controversial and may include:
 - Observation alone
 - Prophylactic neck dissection and irradiation
 - Factors that may affect whether neck dissection is or is not indicated in early stage cancers (T1 and T2) may include:
 - Pattern of invasion (See [Table 6-3](#))
 - Presence or absence of perineural invasion, lymph-vascular invasion
 - Primary oral tongue carcinomas close to or involving midline have increased risk of

bilateral regional lymph node metastasis; staging neck dissection addresses bilateral nodal basins

- Metastases initially seed to the ipsilateral subdigastric lymph nodes, followed by the submaxillary region, and then to the mid-jugular chain
- Overall 5-year survival rates include:
 - 69% to 90% for Stage I
 - 0 to 26% for Stage II
- Factors negatively influencing prognosis include:
 - Large size of tumor
 - Deeply invasive cancers
 - Infiltrating pattern of advancing front
 - Positive surgical margins
 - Perineural invasion
 - Lymph node metastasis
 - Extranodal extension
 - Presence of distant metastasis:
 - Occurs in 5% to 15%, usually to lung and bone
- Approximately 20% to 30% develop second primary malignancy in the course of their disease.
- Carcinoma of the posterior tongue, also referred to as the base of the tongue, is considered to be oropharyngeal carcinoma see Section 3, Pharynx.

Squamous Cell Carcinoma of the Floor of Mouth ([Fig. 6-51](#))

- Accounts for approximately 20% of all oral carcinomas:
 - Excluding SCC of the lips, floor of mouth SCC is second most common oral malignancy, with lingual SCC being most common.
- More common in men than women; most frequently identified in the sixth to seventh decades of life:

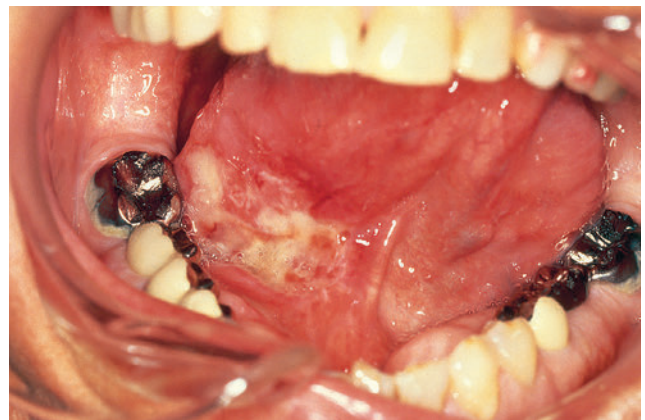


Fig. 6-51. Floor of mouth carcinoma.

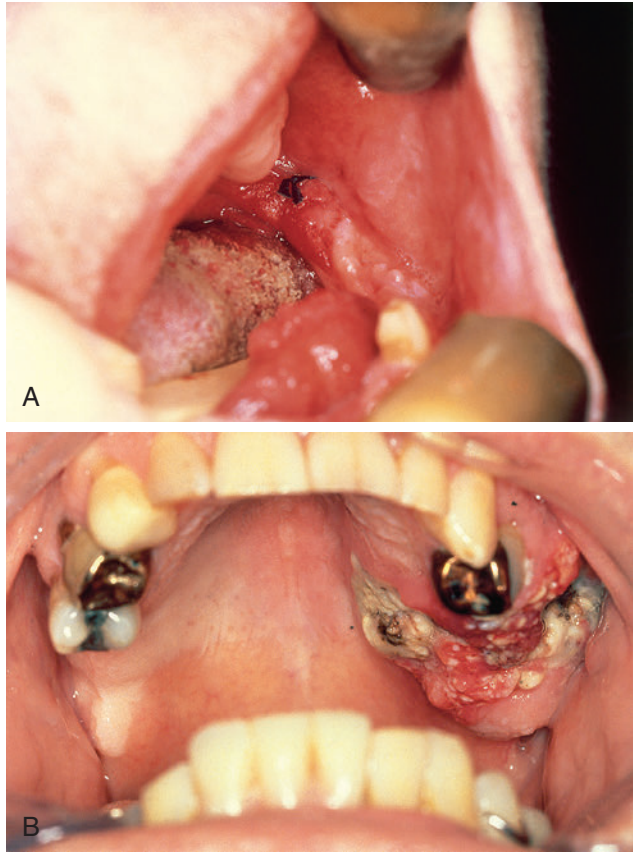
Squamous cell carcinoma of the floor of mouth near the frenulum.

- In women tends to occur in younger patients as compared with the same carcinoma in men (usually in the fourth to fifth decades of life).
- Most common site of occurrence is along the anterior aspect of the floor of mouth rather than the posterior portion:
 - Area near the lingual frenum is considered the most common site of occurrence.
- Presentation includes:
 - Ulcerated mass
 - Red (erythroplakic) or white (leukoplakic) mass:
 - More commonly appears as an erythroplakic than leukoplakic lesion
 - With progression of disease symptoms may include:
 - Pain, bleeding, excessive salivation
 - In as high as 75% of cases there is extension of tumor to adjacent structures (e.g., deep soft tissues, tongue) at presentation, resulting in:
 - Motor and sensory deficits include limitation of movement and difficulty speaking.
 - Invasion into bone (i.e., mandible) may occur in approximately 15% to 30% of patients at presentation:
 - Related to proximity of cancer to bone and not necessarily the size of the tumor
 - Invasion usually occurs directly into bone and/or via propagation along nerves and not via hematogenous spread.
 - Bony invasion via nerves occurs greater in edentulous patients as a result of:
 - Disparity in the vertical height of the occlusional border above the mandibular canal
 - Increase in the proximity of the inferior alveolar nerve to the mucosa
 - Cause:
 - Tobacco and alcohol represent main etiologic factors.
 - Pathology:
 - Conventional well- to moderately differentiated squamous carcinoma is the most common histologic type.
 - Complete surgical excision, either alone or in combination with radiotherapy, is preferred treatment:
 - Early stage cancers (I and II) are often managed by either surgery or radiotherapy alone.
 - More advanced cancers (III, IV) often managed by combined surgery and radiotherapy
 - Preoperative assessment of bone involvement dictates need for mandibulectomy (marginal or segmental):
 - Marginal mandibulectomy for minimal involvement of mandible
 - Segmental mandibulectomy for clearly demonstrable (clinical and/or radiologic) invasion of the mandible

- Management of the neck may include:
 - For patients with clinically positive cervical lymph nodes (N1) at presentation, neck dissection is indicated.
 - For more advanced neck metastasis, neck dissection with or without radiotherapy is recommended.
 - For patients with N0 neck, a more aggressive approach may be warranted given reported presence of metastatic disease in significant number of patients who underwent elective neck dissections with floor of mouth cancer.
- Metastases to regional lymph nodes occur to the submandibular triangle and upper jugular chain.
- Overall 5-year survival rates vary from 21% to 66%.
- Factors negatively influencing prognosis include:
 - Large size of tumor
 - Deeply invasive cancers
 - Infiltrating pattern of advancing front
 - Positive surgical margins
 - Perineural invasion
 - Lymph node metastasis
 - Extranodal extension
 - Presence of distant metastasis

Squamous Cell Carcinoma of the Gingiva, Including Retromolar Trigone and Alveolar Mucosa (Fig. 6-52)

- Accounts for approximately 6% of all oral SCC
- More common in men than women; most frequently identified in the sixth through eighth decades of life
- Mandibular gingiva is more commonly affected than the maxillary gingiva:
 - Most common area of gingival carcinoma occurs posterior to canine teeth
 - Edentulous areas are more commonly affected than those areas in which teeth are present.
- Presentation may be relatively nonspecific, including sore throat and referred pain (e.g., otalgia):
 - Owing to nonspecific symptomatology, diagnosis often made at advanced stage
 - Other symptoms may include:
 - Difficulty opening the mouth (trismus)
 - Pain
 - Toothache
 - Bleeding
- Most common clinical appearance is that of ulcerated or exophytic mass:
 - Early cancers of this region may simulate common dental infections, delaying diagnosis.
 - Gingival cancers may extend along periodontal membrane with destruction of supporting bone.

**Fig. 6-52.**

Squamous cell carcinoma of the (A) retromolar trigone and (B) alveolar ridge.

- Due to the small area composing the retromolar trigone, at presentation many SCCs of this region have already spread to adjacent structures, including to the anterior tonsillar pillar, soft palate, buccal mucosa, and floor of mouth.
- As a result of the proximity of the periosteum and underlying bone, cancers of these areas tend to invade bone early in the course of the disease.
- Spread:
 - For gingival cancers may occur:
 - Laterally to cheek, lower lip
 - Medially to hard palate, floor of mouth, ventral tongue
 - For retromolar trigone cancers may spread to:
 - Buccal mucosa, soft palate, mandible
- Cause:
 - Linked to tobacco, alcohol, and poor oral hygiene
 - Snuff dipping implicated as major risk factor for gingival carcinoma
 - Link of gingival carcinoma to immune-related disorders, including HIV/AIDS patients and

host-versus-graft disease after marrow transplants, suggests an etiologic role.

- Pathology:
 - Conventional well- to moderately differentiated keratinizing squamous carcinoma is the most common histologic type.
- Treatment is by surgical excision and/or radiotherapy.
 - T1 and T2 lesions managed by radiation or surgery alone
 - T3 and T4 lesions usually require combined surgery (wide excision) and radiation.
- Mandibulectomy (marginal or segmental) often required:
 - Marginal mandibulectomy for minimal involvement of mandible
 - Segmental mandibulectomy for clearly demonstrable (clinical and/or radiologic) invasion of the mandible
- Management of the neck may include:
 - For patients with clinically positive cervical lymph nodes (N1) at presentation neck dissection is indicated.
 - For more advanced neck metastasis, neck dissection with or without radiotherapy is recommended.
 - For patients with N0 neck a more aggressive approach may be warranted, given presence of metastatic disease in significant number of patients with carcinomas of gingiva, alveolus, and retromolar trigone.
- Metastases to submandibular and jugulodigastric lymph nodes occur from approximately 27% to 60% of patients, especially with carcinomas of the mandibular gingiva.
- Overall 5-year survival rates for gingival and alveolar mucosa cancers include:
 - 55% to 75% for Stage I and II
 - 24% to 44% for more advanced stages
 - Maxillary gingival cancers have better outcomes than mandibular gingival cancers with 5-year cure rates of 53% and 45%, respectively.
- Overall 5-year survival rates for retromolar trigone carcinomas of 31% reported
- Factors influencing prognosis include:
 - Size and site of the tumor
 - Presence or absence of bone involvement
 - Adequacy of surgical margins
 - Presence or absence of metastasis

Squamous Cell Carcinoma of the Buccal Mucosa (Fig. 6-53)

- Incidence varies from 1% to 10% of all oral carcinomas.



Fig. 6-53. Buccal carcinoma.

Squamous cell carcinoma of the buccal mucosa.

- More common in men than women; most frequently occurs in the sixth through eighth decades of life
- Early lesions may present as irregular white plaque (leukoplakia) or red plaque (erythroplakia) or exophytic verrucous lesion.
- More advanced lesions appear as ulcerated/infiltrative or fungating mass:
- Symptoms may include:
 - Early lesions:
 - May be asymptomatic or produce “soreness” of affected area
 - More advanced lesions:
 - Pain, trismus
- Majority of buccal mucosal carcinomas arise inferior to or along a line opposite the plane of occlusion, most often of the middle to posterior portion of the buccal mucosa:
 - Often presents with tumor invasion into the cheek
 - Spread to other adjacent structures frequently occurs and includes jaws (upper and lower), mandibular ramus mucosa, lips, pharynx, tonsil, palate and retromolar trigone and, in advanced disease, to the mandible and maxilla.
- Cause:
 - Linked to tobacco (smoking or chewing), snuff dipping, and alcohol use/abuse
- Pathology:
 - Conventional moderately differentiated keratinizing squamous carcinoma is the most common histologic type; verrucous carcinoma also involves the buccal mucosa.
- Treatment includes surgical excision and/or radiotherapy:
 - Radiation advocated for early cancers
 - Surgery used for infiltrative tumors, including those into deep soft tissues and skeletal muscle:
 - Wide local resection (even for T1 and T2 tumors) associated with high recurrence rates
 - Composite resection
- Locoregional recurrences commonly occur often within 18 months.
- Management of the neck predicated on dismal prognosis for patients with node metastasis:
 - 5-year survival declined from 70% for N0 patients to 49% for N-positive necks:
 - Elective supraomohyoid neck dissection in N0 necks may be considered in these patients with plan to extend area of dissection if clinical nodal disease is discovered during surgery.
- Metastases occur most frequently to the ipsilateral submandibular lymph nodes:
 - Occurs in from 16% to 59% of patients
 - Typically occurs in association with advanced disease
 - Occult metastasis occurs in less than 10% of cases.
 - Posterior located buccal SCCs have a tendency to spread to periparotid and superior deep jugular lymph nodes.
 - Presence of nodal metastasis necessitates neck dissection.
- Overall 5-year survival rates vary from 16% to 89%.
- Factors influencing prognosis include:
 - Tumor size and location
 - Presence or absence of metastasis
 - Tumor thickness (6 mm considered cut-off size)

Squamous Cell Carcinoma of the Hard Palate (Fig. 6-54)

- Among the rarest primary intraoral sites for the development of SCC in North America:
 - Although minor salivary gland malignant tumors occur fairly frequently in this area, squamous cell carcinoma remains most common malignancy affecting the hard palate.
 - In southern India, SCC of the hard palate is among the more common primary site of intraoral carcinoma due to the custom of reverse smoking with the lit end of the cigarette held in the mouth.
 - Hard palate not uncommonly involved by cancers extending from maxillary gingiva and alveolar ridge mucosa
- More common in men than women; most frequently occurs in patients in the seventh decade of life and older



Fig. 6-54. Palate carcinoma.

Squamous cell carcinoma of the hard palate with involvement of the uvula.

- Generally presents as ulcerative lesion with or without associated pain and/or bleeding:
 - May be exophytic or papillary
- May be localized in extent at presentation but approximately one third of cases present with invasion into adjacent structures:
 - Osseous invasion may occur early in the disease course but tends to be present later in the disease course.
 - Occasionally may invade into the sinonasal tract
- Cause:
 - Linked to tobacco and alcohol use/abuse
- Pathology:
 - Conventional moderately differentiated squamous carcinoma is the most common histologic type.
- Treatment includes wide surgical excision and radiotherapy; large soft palate carcinomas can be treated by radiotherapy alone.
- Treatment modalities include surgery or radiation alone:
 - Surgical excision includes wide excision.
 - Large tumors can be treated by radiotherapy alone to preserve functional anatomy.
 - Some authorities advocate not using radiotherapy for hard palate cancers because of the risk involved to the underlying bone (osteoradionecrosis) and to the limited loss of function to this site after surgery.
- Nodal metastasis occurs in approximately 15% to 30%:
 - Occurs most frequently to the submandibular and subdiaphragmatic lymph nodes
 - May be bilateral in up to approximately 5% of patients
 - Neck dissection is performed in the face of overt neck disease.

- Overall 5-year survival rate ranges from 31% to 59%.
- For stages I to IV, 5-year survival rates reported to be 75%, 46%, 36%, and 11%, respectively
- Factors influencing prognosis include:
 - Size of the tumor
 - Presence or absence of metastasis

Variants of Squamous Cell Carcinoma

- Variants of conventional squamous cell carcinoma that may occur in the oral cavity include:
 - Verrucous carcinoma (Fig. 6-55)
 - Papillary squamous cell carcinoma
 - Spindle cell squamous carcinoma
 - Basaloid squamous cell carcinoma
 - Adenosquamous carcinoma
 - Others
- For a detailed discussion of these histologic variants, see Section 5, Larynx.
- Carcinoma cuniculatum
 - Represents cutaneous equivalent of verrucous carcinoma
 - Term cuniculatum derived from the Latin *cuniculus*, meaning rabbit burrow, so named for the numerous crypts and sinuses on the tumor mass resembling rabbit burrows
 - Primarily occurs on the soles of the feet
 - May rarely occur on the skin of the face and/or in oral cavity
 - Slow but persistent growth and capacity to erode soft tissue structures, including bone
 - Surgical resection is the preferred treatment.
 - Generally behave indolently and do not metastasize but may recur.

MALIGNANT (MINOR) SALIVARY GLAND TUMORS OF THE ORAL CAVITY

- For more detailed discussion see Section 7, Salivary Glands.
- Up to approximately 25% of all salivary gland tumors occur in the oral cavity.
- May occur anywhere in the oral cavity but among the most common sites include:
 - Palate, buccal mucosa, lips
- Large percentage of intraoral minor salivary gland tumors are malignant:
 - Reported to be up to approximately 50%
- All subtypes of malignant salivary gland tumors may occur in minor salivary gland sites, but the most common types include:

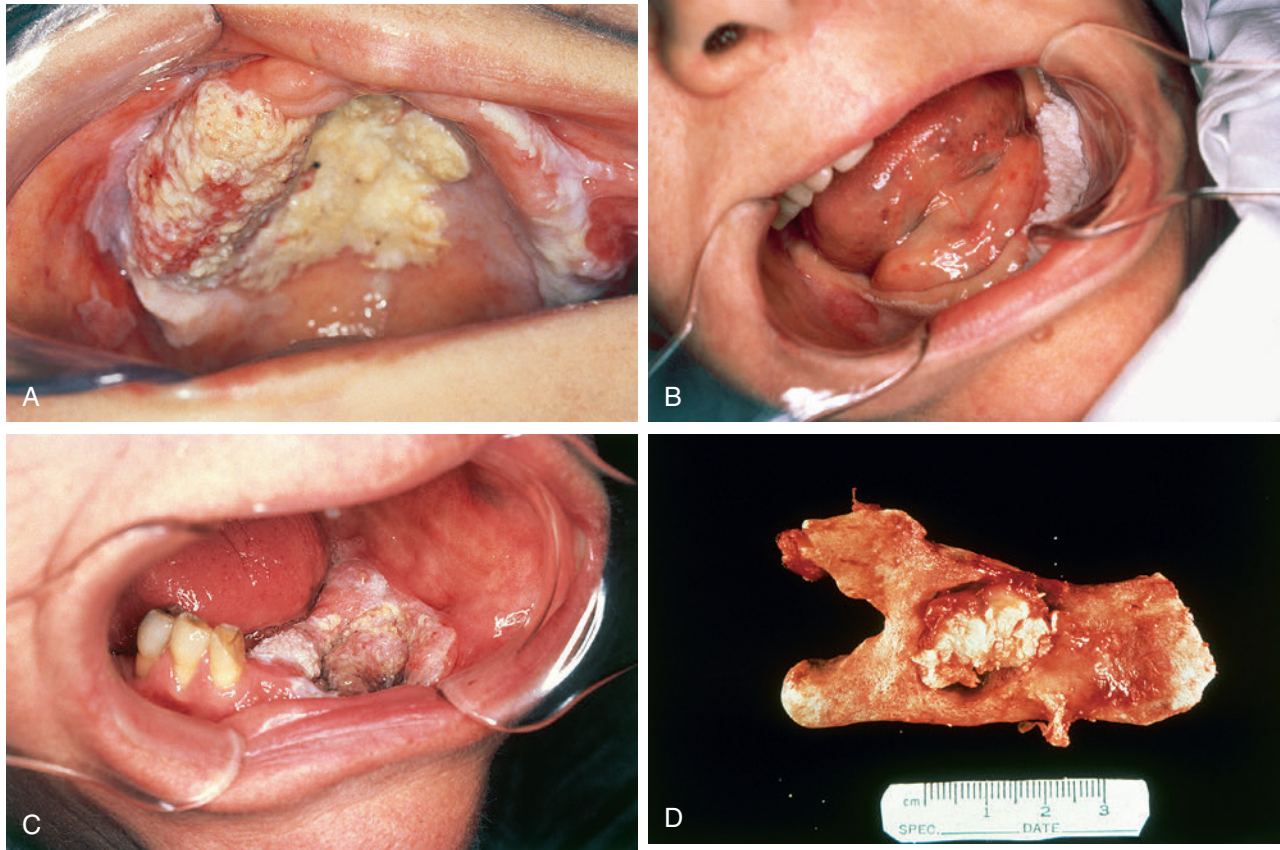


Fig. 6-55. Clinical and gross appearance of oral verrucous carcinoma.

Verrucous carcinoma of various sites of the oral cavity, including one that invaded bone. See Section 5, Larynx, for histologic images of verrucous carcinoma.

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Some of more common malignant major salivary gland tumors are uncommon in minor salivary gland locations, including acinic cell carcinoma:
 - In the presence of a salivary gland neoplasm suggesting a diagnosis of an acinic cell carcinoma, consideration for alternative diagnoses including but not limited to mammary analogue secretory carcinoma (MASC) should be considered; see Section 7, Salivary Glands.
- Select malignant salivary gland carcinomas, including polymorphous low-grade adenocarcinoma and clear cell carcinoma, predilect to minor salivary glands, in particular to the oral cavity.
- All minor salivary gland tumors are unencapsulated; as such, the differentiation of a benign tumor from a malignant tumor is often predicated on the presence or absence of invasion, the latter including:
 - Into adjacent minor salivary gland parenchyma
 - Into fibroconnective tissues (e.g., fat, skeletal muscle)
 - Peri- and intraneural invasion (i.e., neurotropism)
 - Lymph-vascular space invasion
 - Extension to and/or into the surface epithelium is not diagnostic of invasion or malignancy.
 - Metastatic disease is essentially diagnostic of a malignant neoplasm.

Cribriform Adenocarcinoma of Minor Salivary Glands

Definition: Distinct low-grade minor salivary gland neoplasm occurring mostly, but not exclusively, in the base of the tongue that histopathologically resembles papillary thyroid carcinoma with frequent metastases at the time of presentation but overall indolent behavior.

- For a more complete discussion see Section 6, Salivary Glands.

NONEPITHELIAL MALIGNANT NEOPLASMS

Mucosal Malignant Melanoma

Definition: Neural crest–derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation.

- For a more complete discussion see Section 1, Sinonasal Tract.
- Approximately 15% to 25% of all malignant melanomas arise in head and neck sites.
- Of the head and neck malignant melanomas more than 80% are of cutaneous origin.
- Mucosal malignant melanomas of the upper aerodigestive tract represent from 0.5% to 3% of malignant melanomas of all sites:
 - Of noncutaneous head and neck malignant melanomas, majority are of ocular origin
 - Most common site of the upper aerodigestive tract is oral cavity followed by the sinonasal tract
 - Approximately 6% to 8% originate in the mucous membranes of the upper aerodigestive tract.

Oral Cavity Mucosal Malignant Melanoma

- No gender predilection; wide age range but most often occurs in the fourth to seventh decades of life; rarely occurs in pediatric ages
- May occur in any site of the oral cavity:
 - Most common sites of occurrence in the oral cavity include palate, maxillary alveolus, and gingivae
 - Less common sites of occurrence include buccal mucosa, floor of mouth, tongue, and lips.
- Presentation includes presence of a pigmented, painless mass:
 - Rapid enlargement of the lesion may be associated with pain.
 - Surface ulceration may be identified in up to one third of cases.
- No known cause
- Macroscopic, microscopic, histochemical, immunohistochemical, and ultrastructural features are similar to those of melanomas of other sites (see Section 1, Sinonasal Tract):
 - Junctional activity and/or in situ melanoma can be identified but is not required for diagnosis.
 - Although uncommon, desmoplastic subtype may also occur in mucosal sites, including the oral cavity.
- Molecular genetics:
 - Molecular findings of primary mucosal malignant melanomas vary from those of malignant melanomas of sun-exposed (i.e., cutaneous) sites.
 - Mutations in *BRAF* gene:
 - Uncommon in mucosal malignant melanomas
 - Present in 50% to 60% of cutaneous melanomas
 - Suggest that ultraviolet exposure plays a role in genesis of *BRAF* mutations in cutaneous melanoma
 - Subset of mucosal malignant melanomas harbor somatic mutations in c-kit gene in <20%:
 - Strong immunoreactivity for CD117 associated with oncogenic mutations
 - May have clinical implications because tyrosine kinase inhibitor–targeted therapy may be effective for c-kit–mutated tumors
- Similar to other mucosal malignant melanomas, possibility of metastasis to the oral cavity from a separate melanoma must be considered prior to rendering the diagnosis of a primary oral mucosal malignant melanoma:
 - Cutaneous melanomas may metastasize years to decades after initial diagnosis, so detailed clinical history to include prior diagnosis of a cutaneous melanocytic lesion is indicated.
 - Histologic review, if possible, of any previously excised melanocytic lesion is highly desirable.
- Melanin pigmentation of oral cavity can also be seen in association with exogenous and endogenous pigmentation, which may clinically raise concern for a diagnosis of malignant melanoma:
 - Amalgam tattoo (Fig. 6-56)
 - Exogenous pigmentation of oral cavity includes foreign body material and oral tattoo most commonly associated with amalgam, although any implanted, pigmented material may result in “tattoo” such as graphite (from pencils), coal, metal, and plant material.
 - Amalgam or other metal tattoo may be observed on radiograph if the metal fragments are of sufficient density.
 - Macules appear black, blue, or gray, and borders may be well defined or diffuse; borders may change over time and may be asymmetric, potentially raising clinical concern for a melanoma.
 - Any mucosal surface may be affected by tattoo:
 - Palate is more often involved in pencil implant
 - Histologically, foreign material identified in submucosa appearing as scattered solid fragments of fine black or dark-brown granules surrounded by a mild chronic inflammatory cell infiltrate, although marked chronic inflammation and granulomatous response may be identified.
 - Biopsy to exclude melanoma is generally adequate therapy for a pigmented macule.

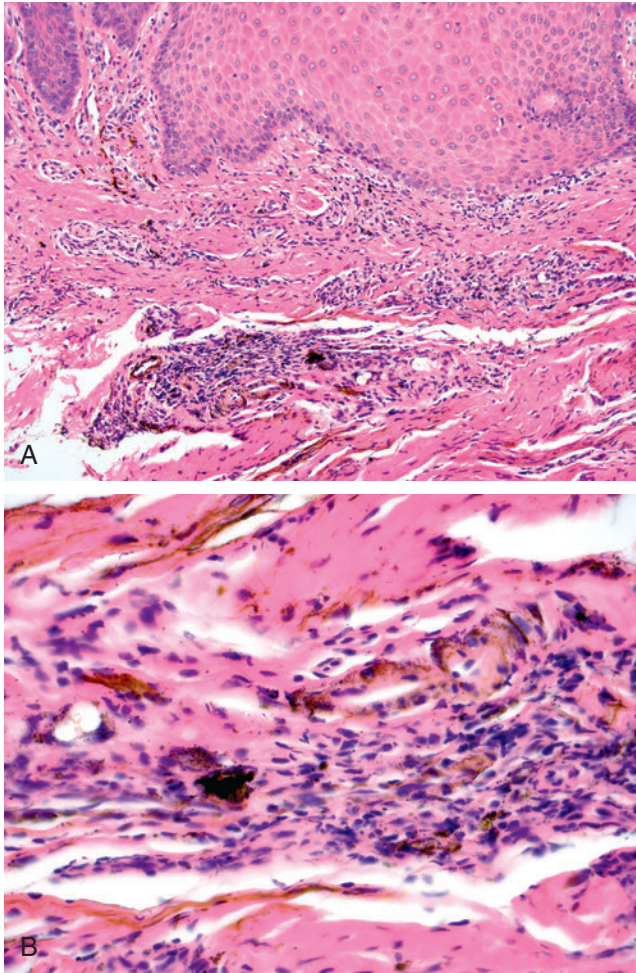


Fig. 6-56. Amalgam tattoo.

Foreign material is present within the submucosa appearing as scattered fine black or dark-brown granules surrounded by a mild chronic inflammatory cell infiltrate.

- Endogenous pigmentation of oral cavity includes byproducts of red blood cells or melanocytes and includes melanotic macule and black hairy tongue.
 - Melanotic macule:
 - Mucosal lesion similar to a freckle or ephelis of the skin, but association with sun exposure is less clear as the lesion may occur on the lips or the intraoral mucosa
 - May occur at any age but is more common in adulthood
 - Appears as a solitary, small, tan to brown, homogeneous, symmetric, nonpalpable pigmentation of the oral mucosa
 - Labial melanotic macule has been found to be more common in the lower lip of adult women.

- Increased melanin without atypia or pleomorphism in the basal layer of the mucosa is the hallmark of melanotic macule:
 - Melanocytes are seen as individual cells that do not show a tendency to nest and/or migrate throughout the surface epithelium.
 - Absence of nuclear atypia and mitotic activity
 - Melanin is accumulated in the cell body of the keratinocytes and is scarce in the dendritic cells of the upper layers of the epithelium.
 - Melanin accumulation may be more prominent at the tips of the rete ridges.
 - Melanin incontinence and melanophage activity may be a finding in the lamina propria.
 - Fontana stain and melanin bleach support the pigment identification as melanin.
- Black hairy tongue
 - Reactive condition resulting in an exaggerated form of filiform papillae on the dorsal surface of the tongue
 - Common condition, particularly found in smokers
 - Dorsal tongue most commonly affected and may be stained yellow, brown, or black
 - Elongation of the filiform papillae results in the hairy appearance, which may range from a coating to a shaggy, matted manifestation
 - Often asymptomatic, but patients may be concerned about the appearance of their tongue.
 - Generally diagnosed clinically but occasionally may be biopsied for confirmation
 - Exact cause is unknown, but black hairy tongue has been associated with a number of predisposing factors, including smoking, medications (e.g., antibiotics), microorganisms (e.g., bacteria, fungi), chemical irritants, and poor oral hygiene; there is no association with Epstein-Barr virus.
 - Histologically, includes hyperkeratosis of the filiform papillae arranged into tall orthokeratin spires is the hallmark of hairy tongue; superficial colonies of bacteria and fungal elements, easily seen in cytologic scraping, admixed with benign squamous cells
 - Improved oral hygiene, tongue brushing, and reduced tobacco use diminish black hairy tongue.
- Treatment for oral mucosal malignant melanoma includes:

- Radical surgical resection
- Lymph node dissection is usually indicated based on the fact that a majority of oral cavity melanomas are advanced at presentation, including reported nodal metastatic rate of up to 75% of cases.
- Adjunctive radiation and chemotherapy of questionable utility but may be given for palliation
- High rate of local recurrence ranging from 31% to 85%
- High rate of distant metastasis:
 - As high as 50% of cases
 - Most frequently to lungs and liver
- Prognosis is poor:
 - 5-year survival rates range from 15% to 25%.
 - Death often occurs within 2 years of diagnosis.
- Unlike cutaneous melanomas, depth of invasion (i.e., Clark levels and Breslow thickness) is not applicable for mucosal malignant melanomas, including those of the oral cavity:
 - Most oral cavity mucosal malignant melanomas are deeply invasive at presentation (i.e., greater than 4 mm).

Neuroendocrine Carcinomas

- Neuroendocrine carcinomas (NEC) represent a heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines.
- Uncommon tumor type in the oral cavity.
- See Section 3, Pharynx, and Section 5, Larynx, for a more detailed discussion.

Hematolymphoid Malignant Neoplasms

General Considerations

- Classification schemes have varied over the past few decades to include the Rappaport Classification (1966), National Cancer Institute Working Formulation (1982), Lukes-Collins Revised Classification (1992), and Revised European-American Lymphoma (REAL) Classification (1994); currently, the WHO Classification (2007) is a modification of the REAL Classification.
- Fourth edition of the WHO Classification stratifies neoplasms primarily according to lineage to include:
 - Myeloid
 - Lymphoid
 - Histiocytic/dendritic
- In addition, fourth edition of the WHO Classification incorporates new information, including:
 - New defining criteria for some diseases
 - New entities defined by genetic criteria or by their morphology, immunophenotype, and clinical features
- Lymphomas are subdivided into non-Hodgkin lymphomas (NHL) and Hodgkin lymphoma:
 - In the head and neck, NHL are more common.
- The vast array of clinical and pathologic features of the malignant lymphoproliferative diseases is beyond the scope of this text; the approach here is to describe the more common types of malignant lymphomas affecting the extranodal lymphoid sites of the head and neck primarily of the oral cavity; other site-specific malignant lymphomas are discussed in those specific sections to include:
 - Nasal-type NK/T lymphoma in Section 1
 - Waldeyer ring malignant lymphomas in Section 3
 - Salivary gland malignant lymphomas in Section 6
 - Thyroid gland malignant lymphomas in Section 8

Oral Cavity Hematolymphoid Malignancies

- Hematolymphoid neoplasms of oral mucosal sites are uncommon and include non-Hodgkin lymphomas (NHL) and plasma cell neoplasms:
 - Represent approximately 2% of all extranodal lymphomas
- No gender predilection; may occur at any age but most common in older individuals with median in sixth to seventh decades
- Sites of involvement include palate, gingiva, tongue, buccal mucosa, floor of mouth, and lip:
 - May also include primary intraosseous lymphomas with extension into oral cavity
- Symptoms may include:
 - Discrete mass, mucosal ulceration, paresthesias, pain, and loosening of teeth
 - Lymphomas of the oral cavity include immunocompetent and immunodeficient patients:
- Immunodeficiency-associated lymphomas occur in HIV-positive and post-transplantation patients:
 - HIV-associated oral cavity lymphoma:
 - Almost all occur in men at younger ages than with approximate median age of 40 years
 - Most often are diffuse large B-cell lymphomas (DLBCL)
 - Are EBV positive in a majority of cases (60% to 75%)
 - May also include subtype of DLBCL referred to as plasmablastic lymphoma (Fig. 6-57):
 - Represents a diffuse proliferation of large neoplastic cells, most with morphology of immunoblasts but with immunophenotype of plasma cells

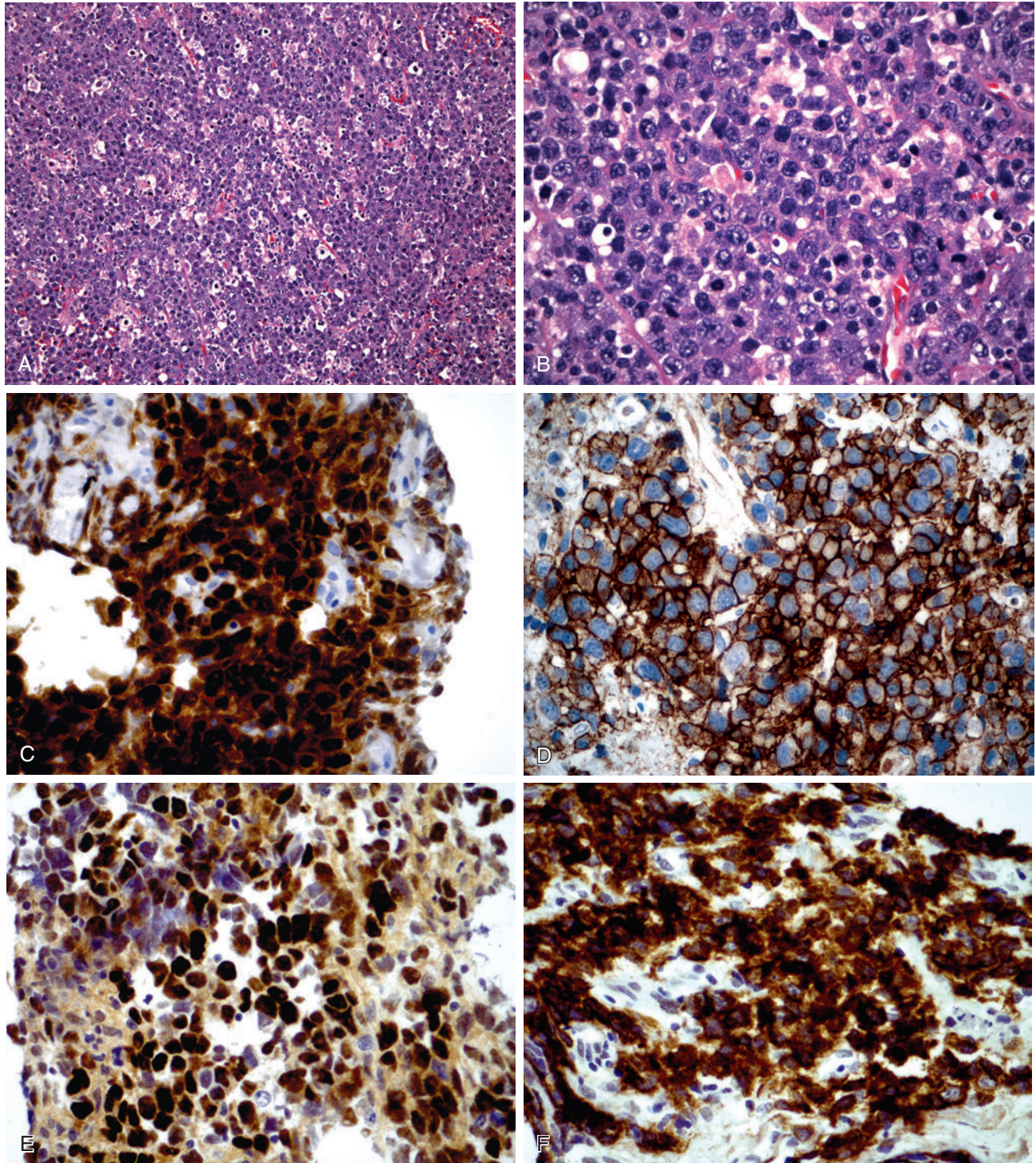


Fig. 6-57. Plasmablastic lymphoma of the oral cavity.

A, Diffuse cellular infiltrate with interspersed macrophages can be seen that on low power create a starry sky appearance. **B**, Neoplastic cells are large with eccentric vesicular-appearing nuclei, prominent nucleoli, and basophilic cytoplasm. Lesional cells are immunoreactive for **(C)** melanoma-associated antigen (MUM1) (nuclear staining) and **(D)** CD138. **E**, In situ hybridization for Epstein-Barr–encoded RNA (EBER) is positive (nuclear staining). In situ hybridization shows **(F)** lambda light chain positive and **(G)** kappa light chain negative.

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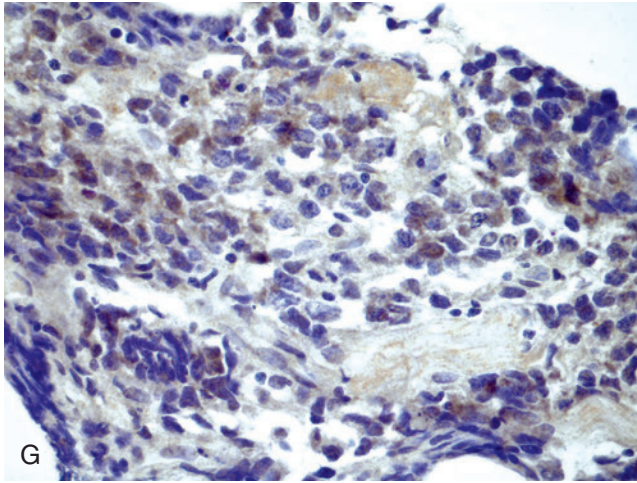


Fig. 6-57, cont'd

- Occurs primarily in HIV-positive individuals but also identified in iatrogenically immunosuppressed patients, HIV-negative, immunocompetent individuals (mostly older adults); rare in children
- Rapidly growing tumors localized to oral cavity and jaw
- Histology:
 - Neoplastic cells show plasmablastic morphology characterized by large cells with eccentric vesicular-appearing nuclei, central prominent nucleoli, paranuclear hof, and basophilic cytoplasm.
 - Generally there is an absence of maturation to plasma cells, although some cases may show maturation toward plasma cells.
 - Frequent single cell or zonal necrosis
 - Starry sky appearance (diffuse growth interspersed by macrophages)
 - High mitotic rate activity
- Immunohistochemistry:
 - Typically express markers associated with post-germinal center stage of differentiation or with plasma cells, including melanoma-associated antigen (MUM1) expression (nuclear staining)
 - CD38, CD138, VS38
 - >50% express monotypic cytoplasmic immunoglobulin (kappa < lambda)
 - Subset are CD79a positive
 - Usually negative for CD45, CD20, and PAX5
 - High proliferative index (60% to 90%)
 - EBV positive (in situ hybridization for Epstein-Barr encoded RNA [EBER]) in approximately 75% of cases

- No association with human herpesvirus-8 (HHV-8, Kaposi sarcoma-associated herpesvirus)
- Molecular genetics:
 - Translocation between *MYC* and *IGH* [t(8;14)] reported but prevalence is uncertain
- Other oral cavity HIV-associated lymphomas:
 - Almost all are diffuse high-grade lymphomas.
 - Most are diffuse large B-cell lymphomas.
 - Occasional cases include peripheral T-cell lymphoma, Burkitt lymphoma, and anaplastic large cell lymphoma of T-lineage.
 - Most contain EBV whether of B-cell or T-cell lineage.
- Oral cavity lymphomas in immunocompetent individuals
 - Wider variety of high-grade and low-grade types than in immunodeficient individuals
 - Almost all are B-cell lymphomas
 - Majority are EBER negative (9% to 19% may be EBER positive):
 - Diffuse large B-cell lymphomas (50%) > follicular lymphoma > marginal zone lymphoma >> others:
 - Follicular lymphomas predilect to palate
 - Marginal zone lymphomas arise in minor salivary glands
- Treatment and prognosis:
 - Staging reveals localized disease in approximately 70% of cases.
 - Outcome depends on:
 - Stage, type of lymphoma, patient's HIV status
 - Excellent prognosis seen in patients with localized, histologically low-grade lymphomas
 - Significantly worse prognosis in patients with disseminated, high-grade lymphomas
 - Patients with HIV/AIDS, including those with plasmablastic lymphoma, have poor prognosis.

Extramedullary Plasmacytoma

- Uncommon but may occur in the oral cavity
- See Section 4, Pharynx, for a more complete discussion.

SARCOMAS OF THE ORAL CAVITY

- In general, sarcomas of the oral cavity are uncommon.

- Although uncommon, virtually all types of sarcomas may occur in these sites.

Rhabdomyosarcoma (RMS)

Definition: Malignant neoplasm showing skeletal muscle differentiation.

- For more complete discussion see Section 3, Pharynx.

Leiomyosarcoma (LMS)

Definition: Malignant neoplasm with smooth muscle differentiation.

- LMS is covered in greater detail in Section 1, Sinonasal Tract.

Liposarcoma

Definition: Malignant neoplasm with adipocyte cell differentiation.

- For more complete discussion see Section 5, Larynx and Trachea.

Malignant Peripheral Nerve Sheath Tumors (MPNST)

Definition: Malignant tumor of peripheral nerves or having differentiation along the lines of various elements of the nerve sheath.

- For more complete discussion see Section 4, Neck.

Undifferentiated Pleomorphic Sarcoma

Definition: High-grade, pleomorphic malignant neoplasm without specific differentiation and not associated with differentiated sarcoma:

- For more complete discussion see Section 1, Sinonasal Tract.

Fibrosarcoma

Definition: Malignant tumor of fibroblasts and myofibroblasts lacking evidence of other types of cellular differentiation.

- For more complete discussion see Section 1, Sinonasal Tract.

Alveolar Soft Part Sarcoma (ASPS) (Fig. 6-58)

Definition: Rare clinically and morphologically distinct, slow-growing but highly malignant soft tissue sarcoma of uncertain histogenesis.

Clinical

- Represents less than 1% of all sarcomas
- More common in women than men prior to age 30; slightly more common in men than women after age 30
- Occurs at any age but is most frequent in the second through fourth decades of life:
 - Rarely occurs prior to 5 years of age
- Most common sites of occurrence is age dependent:
 - In adults, most often occurs in the lower extremities, especially the anterior upper thigh, as well as the buttock
 - In infants and children, most often occurs in the head and neck, in particular the tongue and orbit
 - Isolated cases occur in a wide variety of other sites, including chest wall, trunk, upper extremities, mediastinum, lung, female genital tract, retroperitoneum, stomach, and bone.
- Presentation is usually as a slow-growing, painless mass:
 - Due to slow growth and lack of pain, these lesions may be clinically overlooked and initial presentation may be that of metastatic disease:
 - Early metastasis is a characteristic clinical feature.
 - Common metastatic sites include the brain and lungs:
 - As a result of metastatic disease, especially to the brain, initial complaints may include headache and visual disturbances.
 - Orbital involvement may be associated with proptosis and lid swelling.
- As a result of its rich vascularity, some lesions may be associated with:
 - Pulsation with an audible bruit
 - Massive hemorrhage during surgery
- Radiology:
 - Angiography and contrast-enhanced CT scans: hypervascularity and prominent draining veins
 - MRI: high signal intensity on T1- and T2-weighted images
- No known cause

Pathology

Gross

- Poorly delineated or circumscribed, soft to friable lesions appearing pale gray to yellow; necrosis and hemorrhage may be evident, especially in larger tumors

Histology

- Characterized by an alveolar, organoid, or nestlike growth separated by thin-walled fibrovascular septae lined by a single layer of flattened endothelial cells:

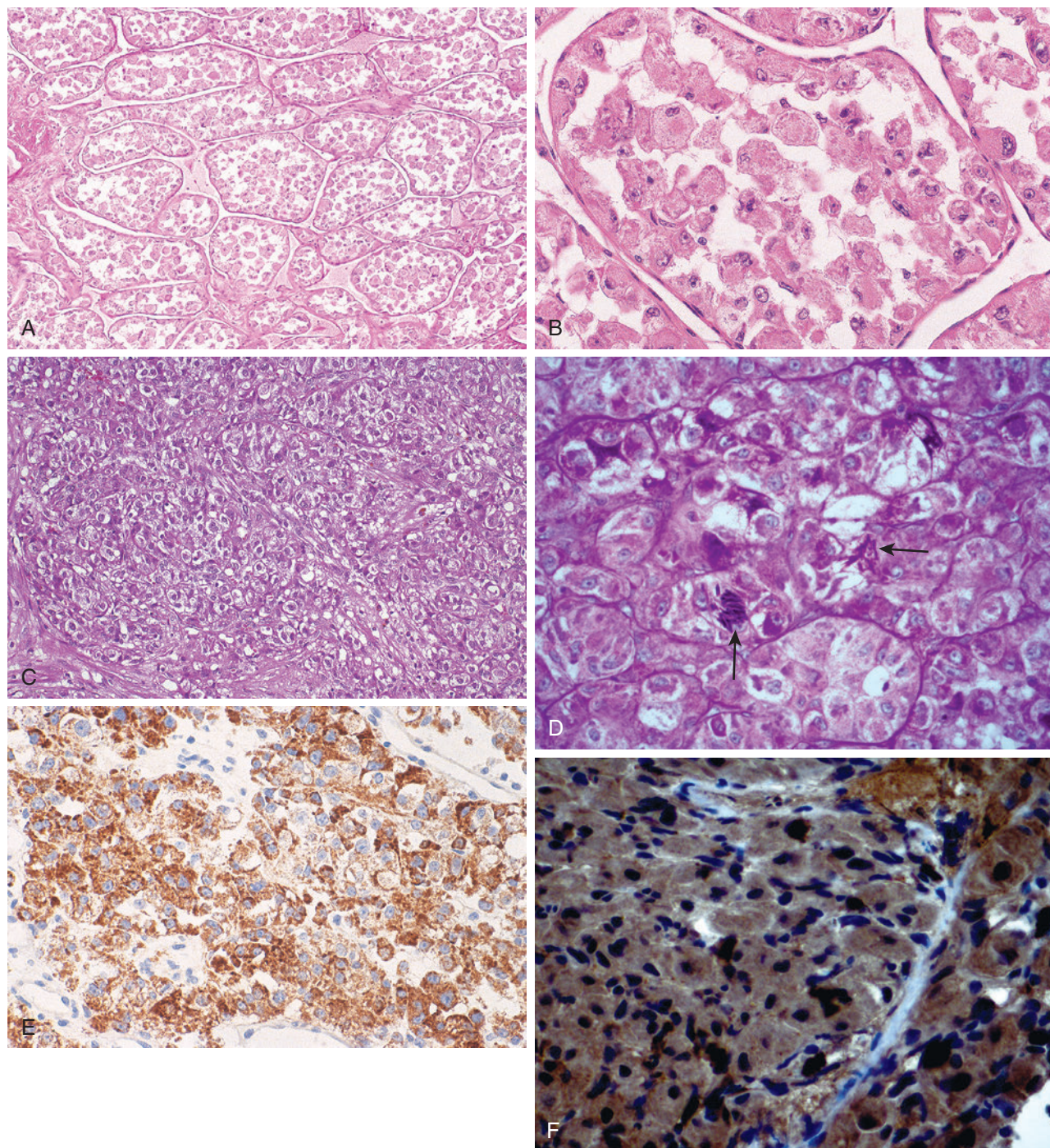


Fig. 6-58. Alveolar soft part sarcoma of the tongue.

A, Characteristic alveolar growth separated by thin-walled fibrovascular septae. **B,** Neoplastic cells are large, round to polygonal in shape with vesicular nuclei, eosinophilic nucleoli, and abundant granular, eosinophilic cytoplasm. **C,** More solid to diffuse growth pattern with less conspicuous or even absent alveolar or nest-like growth may occur in infants and children. **D,** Characteristic diastase-resistant, PAS-positive intracytoplasmic crystalline-like material (*arrows*). **E,** Intracytoplasmic MyoD1 immunoreactivity. **F,** TFE3 (nuclear) staining.

- Loss of cohesion due to necrosis and/or central degeneration within the cell nests results in pseudoalveolar pattern of growth.
- In younger ages (i.e., infants and children) there is a greater tendency to more solid/diffuse pattern of growth, in which the nestlike pattern is inconspicuous or absent.
- Neoplastic cells are large and round to polygonal in shape with little variation in size and shape characterized by:
 - Large, vesicular nuclei with one or more nucleoli
 - Abundant granular, eosinophilic to occasionally clear/vacuolated cytoplasm with distinct cell borders
 - Concave “apple bite” contour to nuclei may be seen especially relative to lingual-based tumors
 - Intramuscular localization for lingual tumors
 - Scarce mitotic activity; nuclear atypia, and multinucleation may infrequently be present.
 - Superficial ulceration may be identified in mucosal-based (e.g., lingual) lesions.
 - Necrosis, cystic change, hemorrhage, and myxoid change may infrequently be identified.
- Prominent dilated veins can be found along the periphery of the tumor.
- Lymph-vascular invasion is a frequent and readily identifiable finding, explaining the tendency to early metastasis associated with this tumor; perineural invasion may be identified.
- Histochemistry:
 - Intracytoplasmic diastase-resistant, PAS-positive rhomboid, or rod-shaped crystalline material considered to be a diagnostic feature for this tumor:
 - Seen in approximately 80% of tumors
 - Can be identified in primary and metastatic lesions
 - Variably identified from case to case:
 - In some tumors crystals are abundantly present and readily identified whereas in other tumors may be rare to absent.
 - Intracytoplasmic diastase-resistant, PAS-positive granules are present, believed to represent precursors of the crystals
 - Nature of crystals not been entirely determined but expression of a monoclonal antibody to monocarboxylate transporter 1 (MCT1) identified in cytoplasm of cells:
 - MCT1 belongs to family of transporter proteins that catalyzes rapid transport of monocarboxylates across plasma membranes.
 - Protein normally associated with rough endoplasmic reticulum and is transported to plasma membrane in association with its chaperone CD147
 - MCT1 and CD147 identified in surface of cells of ASPS as well as in cytoplasm in region of crystals
- Immunohistochemistry:
 - Neoplastic cells:
 - Variable reactivity for vimentin and myogenic markers, including desmin, muscle-specific actin, and MyoD1:
 - MyoD1 reactivity is cytoplasmic, not nuclear.
 - Initially expression of *MyoD1*, a regulatory gene in the control of myogenic differentiation, strongly supported skeletal muscle differentiation for ASPS, but the inability to consistently duplicate this finding, as well as the absence of convincing evidence of skeletal muscle differentiation utilizing more sophisticated techniques, raises doubts relative to skeletal muscle differentiation.
 - Myogenin (Myf-4), myoglobin negative
 - TFE3 immunoreactivity (nuclear staining) present in most but not all cases:
 - Can be identified in other neoplasms including paraganglioma, granular cell tumor, adrenal cortical carcinoma, renal Xp11 translocation carcinoma
 - S100 protein and neuron-specific enolase may be identified in approximately 25% of cases but considered nonspecific reactivity.
 - Negative for cytokeratins, epithelial membrane antigen, neurofilament protein, GFAP, chromogranin, synaptophysin, HMB45, and CD68 (KP-1), and inhibin
 - Intracytoplasmic granules:
 - Immunoreactive for MCT (a monocarboxylate transporter) and CD147 (chaperone protein for MCT)
- Electron microscopy:
 - Characteristic feature is the presence of membrane-bound or free rhomboid to rod-shaped crystals arranged in parallel with a periodicity of 10 nm
 - Cytoplasm contains numerous mitochondria, prominent rough endoplasmic reticulum, well-developed Golgi complexes, and glycogen.
 - Tumor cells are surrounded by discontinuous basal lamina.
 - Rare junctional complexes (desmosomes and hemidesmosomes) are identified.
- Cytogenetics and molecular genetics:
 - Specific translocation der(17)t(x;17)(p11;q25)
 - Unbalanced translocation results in fusion of the TFE3 transcription factor gene on Xp11.2 (a member of the basic-helix-loop-helix family of transcription factors) to *ASPCR1* gene (referred to as ASPL) at 17q25

- *ASPCR1/TFE3* fusion gene:
 - Encodes for a fusion gene that localizes to nucleus
 - Functions as aberrant transcription factor
 - Among soft tissue sarcomas considered highly specific and sensitive for ASPS
 - Also found in association with subset of pediatric renal cell carcinoma characterized by:
 - Pseudopapillary architecture, epithelioid cells with abundant clear cytoplasm and well-defined borders, and psammomatous calcifications
 - These tumors have been termed Xp11 translocation carcinoma.

Differential Diagnosis

- Rhabdomyoma
- Paraganglioma
- Granular cell tumor
- Metastatic renal cell carcinoma
- Alveolar rhabdomyosarcoma
- Crystal storing histiocytosis
- Metastatic ASPS from soft tissue site (e.g., thigh) to the oral cavity:
 - Rare but reported occurrence

Treatment and Prognosis

- Complete surgical resection is the preferred treatment:
 - Surgery includes radical excision of the primary and any metastatic foci.
- Adjunctive radiation and/or chemotherapy have been advocated predicated on several factors:
 - Resectability of the tumor
 - Presence of metastatic disease
- Local recurrence is uncommon.
- Metastatic disease is a frequent occurrence:
 - Can be seen early in the disease course
 - May be the initial presentation
 - Frequently occurs to brain, lungs, and bone
 - Nodal metastasis is uncommon.
- Prognosis is poor:
 - 60% 5-year survival
 - 38% 10-year survival
 - 15% 20-year survival
- Prognostic findings include:
 - Age at diagnosis:
 - Improved prognosis associated with younger age:
 - Less tendency to metastasize
 - Tend to be smaller tumors
 - More amenable to complete resection
 - Localization to the tongue and orbit may allow for earlier diagnosis and smaller tumor size.

- Tumor size:
 - Larger tumors often associated with distant metastasis
- Presence of metastasis:
 - Portends poor prognosis but resection of solitary metastasis may be of prognostic benefit
- Location of tumor:
 - Lingual alveolar soft part sarcoma reported to have a substantially better prognosis than alveolar soft part sarcomas of other sites

Angiosarcoma

Definition: Malignant neoplasm with endothelial cell differentiation.

- For more complete discussion see Section 1, Sinonasal Tract.

Kaposi Sarcoma (KS)

(Figs. 6-59 and 6-60)

Definition: Locally aggressive endothelial tumor uniformly associated with human herpesvirus-8 (HHV-8) infection.

Synonym: Angiosarcoma complex

Clinical

- Occurs in four clinical forms:
 - Classic indolent or chronic KS
 - AIDS-related KS
 - Iatrogenic (transplantation-associated) KS
 - Endemic (African) KS
- Cause:
 - Human herpesvirus-8 (HHV-8) is etiologic agent:
 - Large enveloped double-stranded DNA virus
 - Represents eighth human herpesvirus, hence the designation as human herpesvirus-8 (HHV-8)
 - Also known as Kaposi sarcoma–associated herpesvirus (KSHV)
 - HHV-8 infects endothelial cells as well as peripheral blood monocytes and B lymphocytes in patients with KS.
 - Transmission occurs primarily through saliva.
 - Found in all forms of KS

“Classic” Indolent or Chronic KS

- Considered rare
- More common in men (90%) than women; most common in the sixth through eighth decades of life
- Most common in people of Eastern European and/or Mediterranean descent, as well as in equatorial region of Africa

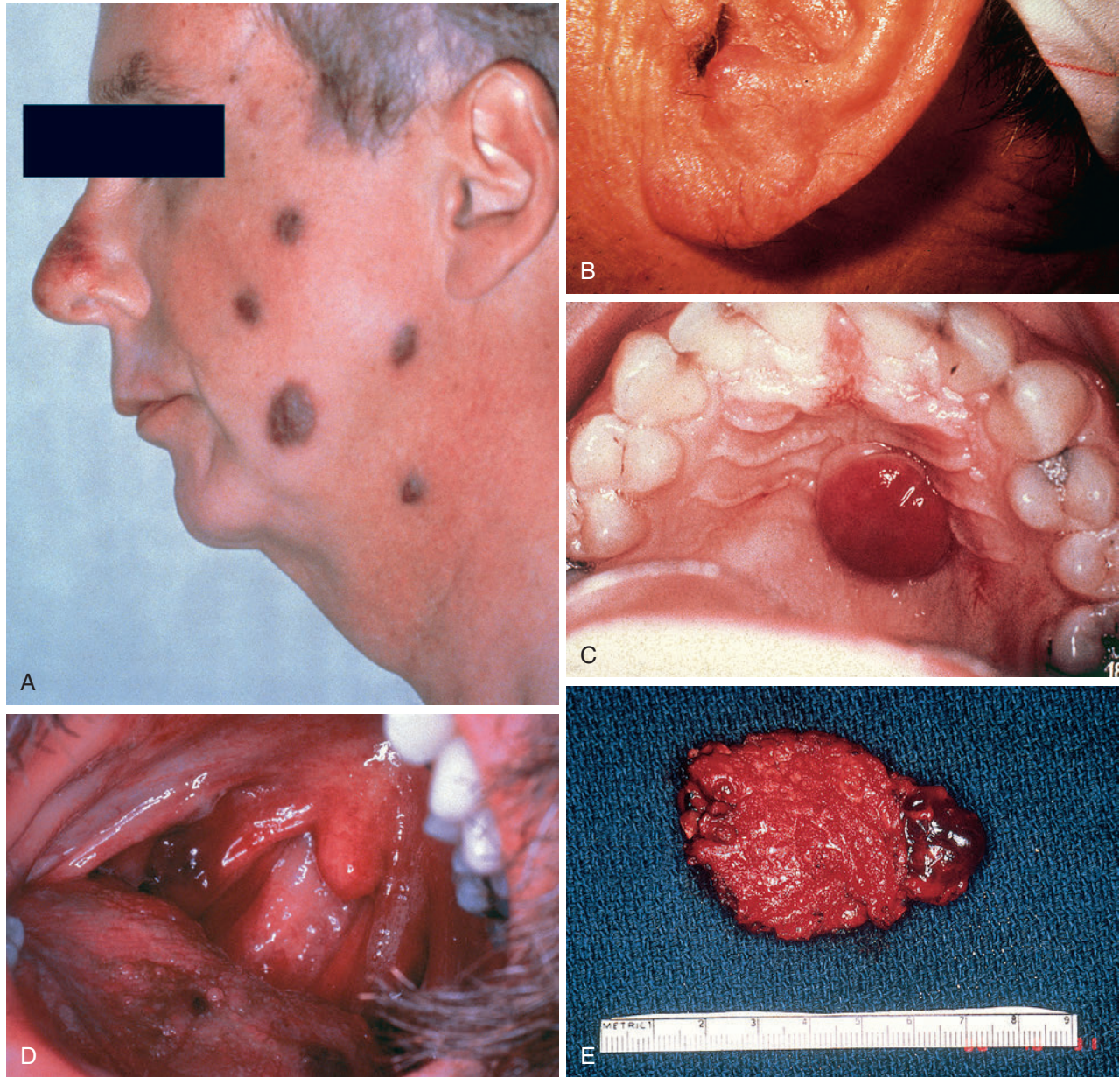


Fig. 6-59. Kaposi sarcoma of various head and neck sites.

A, Multiple, discrete, oval, raised, blue-red, or violaceous cutaneous papules or nodules. **B**, Raised, reddish-appearing nodule located immediately outside to the external auditory canal. **C**, Well-delineated and raised palatal mass with a bright red appearance. **D**, Ill-defined deep-red tonsillar polypoid mass. **E**, Circumscribed, raised, red parotid lesion.

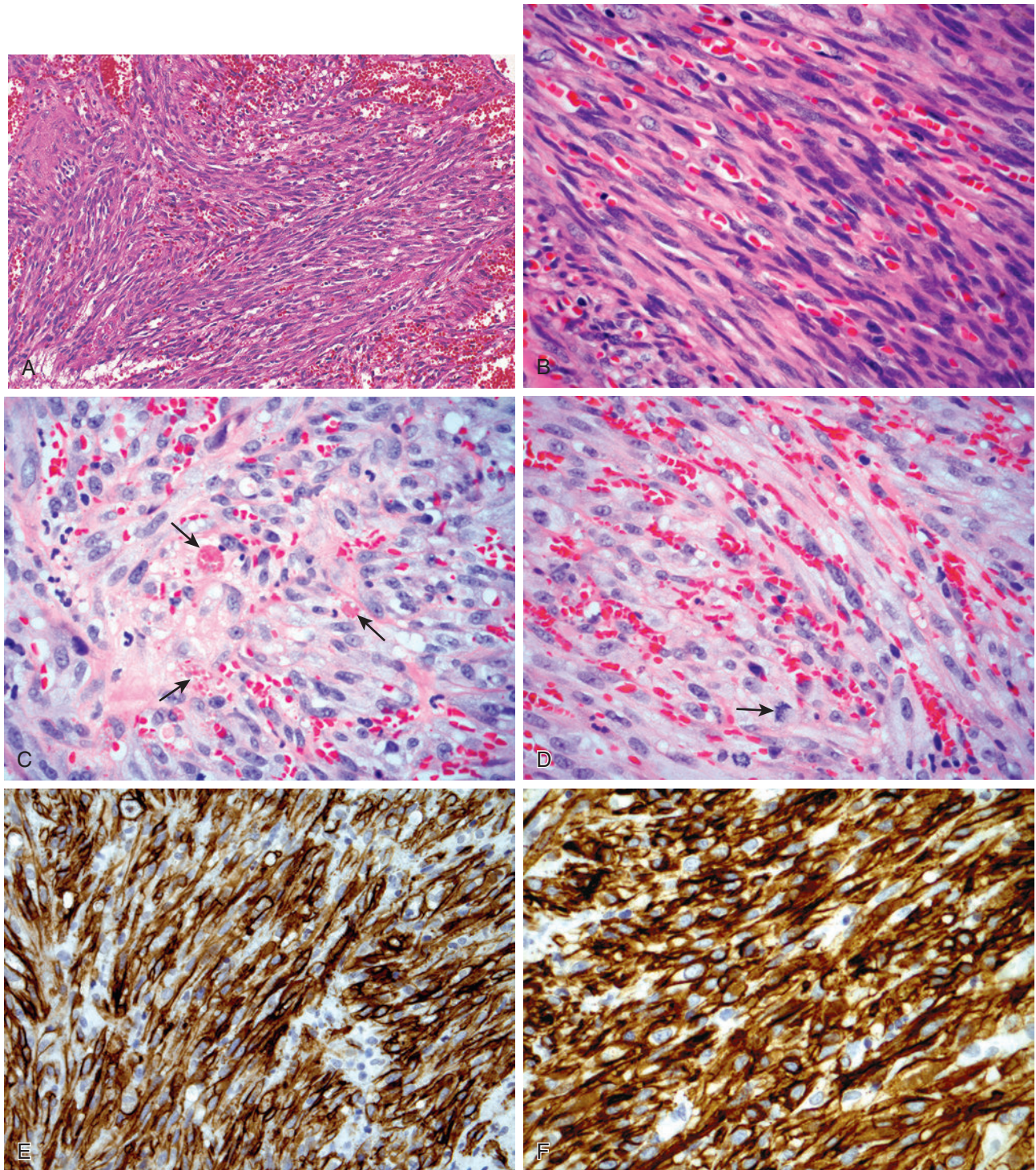


Fig. 6-60. Kaposi sarcoma.

A, Spindle cell proliferation with fascicular growth and presence of slit-like spaces containing erythrocytes that extravasate into the spindle cell component. **B**, Spindle cells are elongated with scant cytoplasm and indistinct cell borders; separating the spindle cell proliferation are slit-like spaces containing erythrocytes. **C**, Hyaline globules (*arrows*) are a characteristic but not specific finding. **D**, Scattered mitotic figures can be found (*arrow*). Lesional cells are immunoreactive for **(E)** CD31, **(F)** CD34, and **(G)** latency-associated nuclear antigen (LANA-1).

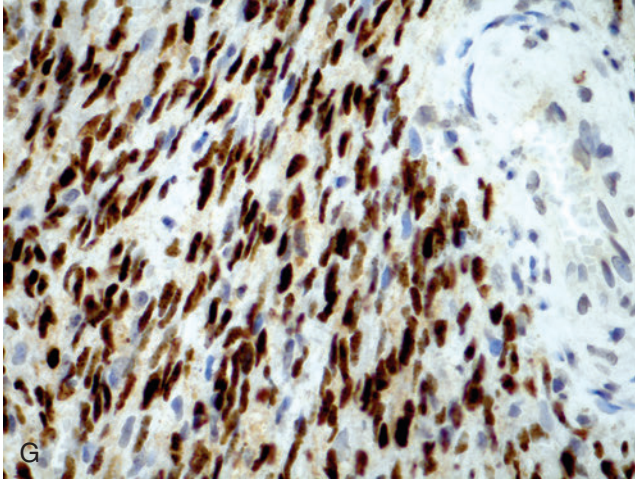


Fig. 6-60, cont'd

- Predominantly a cutaneous-related tumor occurring on extremities, with the lower extremity more common than the upper extremity:
 - Visceral and lymph node involvement is unusual in the absence of cutaneous disease.
 - Initial presentation in the head and neck is decidedly uncommon; with progression of disease from more usual locations, mucosal sites in the head and neck can be affected, including:
 - Oral cavity (palate, tongue, gums, lips, buccal mucosa), tonsils, pharynx, and larynx
- Cutaneous lesions characterized by the presence of purplish-reddish to blue-appearing plaques or nodules with or without ulceration; lymphedema of the involved extremity may also be present.
- Association with a second malignant neoplasm (leukemia, lymphoma, myeloma) or autoimmune disease (autoimmune hemolytic anemia)
- Not associated with the human immunodeficiency virus (HIV) or with the development of AIDS

AIDS-Related KS

- Most aggressive form
- Found in HIV-infected individuals and/or AIDS patients; occurs in approximately 10% of all patients with AIDS
- May be seen in all AIDS-related risk groups but appears to be more common among male homosexuals; occurs at a much younger age as compared with the classic form, most frequently occurring in the fourth decade of life
- Cutaneous lesions most common on the face, lower extremities, and genitals:
 - Visceral and lymph node involvement may occur in the absence of cutaneous disease:
 - Oral mucosa, lymph nodes, gastrointestinal tract, and lungs frequently involved

- Mucosal lesions may be seen throughout the upper aerodigestive tract with the oral cavity and pharynx (oropharynx and hypopharynx) among the more common sites of occurrence:
 - Intraoral sites include palate, gingiva, tongue, buccal mucosa, other
 - Salivary glands (i.e., parotid gland) may be involved.
 - Sinonasal, nasopharyngeal, and laryngeal involvement is uncommon.
- Mucocutaneous lesions vary and include:
 - Early lesions:
 - Solitary or multiple bright red to blue-appearing lesion(s)
 - Later lesions:
 - Purplish-reddish to violaceous mucosal plaque, papule, or nodule with or without ulceration
 - Multiple mucocutaneous lesions are commonly seen.
 - Generalized lymphadenopathy and visceral involvement also frequently occur:
 - Visceral involvement may be clinically silent or may be symptomatic, depending on location of lesion(s) and extent of involvement.
- Identification of KS often is the initial manifestation of AIDS leading to its diagnosis.

Iatrogenic (Transplantation-Associated) KS

- Occurs in solid organ transplant recipients (e.g., renal transplantation) and in patients receiving immunosuppressive therapy
- In this setting, KS may develop months to years after transplantation or immunosuppressive therapy.
- May occur at any age
- May occur in cutaneous or visceral sites:
 - Predilection to skin of the lower extremities
 - Visceral involvement frequently occurs.
- Appearance similar to that of other forms of KS

Endemic (African) KS

- Not associated with HIV infection or AIDS
- More common in males than females; occurs in children and middle-aged adults in equatorial Africa
- Present with localized or generalized lymphadenopathy, including cervical, inguinal, or hilar lymph node chains:
 - Lymph node involvement frequently occurs in children.
- May be localized to cutaneous sites of the extremities:
 - Visceral involvement is fairly common in adults.
- Appearance similar to that of other forms of KS
- Clinical course is variable:
 - In adults typically indolent although may be protracted

- In children may be aggressive:
 - Lymphadenopathic form is rapidly progressive and highly lethal.

Pathology

Gross

- Early lesions in the AIDS group appear as flat, red to pink areas and tend to be small.
- More advanced AIDS-related and “classic” type of Kaposi sarcoma appear as raised, blue-red, or violaceous papules or nodules of varying sizes that with time may coalesce to form plaques.

Histology

NOTE: Regardless of the clinical setting, the histology of the more advanced lesions is essentially the same.

- Differs according to stage of the disease:
 - Early (patch) stage:
 - Slight increase in vascular spaces
 - More advanced (nodular) stage:
 - Unencapsulated and infiltrative composed of spindle cells in a fascicular growth
 - Spindle cells are elongated and rather uniform with scant cytoplasm and indistinct cell borders.
 - Scattered mitotic figures can be identified.
 - Separating the spindle cell proliferation are slit-like spaces containing erythrocytes that commonly extravasate into the spindle cell component.
 - Characteristic but not specific feature is presence of hyaline globules:
 - Intracellular and extracellular
 - Diastase-resistant, PAS-positive
- Typically there is an absence of nuclear pleomorphism and increased mitotic activity:
 - Aggressive forms of KS may include marked nuclear pleomorphism and increased mitotic activity.
 - May occur from beginning (ab initio)
 - May occur as transitional from areas of limited nuclear pleomorphism and increased mitotic activity
- Lymph node involvement may include multiple tumor foci located in capsular and sinusoid regions:
 - Early lesions may appear as foci of mild angiectasia and vascular proliferation in subcapsular sinuses.
- Histochemistry:
 - Intracellular and extracellular hyaline globules are diastase resistant, PAS positive.
- Immunohistochemistry:
 - Latency-associated nuclear antigen (LANA-1) is KSHV latent protein:
 - LANA expressed during latent HHV-8 infection:

- Expression (nuclear staining) by immunohistochemical staining found in all cases of KS
- More than 90% of cases show strong nuclear staining.
- Present in infected cells (both endothelium and spindle-shaped cells)
- Expression not reported in non-KS neoplasms except for primary effusion lymphoma and Castleman disease
- Very useful in early lesions with subtle histologic features
- Additional immunohistochemical findings include:
 - CD31, CD34, and ERG:
 - Both endothelium and spindle-shaped cells:
 - Typically negative for factor VIII-related antigen
 - Vascular endothelial growth factor 3 (VEGFR-3) and podoplanin (D2-40) positive (membranous and cytoplasmic)
- Electron microscopy:
 - Presence of hexagonal nucleocapsids and mature enveloped virions typical for herpesvirus may be found
 - Two abnormalities of the rough-surfaced endoplasmic reticulum may be identified in KS cells including tubuloreticular structures (TRS) and intracisternal paracrystalline inclusions (IPI):
 - 2 types of TRS are distinguished: loose TRS (LTRS) and compact TRS (CTRS)
 - LTRS is observed in endothelial cells from all types of KS.
 - CTRS confined to AIDS-associated KS
 - CTRS, but not LTRS, may represent an ultrastructural marker for AIDS-associated KS.
- Cytogenetics and molecular genetics:
 - No relevant genetic changes reported

Differential Diagnosis

- Lobular capillary hemangioma
- Angiosarcoma
- Spindle cell hemangioma/hemangioendothelioma:
 - Presence of cavernous blood vessels and epithelioid endothelial cells allow for differentiation from KS.
- Kaposiform hemangioendothelioma ([Fig. 6-61](#)):
 - Rare, locally aggressive vascular neoplasm often associated with consumptive coagulopathy and thrombocytopenia (Kasabach-Merritt syndrome) and characterized by a Kaposi sarcoma-like fascicular spindle cell growth
 - Typically occurs in infants and children in the first decade of life:
 - Rare in adults

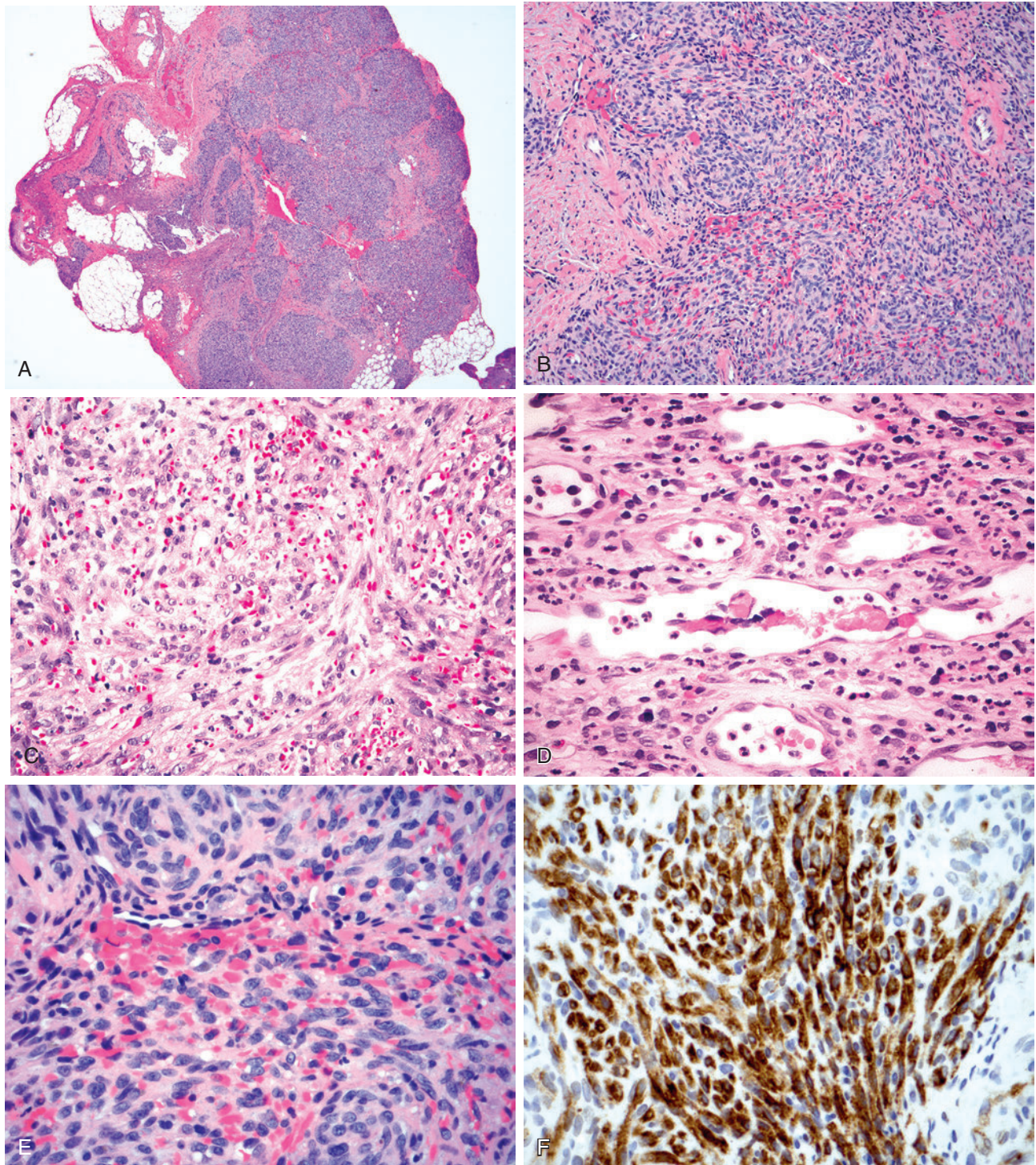


Fig. 6-61. Kaposiform hemangioendothelioma of the palate.

A, Irregular tumor nodules within soft tissue. **B**, Spindle cell areas merge with glomeruloid nests of epithelioid-appearing cells. **C**, Capillary-like areas as well as slit-like vascular lumina containing erythrocytes resemble Kaposi sarcoma. **D**, Intravascular fibrin thrombi can be seen. **E**, High magnification of areas resembling Kaposi sarcoma; immunoreactivity for **(F)** D2-40 (podoplanin) and **(G)** CD31.

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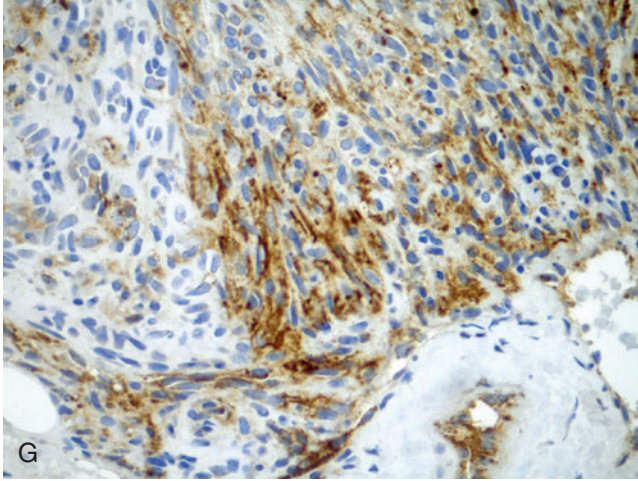


Fig. 6-61, cont'd

- Common site of occurrence includes soft tissue of extremity; less common sites include retroperitoneum, mucosal sites of head and neck, mediastinum
- No known association with HHV-8 or any other viruses
- Histology includes:
 - Lobular architecture separated by fibrous septa
 - Presence of a spindle cell proliferation in a fascicular growth interspersed with numerous capillaries
 - Fascicles may be tightly packed or loosely arranged, containing slit-like or sieve-like vascular lumina.
 - Fibrin thrombi can be found in slit-like spaces and capillaries.
 - “Glomeruloid” bodies may uncommonly be identified.
 - Immunohistochemistry (spindle cells):
 - Slit-like KS-like vascularity reactive for lymphatic markers (PROX1, D2-40 [podoplanin], VEGFR-3)
 - Spindle cell reactive for CD31 and CD34
 - No expression of HHV-8
 - Negative for GLUT-1, a marker found in association with infantile hemangioma
 - Mucosal lesions are treated by surgical resection.
 - Prognosis varies per site and size of the tumor:
 - Large intraabdominal lesions associated with consumptive coagulopathy, has a poor prognosis
 - Mucosal-based lesions associated with more favorable outcome and rarely recur after resection

- Spindle cell squamous carcinoma
- Fibrosarcoma

Treatment and Prognosis

- Other than for diagnostic purposes, surgery is generally not used in treatment.
- Radiation and/or chemotherapy are the preferred treatments:
 - Chemotherapeutic management used in AIDS patients, including azidothymidine (AZT), vincristine, and vinblastine
- Classic indolent form is associated with a prolonged clinical course and low mortality rates:
 - 10% to 20% disease-related mortality
- AIDS-related KS:
 - Prior to advent of highly active anti-retroviral therapy (HAART) had much more aggressive disease course, with increased mortality rates (90%) as a result of the constellation of problems in this group including opportunistic infections and visceral KS
 - Advent of HAART resulted in:
 - Prevention in the development of KS
 - Substantial disease regression
 - Current treatments for AIDS-related KS include ART and chemotherapy for patients with advanced symptomatic disease
- Iatrogenic KS:
 - Clinical course is variable:
 - May resolve after cessation of immunosuppressive therapy
 - May behave aggressively with higher mortality rates due to pulmonary and gastrointestinal involvement

MATRIX-FORMING AND RELATED MALIGNANT NEOPLASMS

Osteosarcoma

Definition: Malignant osteoid-producing neoplasm arising from bone.

Synonym: Osteogenic sarcoma

- Osteosarcomas are broadly classified into those occurring primarily in medullary cavity and those predominantly situated on surface of bone.
 - Medullary osteosarcoma:
 - Conventional (see later)
 - Osteosarcoma of jawbones (see later)
 - Postradiation sarcoma
 - Osteosarcoma in Paget disease
 - Osteosarcoma in other benign conditions
 - Telangiectatic osteosarcoma
 - Small cell osteosarcoma

- Low-grade osteosarcoma
- Multicentric osteosarcoma
- Surface (juxtacortical) osteosarcoma:
 - Paraosteal osteosarcoma:
 - Well-differentiated (low-grade) osteosarcoma arising on surface of bone
 - All surface osteosarcomas are rare but paraosteal osteosarcoma is the most common type, representing approximately 65% of all surface osteosarcomas.
 - Cause unknown
 - More common in females than males; affects young adults approximately decade older than conventional osteosarcoma
 - Symptoms include painless swelling, but pain with or without swelling may be present.
 - Most common site of occurrence is femur (posterior cortex of distal femoral metaphysis) followed by the proximal portions of tibia and humerus:
 - Flat bones rarely involved
 - Plain radiographs almost always diagnostic:
 - Appears heavily mineralized mass attached by broad base to underlying cortex
 - Histology includes relatively hypocellular stroma and well-formed bony trabeculae:
 - Spindle cells show minimal cytologic atypia and rare mitotic figures.
 - Bony trabeculae arranged in parallel arrays
 - Invasion of medullary cavity may occur.
 - Cartilaginous differentiation appearing as hypercellular nodules interspersed among bony trabeculae seen in approximately 50% of cases; may form “caps” along periphery of lesion
 - Approximately 15% have foci of high-grade sarcoma (dedifferentiation) at initial presentation or in recurrent tumor.
 - Areas of dedifferentiation may include osteosarcoma, fibrosarcoma, undifferentiated pleomorphic sarcoma (formerly malignant fibrous histiocytoma).
 - Aggressive tumors associated with early metastasis (to lungs) poor prognosis
 - Metastatic disease may include either low-grade, high-grade, or both components.
 - Surgical resection is preferred treatment:
 - Pre- and postoperative chemotherapy not usually indicated
 - Locally aggressive but limited metastatic potential
 - Very good prognosis with 90% long-term survival
 - Periosteal osteosarcoma
 - Predominantly chondroblastic, moderately differentiated osteosarcoma arising on surface of bone without medullary involvement
 - Much less common than parosteal osteosarcoma but more common than high-grade surface osteosarcoma
 - More common in females than males; occur in children and young adults; highest incidence in second decade
 - Symptoms may include pain and/or swelling; a palpable mass may be present.
 - Almost exclusively found in appendicular skeleton, especially the diaphyseal region of tibia and femur
 - Plain radiographs show a lucency in saucer-shape depression in cortex.
 - CT and MRI assist in excluding marrow involvement.
 - Histologic findings include:
 - Lobulated, chondroid-appearing neoplasm
 - Irregular spicules of bone in center of cartilaginous nodules
 - Moderate cytologic atypia is present.
 - Surgical resection is the preferred treatment; preoperative and postoperative chemotherapy not usually indicated
 - Better prognosis than conventional osteosarcoma but may be metastatic in up to 18% of cases
 - High-grade surface osteosarcoma:
 - Malignant bone-forming neoplasm with high-grade cytomorphology arising on surface of bone
 - Least common surface osteosarcoma representing approximately 10% of all cases
 - More common in males than females; occurs in young adults with highest incidence in second to third decades
 - Most common in long tubular bones, including distal femur, proximal humerus, and distal radius:
 - >50% are diaphyseal.
 - Histologically high grade
 - Multimodality therapy including preoperative chemotherapy followed by surgery
 - Very aggressive with poor prognosis:
 - 5-year survival of approximately 46%
- Extraosseous type:
 - Arises in soft tissues and viscera without connection to bone
 - Diagnosis is predicated on:
 - No connection to an osseous site
 - Presence of osteoid in association with a sarcomatous stroma
 - Exclusion of a metastasis to a soft tissue site from a osseous-related osteosarcoma

- May occur de novo or secondary to radiotherapy
- Majority occurs in the lower extremity, especially the thigh.
- Complete surgical resection to include tumor-free margins is the preferred treatment.
- Aggressive tumors with tendency to local recurrence and distant metastasis:
 - Recur within 1 year of diagnosis
 - Metastasize most frequently to the lungs, but may also spread to lymph nodes, bone, liver
 - Up to 20% of patients have metastatic disease at initial presentation.
- In general, for all sites, including the head and neck, the conventional type is the most common; juxtacortical and extraosseous types are uncommon in the head and neck.

General Considerations

- Second to multiple myeloma, osteosarcoma is most common malignant bone tumor, representing approximately 35% of all malignant bone tumors.
- More common in males than females; most common in children, especially in the second decade of life
- Cardinal symptom is pain with or without a palpable mass:
 - Pathologic fracture or detections as incidental finding on imaging uncommon
- Commonly arises in metaphyseal area of long bones of appendicular skeleton, including:
 - Distal femur, proximal tibia, and proximal humerus:
 - Greater than 90% arise in metaphyseal region
 - Less than 10% arise in diaphyseal region
 - Rare in epiphyseal region
- Radiology:
 - Appears as geographic area of destruction in metaphyseal region
 - Poorly demarcated borders/margins
 - Cortex almost always destroyed and tumor extends into soft tissues
 - Periosteum is lifted from underlying cortex giving rise to periosteal new bone formation usually proximal to tumor referred to as Codman's triangle
 - Varying degrees of bone-producing matrix, including calcifying and ossifying osteoid substance seen within the lesion:
 - Matrix has been termed cloud-like
 - Densities may be present in soft tissue extension considered virtually diagnostic.
 - Soft tissue mineralization may be in the form of striation perpendicular to involved bone and referred to as "sunburst" pattern.
- Cause:
 - In young patients remains unknown
 - In adults, increased incidence in association with Paget disease and postradiotherapy:
 - Referred to as secondary osteosarcomas
 - Approximately 15% to 30% occur in adults secondary to a pre-existing condition.
- Osteosarcoma in association with Paget disease:
 - More common in men
 - Overall median age in the mid seventh decade of life
 - Accounts for greater than 20% of all osteosarcomas in patients over 40 years of age
 - Most common complaint is pain of increasing severity often associated with a palpable mass
 - Approximately two thirds occur in long bones.
 - Up to 17% may occur in skull, which is most common site in the head and neck.
 - Majority arise in medulla; rare to arise on surface of bone
 - May be multifocal:
 - Occurs in up 17% of cases
 - May be superimposed on polyostotic Paget disease
 - May represent multiple primary malignancies
 - May represent metastatic spread from an index malignancy
 - Histologically most are conventional osteosarcomas with tendency to be high grade.
 - Distant metastatic disease at presentation in approximately 25% of cases
 - Poor prognosis with 5-year survival rates of <10%
- Postradiation osteosarcoma:
 - One type of sarcoma that may develop after radiation treatment (postradiation sarcoma); see Section 5, Larynx, for more complete discussion
 - Greatest risk in children treated with high-dose radiotherapy and chemotherapy
 - Prevalence increasing given increased survival after treatment of other malignancy
 - Can develop in any irradiated bone but most common in pelvic and shoulder region
 - Latent period is generally long with a median of 11 years
 - Related to radiation dosage:
 - Uncommon (approximately 0.2%) after usual therapeutic dosages in range of 7000 rads (cGy) or 70 Gy
 - Radiation doses are usually greater than 2000 Rads (cGy) or 20 Gy with most

sarcomas occurring with doses of 5500 rads (cGy) or 55 Gy or higher.

- Histology that of conventional osteosarcoma with no morphologic features distinguishing postradiation osteosarcoma from a de novo osteosarcoma:
 - Tend to be histologically high grade
- Prognosis somewhat dependent on site:
 - 68% 5-year survival for extremity lesions
 - 30% 5-year survival for those of skull and jaw bones
 - 27% 5-year survival for axial lesions
 - Prognosis worse for lesions of the pelvic, vertebral, and shoulder regions
- Other conditions/lesions that predispose to or may be associated with development of osteosarcoma include:
 - Hereditary retinoblastoma
 - Li-Fraumeni syndrome
 - Fibrous dysplasia
 - Osteoblastoma
 - Hereditary multiple exostosis
 - Ollier disease
 - Werner syndrome
 - Rothmund-Thomson syndrome
 - Congenital hypoplastic or absent thumbs

Craniofacial Conventional Osteosarcoma (Excluding in Association with Paget Disease): Gnathic Osteosarcoma (Osteosarcoma of Jaw Bones) (Figs. 6-62 and 6-63)

- Up to about 10% of conventional osteosarcomas occur in the head and neck region, with about 7% occurring in jaw bones.
- More common in men than women; occur in patients who are generally a decade or two older than those with extrafacial (i.e., long bones) osteosarcomas:
 - Mean in fourth decade
- Involvement of the mandible is more common than the maxilla:
 - Mandibular involvement in descending order of frequency includes body, symphysis, angle, and ramus.
 - Maxillary involvement in descending order of frequency includes alveolar ridge, maxillary antrum, anterior midline.
- Most common clinical complaints include:
 - For mandibular lesions: painful swelling of the face, dentition problems (toothache, loose teeth), numbness of the cheek or face
- For maxillary lesions: in addition to above may also include nasal obstruction, epistaxis, proptosis, diplopia
- Laboratory findings:
 - Not specific
 - Elevated serum alkaline phosphatase is only laboratory value of clinical import in osteosarcoma:
 - Abrupt elevation in patients with pre-existing benign bone lesion (e.g., Paget disease, other) may be indicative of malignant transformation.
- Radiology:
 - Destructive, poorly delineated osteolytic, osteosclerotic, or mixed lesion

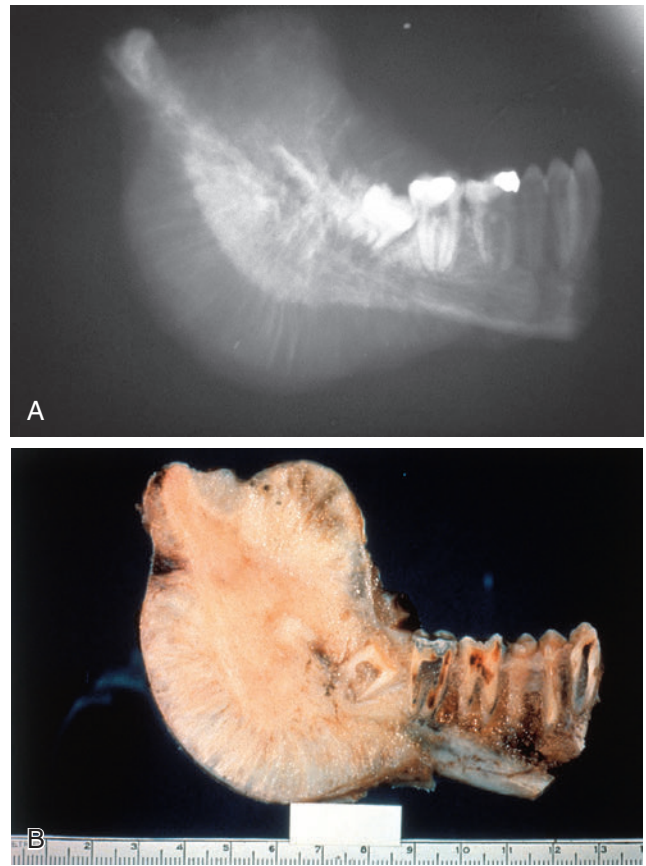


Fig. 6-62. Osteosarcoma of the mandible.

A, Radiograph of resection specimen showing a large mass of the angle of the mandible. Multiple radiodensities representing new bone formation beneath an elevated periosteum ("sunburst" pattern) are seen. This pattern is typically associated with osteosarcoma. **B**, Corresponding gross specimen showing destruction of the mandible and extension of the tumor into adjacent soft tissue; the tumor has speculations at its peripheral portion.

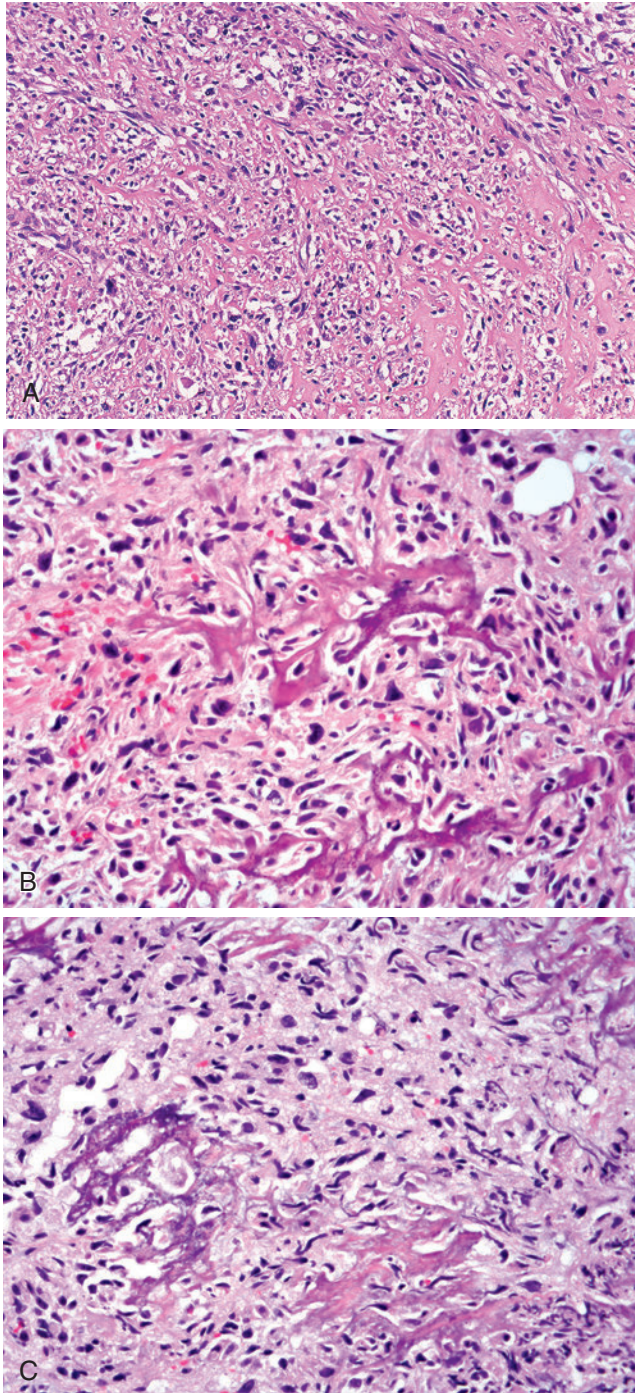


Fig. 6-63. Osteosarcoma.

A, Low magnification shows a matrix-producing lesion with associated cellular proliferation including pleomorphic nuclei. **B** and **C**, Histologic features include a sarcomatous stroma intimately associated with lace-like osteoid appearing as eosinophilic, hyaline-like material with irregular contours and variable extent of dark blue-purple matrix calcification.

- Periosteal reactions include:
 - Cupping out of subperiosteal cortical bone
 - Thin, bulging, opaque, noncontinuous line of new bone formation beneath the periosteum in the adjacent soft tissue
 - Irregular, sclerotic mass of subperiosteal new bone with multiple laminations
- Codman's triangle and "sunburst" pattern (see above for descriptions) may be present but in a small percentage of cases.
- Involvement of alveolar bone between teeth may result in projection of sclerotic material beyond height of the crestal bone into adjacent soft tissue:
 - Highly suggestive of osteosarcoma
- Widening of the periodontal membrane space along one side of one or more roots is a highly characteristic feature of malignant neoplasms, including osteosarcoma:
 - Represents early radiographic finding
 - Unusual finding as most cases do not present in such early stages
- Other head and neck sites of occurrence may include:
 - Skull:
 - Represent less than 2% of head and neck osteosarcomas
 - Often occur secondary to Paget disease or previous radiotherapy to the region of involvement
 - Poor prognosis with 5-year survival rates of less than 15%
 - Larynx:
 - Rare location
 - Of bona fide examples reported in the literature, majority are extraosseous, arising in laryngeal soft tissues in and around the true vocal cords and anterior commissure
 - Poor prognosis with death usually occurring within 2 years of diagnosis

Pathology

Gross

- Dependent on the extent of mineralization versus extent of the stromal component such that the tumor may vary from firm, hard, and gritty to fleshy and fibrous
- Gnathic osteosarcomas generally do not exceed 5.0 cm in greatest diameter.

Histology

- Sarcomatous stroma intimately admixed and giving rise to osteoid
- Diagnosis is predicated on the identification of osteoid:
 - Osteoid, uncalcified precursor of bone, is a dense, eosinophilic, amorphous, hyaline-like material

- with irregular contours surrounded by a rim of osteoblasts.
 - Is refractile
 - Variable present from case to case
 - Often predisposed to “scaffolding” or appositional deposition on existing normal bony trabeculae
 - Can be difficult to differentiate from nonosseous eosinophilic extracellular materials such as collagen and amyloid:
 - Osteocalcin and osteonectin usually present in osteoid is absent in collagen and amyloid.
 - Amyloid shows apple green birefringence on Congo red staining and will be reactive for amyloid immunostains, staining patterns not seen in osteoid.
 - Stromal cells (osteoblasts):
 - May be spindle-shaped, ovoid, polygonal, round, fusiform, plasmacytoid, epithelioid, or clear with hyperchromatic nuclei with or without nucleoli
 - Display variable anaplasia but usually markedly pleomorphic and anaplastic with associated necrosis, increased mitotic activity (normal and bizarre mitoses), and invasive growth (into adjacent structures and angioinvasion)
 - Are multipotential cells capable of producing osteoid, cartilage, and collagen or fibroblastic foci; depending on which component predominates, osteosarcomas can be divided into:
 - Osteoblastic type:
 - Bone and osteoid represent the predominant matrix
 - Chondroblastic type:
 - Cartilage/chondroid matrix predominates
 - Approximately 50% of cases are chondroblastic and may be mistaken for chondrosarcoma (see later in chapter).
 - Cartilage is hypercellular and arranged in lobules; osteoid is present in center of lobules as short, poorly formed bony trabeculae or within spindle cells at periphery of lobules
 - Fibroblastic type:
 - High-grade spindle cell malignant tumor with minimal amounts of osseous matrix
 - Cartilage/chondroid matrix may or may not be present
 - In the head and neck, osteoblastic and chondroblastic are most common.
 - Prognosis not believed to correlate with above histologic subtype
 - Tumor giant cells are often seen, and benign osteoclast-like multinucleated giant cells are identified in approximately 25% of cases.
 - Vascularity varies from relatively inconspicuous to dominant.
 - Immunohistochemistry:
 - Utility of immunohistochemistry in diagnosis is limited.
 - Main use is to exclude other diagnostic considerations.
 - Osteoblasts often are vimentin and CD99 (intracytoplasmic) positive; cytokeratin and smooth muscle actin staining may be positive.
 - Osteoid is immunoreactive for osteocalcin and osteonectin in a majority of cases.
 - Cytogenetics and molecular genetics:
 - Clonal chromosomal aberrations are common but there are no specific translocations or other diagnostically significant alterations.
 - Loss of retinoblastoma (*RB1*) tumor suppressor gene common occurrence
 - p53 abnormalities common finding
- ### Histologic Variants of Osteosarcoma
- Histologic variants include:
 - Small cell:
 - Uncommon variant in the head and neck
 - Predominantly composed of small cells with variable degree of osteoid production
 - Cells have round to oval nuclei with fine to coarse chromatin and scant cytoplasm.
 - Increased mitotic activity
 - Lace-like osteoid is present but may be limited in extent and can be difficult to differentiate from collagenized stroma
 - Immunoreactivity may include CD99, vimentin, osteocalcin, osteonectin, Leu-7, and smooth muscle actin
 - *EWSR1* translocation associated with Ewing sarcoma family of tumors absent
 - Telangiectatic:
 - Rarely identified in head and neck osteosarcomas
 - Composed of prominent blood-filled cystic spaces separated by septae containing the highly malignant mononuclear neoplastic cells characterized by markedly pleomorphic cells with increased mitoses, including atypical mitoses
 - Osteoid varies in amount and tends to be fine and lacelike
 - Resembles aneurysmal bone cyst:
 - Occasionally may be solid with smaller cystic spaces
 - Cystic spaces lack endothelial cell lining and may be lined by benign-appearing giant cells.
- ### Differential Diagnosis
- As a result of the histomorphologic variability of osteosarcoma the differential diagnosis may include:

- Benign lesions, including:
 - Fracture callus
 - Myositis ossificans
 - Benign fibro-osseous lesions (fibrous dysplasia, psammomatoid ossifying fibroma, fibrous dysplasia); aneurysmal bone cyst
- Osteoblastoma
- Giant cell tumor
- Chondrosarcoma
- For small cell osteosarcoma:
 - Ewing sarcoma family of tumors
 - Other small round cell malignant tumors

Treatment and Prognosis

- Treatment for gnathic osteosarcomas is primarily surgical to include radical extirpation with tumor-free margins.
- Utility of adjuvant therapy (preoperative or postoperative radiation and/or chemotherapy) remains unclear:
 - Advocated in cases with positive margins or metastatic disease
- Regional nodal metastasis uncommon (less than 10%):
 - Neck dissections are usually not indicated.
- Overall 5-year survival rates vary in the literature, including:
 - Approximately 43%
 - 60% to 70% in other reported series
 - Earlier diagnosis and initiation of treatment are associated with a significantly better prognosis.
 - Craniofacial osteosarcomas are associated with a better prognosis than extrafacial tumors attributed to:
 - Tendency to remain localized with metastatic spread only late in the disease course
 - Lower histologic grade
- In spite of the overall better prognosis of craniofacial osteosarcomas, these are still potentially lethal tumors requiring radical management.
- Gnathic osteosarcomas prone to local recurrence:
 - Maxillary osteosarcomas recur in higher percentage of cases as compared with mandibular tumors.
 - Recurrence usually occurs within the first postoperative year.
- Metastases are uncommon and occur late in the course of disease:
 - Usually disseminate to the lungs and brain
 - Associated with a mean survival of approximately 6 months
- Prognostic factors include:
 - Positive prognostic factors include:
 - Younger age
 - Tumor-free resection margins
 - Adverse prognostic factors include:
 - Larger tumors
 - Higher grade tumors
 - Recurrent tumor
 - Developed secondary osteosarcomas

Chondrosarcoma

General Considerations

Definition: Malignant tumor of (hyaline) cartilage differentiation including chondrocytes in lacunae:

- As detailed previously, osteosarcomas may produce cartilage but lesional cells of chondrosarcomas do not produce osteoid.
 - Presence of osteoid confers a diagnosis of osteosarcoma (e.g., chondroblastic type); see below
 - In general, chondrosarcoma is one of more common primary malignant bone tumors, representing approximately 20% of all malignant bone tumors.
 - Types of chondrosarcomas:
 - Primary (conventional) chondrosarcoma arises centrally in normal bone.
 - Secondary chondrosarcoma arises in a benign precursor lesion (e.g., osteochondroma or enchondroma):
 - May occur in association with Ollier disease and Maffucci syndrome (enchondromatoses):
 - Ollier disease is a sporadically occurring developmental disorder characterized by the presence of multiple cartilaginous tumors (enchondromas, chondrosarcoma), especially of the tubular bones of the extremities.
 - Maffucci syndrome is sporadically occurring developmental disorder characterized by the presence of multiple cartilaginous tumors (enchondromas, chondrosarcoma) especially of the tubular bones of the extremities as well as cutaneous and visceral vascular tumors (hemangiomas, including spindle cell and angiosarcoma)
 - Periosteal chondrosarcoma arises on the surface of bone; also referred to as juxtacortical chondrosarcoma
 - Histologic variants of “conventional” chondrosarcoma include:
 - Clear cell
 - Dedifferentiated
 - Mesenchymal
- NOTE:** Extraskelatal myxoid chondrosarcoma is categorized by the WHO as a tumor of uncertain differentiation owing to the paucity of convincing evidence of cartilaginous differentiation:
- Characteristic translocation usually involving NR4A3 and EWSR1

Maxillofacial (Gnathic) and Skull Base Chondrosarcoma

(Figs. 6-64 and 6-65)

Clinical

- Incidence of chondrosarcoma of head and neck sites varies from 5% to 12%:
 - Most common site is the larynx (see Section 5, Larynx)
 - Other common sites of occurrence include:
 - Maxillofacial chondrosarcomas involving the craniofacial area, including the mandible, maxilla, and maxillofacial skeleton, including nasal cavity (septum, turbinates) and paranasal sinuses
 - Neuroaxial or base of skull chondrosarcomas that include base of skull and nasopharynx
- Primary conventional chondrosarcoma is most common type in the head and neck:
 - Secondary and periosteal chondrosarcomas are rare in general, especially in the head and neck.
 - Clear cell and dedifferentiated variants also are rare in general, especially in the head and neck.
- Mesenchymal chondrosarcomas also are rare but can occur in the head and neck, especially in gnathic bones but also in soft tissues of the neck (discussed later).
- Maxillofacial:
 - No gender predilection; occur over a wide age range but are most common in the fourth to fifth decades of life:
 - Approximately 2% of chondrosarcomas occur in patients less than 20 years of age.
 - Most common site of occurrence is maxilla, especially in anterior alveolar region
 - Less common in the mandible where molar region and ramus represent common sites of occurrence
- Skull base region:
 - No gender predilection; occur over a wide age range but most common in the third to sixth decades of life
 - Most arise in middle cranial fossa and much less common in the anterior fossa, posterior fossa, or middle and posterior fossae.
- Symptoms vary according to the site and include:
 - Nasal obstruction, epistaxis, changes in dentition (loosening or eruption of teeth), proptosis, visual

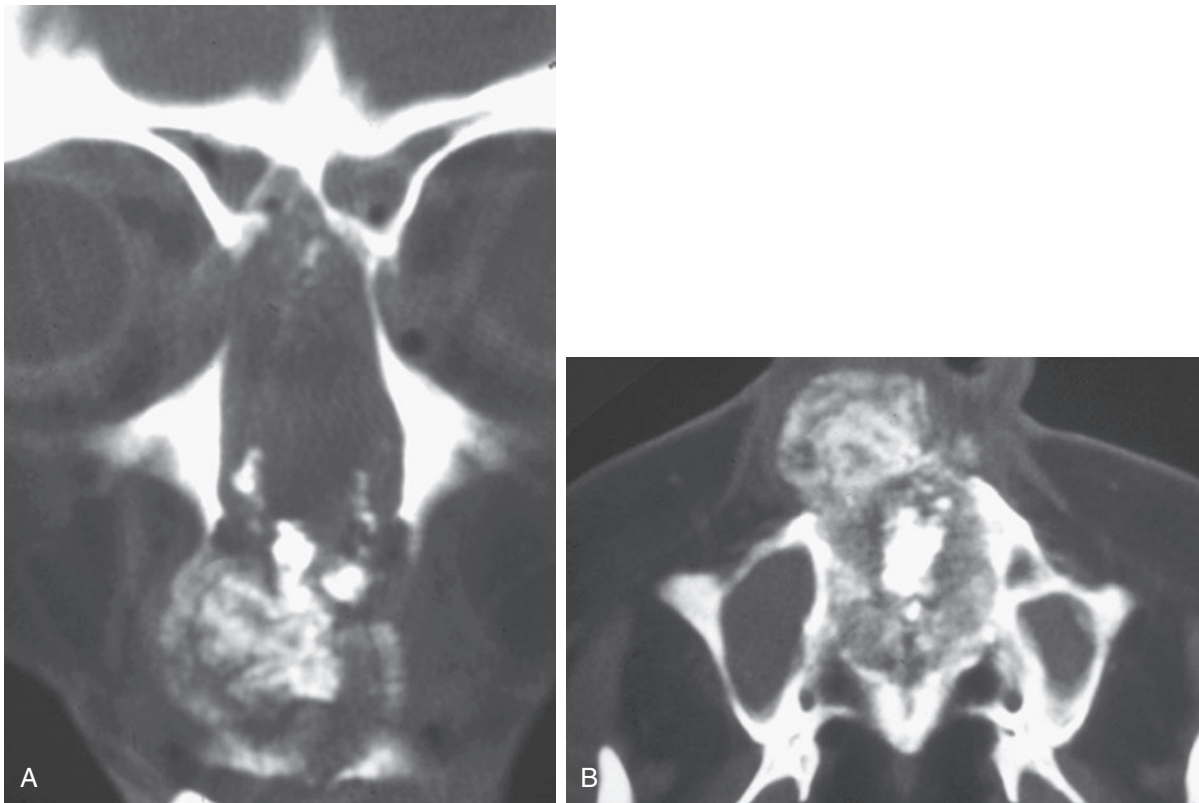


Fig. 6-64.

Coronal (**A**) and axial (**B**) CT scans show a bulky mass arising in the hard palate and extending ventrally into the nose. There are innumerable calcifications spread throughout the tumor. This patient had a chondrosarcoma. (From Som & Curtin: *Head and Neck Imaging*, ed 5. Philadelphia, 2011, Elsevier, Fig. 4-222, p 366.)

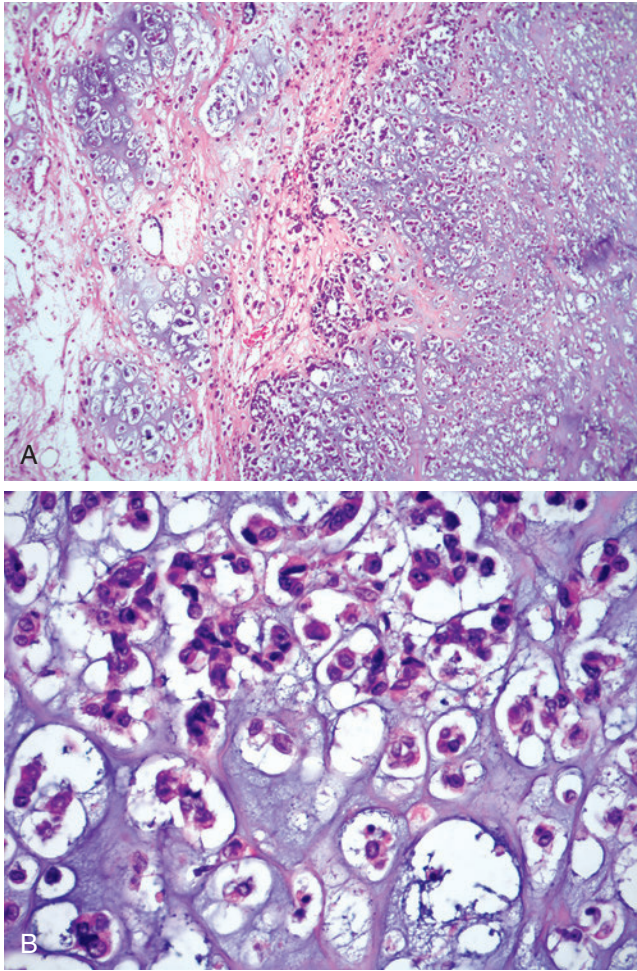


Fig. 6-65. Histology of chondrosarcoma.

Gnathic (mandibular) grade II (moderately differentiated) chondrosarcoma. **A**, The tumor is characterized by lobular architecture and greater cellularity than in grade I lesions. **B**, In addition to greater cellularity there is a greater degree of nuclear hyperchromasia, pleomorphism, bi- and multinucleated cells as compared with grade I tumors but not as anaplastic as seen in grade III lesions. See Section 5, Larynx, for histology of low-grade and high-grade chondrosarcomas.

disturbances and an expanding mass associated with pain, trismus, headaches, and neurologic deficits

- Radiology:
 - Poorly defined, destructive lesion with single or multiple radiolucent, radiopaque, or mixed-appearing areas, and coarse calcifications
 - CT: useful to assess tumor matrix and cortical involvement
 - MRI: useful to characterize extent of bone marrow involvement and soft tissue extension
- No known cause

Pathology

- See Section 5, Larynx, for a complete discussion of the pathologic features of chondrosarcoma.
- Histologic grading of chondrosarcomas includes:
 - Well-differentiated, or grade I:
 - Mild to moderate cellularity with relatively uniform small hyperchromatic nuclei, occasional binucleate cells, and low mitotic activity
 - Matrix varies from chondroid to myxoid.
 - Moderately differentiated, or grade II:
 - Greater cellularity than in grade I lesions with greater degree of nuclear hyperchromasia, pleomorphism/atypia, binucleate cells are frequently identified and there is increased mitotic activity (usually fewer than 2 mitoses per 10 high-power fields)
 - Matrix tends to be more myxoid than chondroid
 - Poorly differentiated, or grade III:
 - Markedly cellular with large hyperchromatic to vesicular nuclei with marked nuclear pleomorphism, prominent nucleoli, increased mitotic activity (greater than 2 mitoses per 10 high-power fields), and necrosis
 - Limited chondroid matrix
 - Irrespective of grade, lobular pattern of growth is at least focally retained.
- Immunohistochemistry:
 - No specific markers
 - Lesional cells are S100 protein, vimentin, and D2-40 (podoplanin) positive
 - Absence of staining for cytokeratins, EMA, brachyury, e-cadherin
- Cytogenetics and molecular genetics:
 - Numerous genetic abnormalities present, including (but not limited to):
 - Amplification of 12q13
 - Loss of 9p21

Differential Diagnosis

- Chondroma
- Chondroblastoma (Fig. 6-66):
 - Benign cartilage-producing neoplasm usually arising in the epiphyses of long bone of skeletally immature patients characterized by cartilaginous differentiation and presence of mononuclear cells and giant cells
 - Accounts for less than 1% of all bone tumors
 - Most common locations in femur, humerus, tibia, and tarsal bones
 - Rare in the head and neck, where the most common site is the skull and temporal bone; less common sites include mandible (condyle and angle) and maxilla

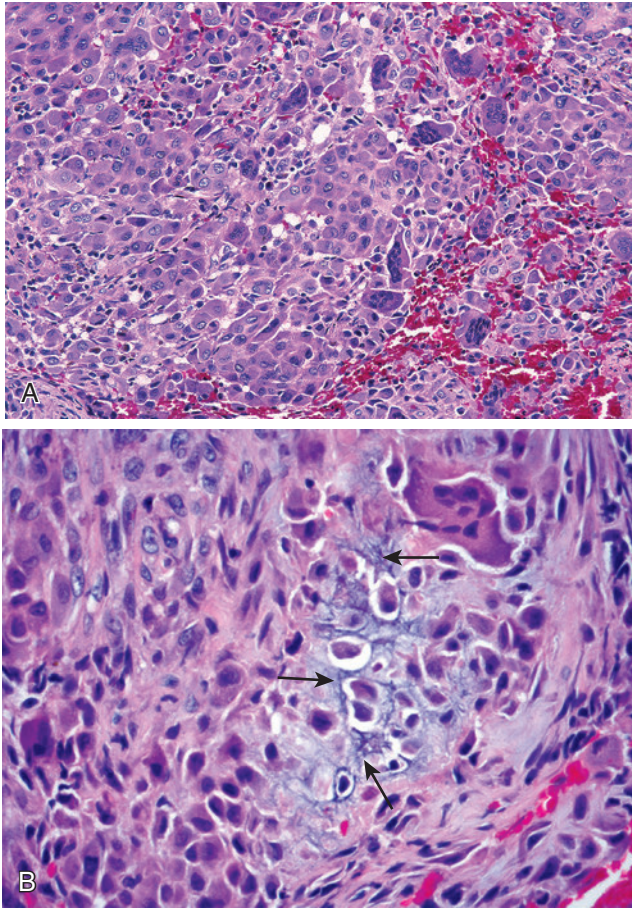


Fig. 6-66. Chondroblastoma.

A, Cellular proliferation composed of admixture of epithelioid cells with round to oval nuclei basophilic to eosinophilic cytoplasm and multinucleated giant cells.

B, Fine (lace-like) network of pericellular calcification referred to as “chicken wire calcification” is present (arrows) between mononuclear lesional cells.

- Temporal bone lesions present with mass effect, hearing loss, otalgia, and tinnitus
- Gnathic lesions present with swelling and limitation in movement.
- Histology:
 - Cellular proliferation composed of sheets of uniform, round to polygonal (epithelioid) cells with round to oval nuclei, inconspicuous to small nucleoli, and clear to slightly eosinophilic cytoplasm with distinct cell borders (chondroblasts)
 - Nuclear indentations and grooves are frequently seen.
 - Giant cells are consistently identified and include two types:
 - Numerous randomly distributed large osteoclast-type giant cells with few to numerous nuclei

- Smaller giant cells with few (2 to 3) nuclei
- Fine (lace-like) network of pericellular calcification referred to as “chicken wire calcification” consistently present but may be very focal in localization
- Chondroid differentiation is almost always present, varying from sparse to extensive and appearing as eosinophilic (rather than basophilic) matrix, within which are cells with chondroblastic differentiation; mature chondrocytes are uncommon.
- Mitotic figures are identifiable but atypical mitoses are not present.
- Aneurysmal bone cyst-like foci seen in approximately one third of cases (referred to as cystic chondroblastoma)
- Immunohistochemistry:
 - Chondroblasts are S100 protein, vimentin, and neuron-specific enolase positive.
 - Variable reactivity with epithelial markers, including cytokeratin and epithelial membrane antigen
- Conservative local excision is the preferred treatment; radiation therapy used in tumors that are difficult to excise in totality due to anatomic location.
- Local recurrence ranges from 10% to 50% and usually occurs within 2 years.
 - 50% recurrence reported in association with temporal bone lesions likely correlated to inadequate excision
- Rare examples of pulmonary metastasis of histologically benign chondroblastoma
- Synovial chondromatosis
- Chordoma (see Section 3, Pharynx) for complete discussion:
 - Chordomas are immunoreactive for cytokeratins, EMA, S100 protein, vimentin, brachyury, e-cadherin but negative for D2-40
 - Chondrosarcomas are immunoreactive for S100 protein, vimentin, and D2-40 but negative for cytokeratins, EMA, brachyury, and e-cadherin
- Osteosarcoma, chondroblastic variant (see earlier):
 - Presence of osteoid even in limited amounts confers a diagnosis of osteosarcoma and excludes chondrosarcoma.
 - Critical to examine all biopsy material or resected tissue in presence of a cartilaginous tumor of jaws

Treatment and Prognosis

- For maxillofacial chondrosarcomas:
 - Radical resection with adequate margins is indicated.
 - Usually a slow-growing but persistent tumor characterized by multiple recurrences

- Local recurrence in approximately one third of cases
- Metastases are rare.
- Overall survival rates reported include:
 - 68% at 5 years
 - 54% at 10 years
 - 44% at 15 years
- Death is generally due to uncontrolled local disease with invasion and destruction of vital structures, including intracranial extension.
- More lethal than laryngeal chondrosarcoma, perhaps because they tend to be of a histologically higher grade, but more likely due to their proximity to vital structures and difficulty in achieving negative margins
- Neuroaxial or base of skull chondrosarcomas:
 - Often are extensively infiltrative at the time of diagnosis, precluding complete resection, therefore, with a tendency for local recurrence
 - Radiotherapy can be used as an adjunct to surgery as part of the primary management of patients.
- Overall 5-year survival rate for head and neck chondrosarcoma is approximately 70%.
- Prognostic factors include:
 - Larger tumors and more central location (near maxillary sinus or mandibular ramus) associated with worse prognosis
 - Pediatric patients may have better prognosis.
- Other head and neck sites may include:
 - Sinonasal tract, oral cavity (palate) nasopharynx, soft tissues of the neck (perimandibular)
- Occurs in cranial and spinal dura mater
- Multifocality with involvement of multiple bones occurs but is rare (less than 1%).
- Most common presentation is that of pain and swelling of the affected site.
- Radiology:
 - Bone:
 - Osteolytic lesion with sharp or poorly defined margins
 - Soft tissue:
 - Plain radiographs and CT scans: well-demarcated density with sharp or poorly defined margins
 - Coarse or granular calcification often (but not always) present
 - T2-weighted MR images: depict two-component structure composed of calcified and uncalcified areas
 - Enhanced MRI: inhomogeneous enhancement in both areas

Pathology

Gross

- Circumscribed to well-defined, lobular, soft to firm, tan-white to blue-gray mass varying in size from 3 to 30 cm in greatest dimension
- Areas of hemorrhage and necrosis may be present.

Histology

- Biphasic tumor composed undifferentiated small round cells with abrupt transition with well-defined islands or nodules of (hyaline) cartilage.
- Undifferentiated small round cells:
 - Closely packed cells with uniform small, round to oval to spindle-shaped hyperchromatic nuclei and a limited amount of barely discernible cytoplasm
 - Growth patterns may include:
 - Solid (similar to the cellular infiltrate in Ewing sarcoma)
 - Alveolar or herringbone
 - Clustered with perivascular localization
- Cartilage:
 - Usually well defined, may be poorly circumscribed composed of relatively cytologically bland cartilage
 - Cartilage may appear malignant.
 - Variable in distribution appearing as large irregular areas or distinct islands admixed with the small round cell infiltrate
 - Amount of cartilage is variable from case to case; in some cases it is readily identifiable, whereas in

Mesenchymal Chondrosarcoma

(Fig. 6-67)

Definition: Rare malignant cartilaginous neoplasm (variant of chondrosarcoma) thought to originate from primitive cartilage-forming mesenchyme occurring in bone or in soft tissues composed of undifferentiated small round cells and islands of well-differentiated (hyaline) cartilage frequently associated with hemangio-pericytomatous vascular pattern.

Clinical

- Represents approximately 3% to 10% of all primary chondrosarcomas:
 - Occurs in bone and in soft tissue (extraskelatal mesenchymal chondrosarcoma)
 - More common in bone than soft tissue
- No gender predilection; occurs over a wide age range but most common in the second to third decades of life
- Common sites of involvement include craniofacial bones, especially jaw bones, orbit, and skull:
 - In head and neck, most often occur in jaws, roughly affecting the mandible and maxilla equally

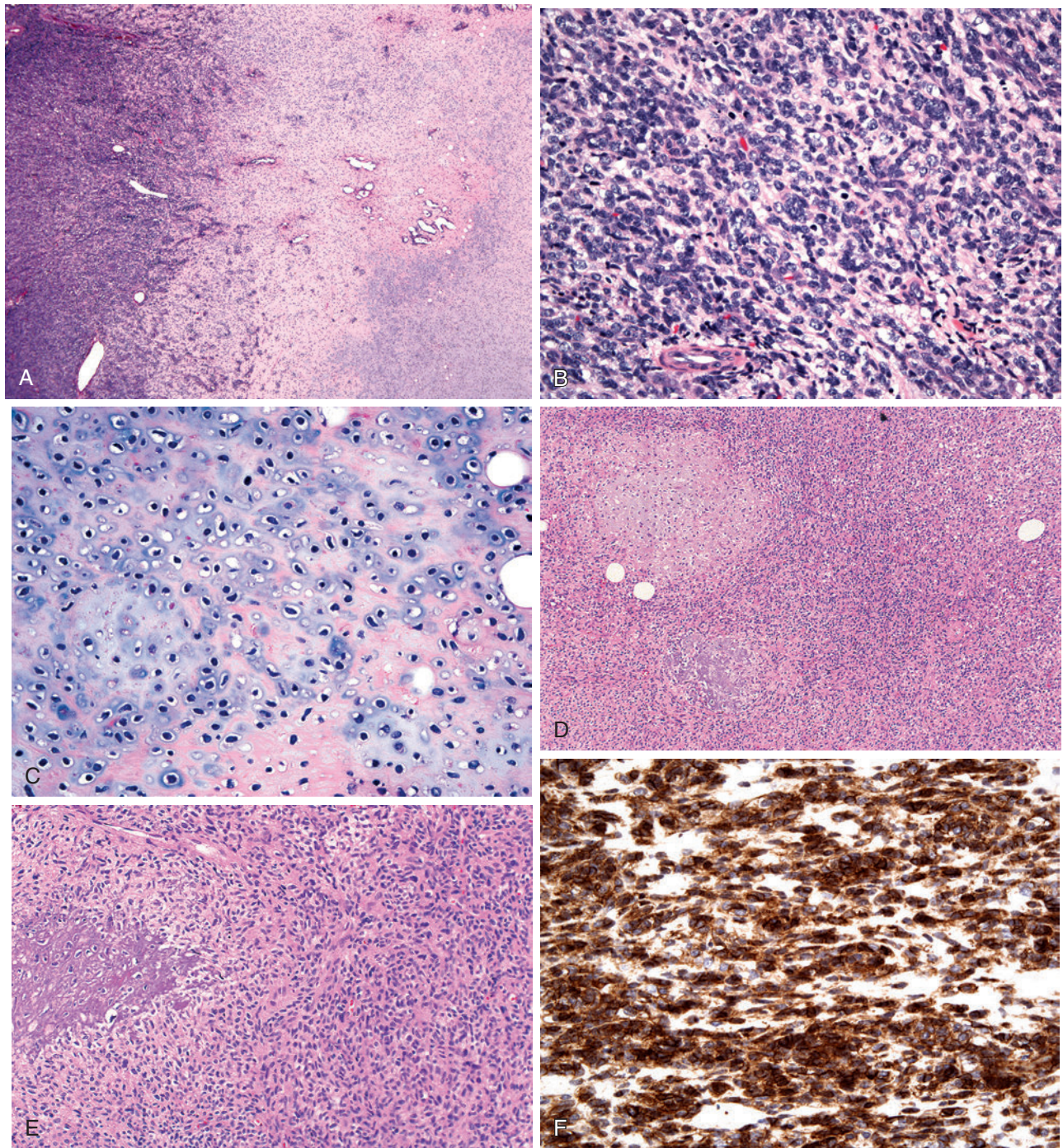


Fig. 6-67. Mesenchymal chondrosarcoma.

A, Tumor showing transition from hypercellular area (*left*) to area with cartilaginous differentiation (*right*). **B**, Undifferentiated cell component shows a solid growth composed of small cells with hyperchromatic nuclei and limited cytoplasm. **C**, Cartilaginous differentiation. **D** and **E**, Another example in which limited foci of cartilage are embedded in a predominant small round cell infiltrate. **F**, Small cell component expresses CD99.

other cases requiring numerous section for identification.

- Prominent vascularity with pattern similar to that seen in hemangiopericytoma is common.
- Increased mitotic figures may be seen.
- Calcification and ossification may be present; osteoclast-like multinucleated giant cells may occasionally be present.
- Histochemistry:
 - Intracytoplasmic glycogen (diastase-sensitive, PAS-positive) may be present.
 - Reticulin stains may show envelopment of individual cells as well as clusters of cells.
- Immunohistochemistry:
 - Small round cells:
 - CD99 positive (membranous)
 - FLI1 negative
 - EMA (focally) positive (35%)
 - Desmin (focally) positive (50%)
 - May be positive for neuron-specific enolase and Leu-7
 - Cytokeratins, neuroendocrine markers, myogenin negative
 - Cartilage:
 - S100 protein positive
- Electron microscopy:
 - Evidence of dual cell differentiation, including cells with chondrocyte-like differentiation as seen in chondrosarcoma and primitive undifferentiated small cells with limited intercellular matrix
- Cytogenetics and molecular genetics:
 - *HEY1-NCOA2* [(8;8)(q21;q13)] fusion identified
 - *SOX9*, a master regulator of cartilage differentiation, expressed in mesenchymal chondrosarcoma but not other small round cell neoplasms

Differential Diagnosis

- Ewing family of tumors:
 - Presence of cartilage allows for differentiating mesenchymal chondrosarcoma from Ewing sarcoma
 - FLI1 positive in many although not all cases
 - Presence of *EWSR1* translocation, which is absent in mesenchymal chondrosarcoma
- Poorly differentiated synovial sarcoma:
 - Metaplastic cartilage may be identified but less common than foci of calcification or ossification
 - Presence of *SS18* (also known as *SYT*) translocation, which is absent in mesenchymal chondrosarcoma
- Hemangiopericytoma
- Rhabdomyosarcoma
- Malignant lymphoma
- Small cell undifferentiated neuroendocrine carcinoma

Treatment and Prognosis

- Complete surgical resection is the preferred treatment.
- Efficacy of radiation and chemotherapy in treatment remains uncertain.
- Variable clinical course:
 - Lethal over short time periods in some cases
 - Protracted clinical course with long disease-free survival in other cases
 - No difference in prognosis whether arising in bone or in soft tissues
- Tendency to local recurrence and metastasize distantly:
 - Most often to lungs and bones
 - May occur years after initial diagnosis
- Given possibility of long-term survival and late metastases, these patients require lifelong follow-up.
- Survival for all sites includes:
 - 5-year: 55%
 - 10-year: 27%
- Survival rates for gnathic tumors suggest a more indolent clinical course as compared with non-jaw-related tumors:
 - 5-year: 82%
 - 10-year: 56%
 - 15-year: approximately 38%

MALIGNANT ODONTOGENIC NEOPLASMS

- Malignant odontogenic neoplasms are rare and include odontogenic carcinomas and odontogenic sarcomas.
- Odontogenic carcinomas include:
 - Malignant ameloblastoma; see Ameloblastoma
 - Ameloblastic carcinoma (primary, secondary); see Ameloblastoma
 - Primary intraosseous squamous cell carcinoma
 - Clear cell odontogenic carcinoma
 - Ghost cell odontogenic carcinoma
 - Others
- Odontogenic sarcomas include:
 - Ameloblastic fibrosarcoma
 - Ameloblastic fibro-odontosarcoma
- Discussion of malignant odontogenic neoplasms is beyond the scope of this book, and the reader is referred to other texts entirely specializing on this topic.

SECONDARY NEOPLASMS TO THE ORAL CAVITY

- Metastatic tumor to oral cavity is rare and occurs via hematogenous spread.

- Most often occurs as part of widely metastatic disease from a known index malignant tumor:
 - May occur at presentation of primary tumor
 - May occur years after treatment for the primary tumor
- Less commonly, may represent initial manifestation of disease (i.e., occult metastasis)
- Metastases to oral cavity:
 - Most commonly occur to gnathic bones
 - Less common to soft tissues
- Virtually every conceivable malignancy may metastasize to the upper aerodigestive tract:
 - For gnathic metastases, most common primary malignant tumors include:
 - Breast, kidney, lung, prostate, thyroid, colon, other
 - For soft tissue metastases:
 - Females: breast > other
 - Males: lung > kidney, skin, others
- Immunohistochemical staining valuable in diagnosis and differential diagnosis

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References may be accessed online at ExpertConsult.com.

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Odontogenic Myxoma

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Secondary Neoplasms to the Oral Cavity

Intraoperative Consultation in Oral Cavity Mucosal Lesions

- Intraoperative consultative diagnosis on mucosal lesions may be performed in the setting of an untreated primary mucosal lesion or in the setting of a recurrent/persistent lesion after prior treatment (i.e., radiation and/or chemotherapy):
 - In general, intraoperative consultation should not be requested to render a primary diagnosis of a mucosal lesion.
 - Rather routinely processed biopsy material is preferred mechanism for rendering a definitive diagnosis in individuals with primary mucosal lesion
 - After biopsy diagnosis many head and neck mucosal carcinomas receive primary nonsurgical adjuvant therapy so that intraoperative consultation is not uncommon in a setting of a post-therapeutic recurrent or persistent mucosal lesion.

INDICATIONS

- Indications for intraoperative consultation of mucosal lesions of upper aerodigestive tract include:
 - Render a histologic diagnosis (e.g., carcinoma/dysplasia) to ensure adequacy when definitive therapeutic intervention is planned immediately.
 - Assessment of adequacy of resection (i.e., surgical resection margins)
 - Preliminary assessment of nature of a planned procedure based on the extent and distribution of the neoplasm (e.g., subtotal versus total resection)
 - Adequacy for diagnostic purposes
 - Determination for special handling (e.g., immunohistochemistry, flow cytometry, microbiologic cultures, other)
 - Determination of neurotropism, lymph-vascular space invasion (LVI), or bone involvement that may necessitate resection of the involved bone (e.g., mandibulectomy)
 - If lymph nodes are excised, then a frozen section may be requested to exclude the presence of metastatic disease and the need for a neck dissection.

SURGEON'S EXPECTATIONS

- Establish the diagnosis of carcinoma/dysplasia and differentiate it from lookalike lesions.

- Confirm presence or absence of lesional tissue at the margins of resection.
- When applicable, identify the presence of osseous involvement.
- When applicable, identify the presence of nodal metastasis.

SPECIMEN HANDLING AND ORIENTATION

- Evaluation of surgical margins of resection for the presence or absence of lesional tissue falls under the purview of the surgical pathologists; however, how the specimen is removed and the orientation of the specimen (Figs. 7-1 and 7-2) are the responsibility of the surgeon:
 - Particularly true for those cases in which the tumor is initially excised and the designated margins are separately removed, the tumor is removed in multiple parts or the specimen is a complex en bloc excision, requiring proper orientation by the surgeon for those margins that are of critical concern.
- Once removed and properly oriented, the specimen becomes the responsibility of the surgical pathologist.
- There is no standard method by which surgeons remove tissue and thereby request intraoperative consultation of the surgical resection margins; some approaches include:
 - Excision of the entire lesion, designation of specific margins, and tissue selection by the pathologist for frozen section
 - Circumferential resection margins are submitted for frozen section irrespective of the number of frozen sections that may be required to completely evaluate the circumferential margins.
 - A limited number of frozen sections (e.g., up to four—anterior, posterior, medial, and lateral) are submitted as determined by the pathologist.

NOTE: Anatomy of the head and neck is complex and in any given resection the risk posed by removing the entire lesion and surrounding structures for intraoperative consultation includes:

- Loss of the three-dimensional orientation of the specimen

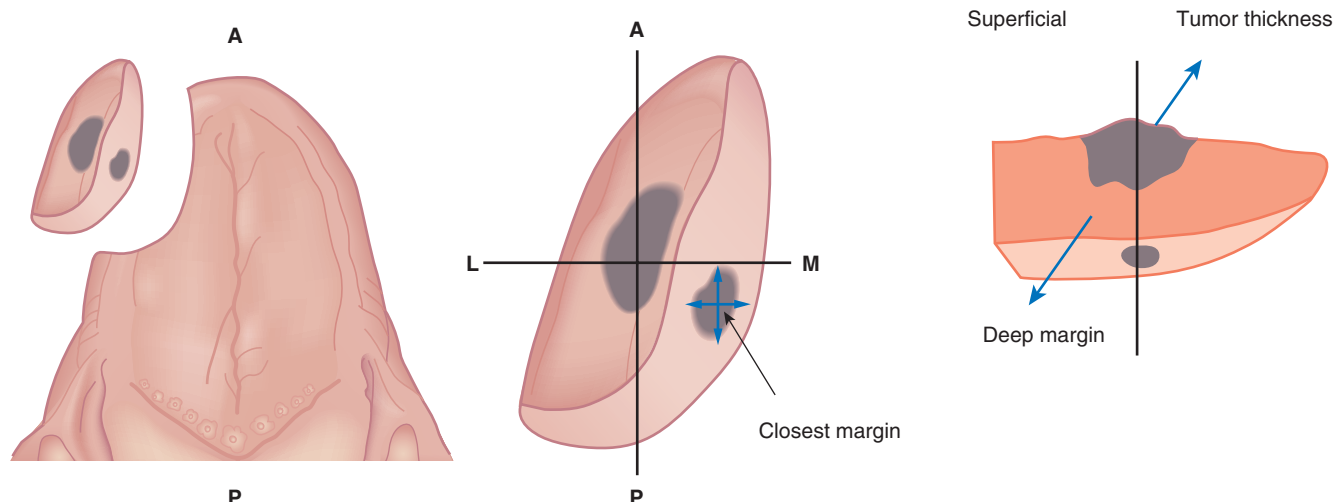


Fig. 7-1. Resection specimen and surgical margins.

Schematic depiction of a tongue resection for carcinoma showing relationship of the resected tumor to surgical margins.

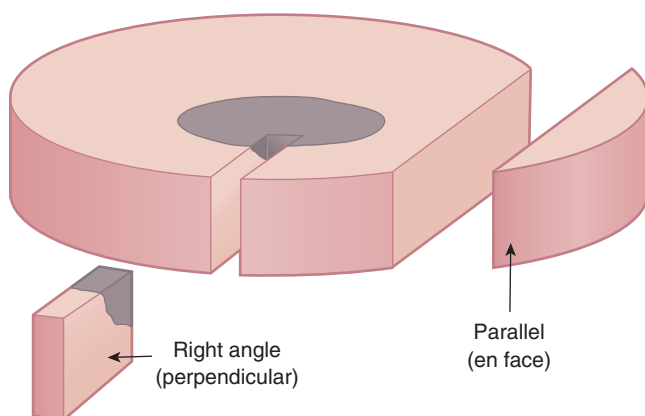


Fig. 7-2. Perpendicular versus parallel sections.

Right angle (perpendicular) versus parallel (en face) sections.

- Erroneous sampling of the areas of concern
- Submission of biopsies from areas of clinical concern after the main resection, and these biopsies are entirely submitted for frozen section.

RIGHT ANGLE (PERPENDICULAR) VERSUS PARALLEL (EN FACE) SECTIONS

- Right angle section advantages include:
 - Technically easier to obtain full thickness sections
 - Distance of the lesion to the resection margin can be viewed and measured.

- Right angle section disadvantages include:
 - Allows for evaluation of a relatively small area of the lesion/margin
- Parallel section advantages include:
 - Allows for evaluation of a larger area of the lesion/margin to include an entire margin if necessary
- Parallel section disadvantages include:
 - If the surgical margin is uninvolved, the distance of the lesion to the resection margin cannot be viewed and/or measured.
 - Due to retraction from the underlying connective tissues the superficial layers (i.e., mucosa and submucosa) may not be optimally seen.

NOTE: If parallel sections are made, the recommendation is to embed the tissue with the true surgical margin deepest in the block.

- Diagnostic accuracy for oral tongue cancer should be the same whether the sample was taken from the patient or from the surgical specimen.

SURGICAL RESECTION MARGINS

- Arguably, the most common request of the pathologist by the head and neck surgeon at the time of intraoperative consultation is assessment of the surgical margins.
- Successful local control of a malignant tumor depends on complete surgical excision of all the disease.
- Presence of gross residual cancer results in local persistence of disease and increased morbidity and mortality.

- There are many factors that affect the assessment of the surgical margins, including the type of surgical specimen, proper orientation of the specimen, proper sectioning of the specimen, and obviously the correct interpretation of the histopathologic changes.
- Unfortunately, even in the best situations an intraoperative report of negative margins may be followed a few days later by a permanent section diagnosis of positive margins.
- Probability of local recurrence in head and neck cancer is reduced when the resection margins are determined by intraoperative frozen section consultation.
- Use of intraoperative frozen sections allows the surgeon to extend the surgical resection without loss of orientation of the operative field, a potential

problem when additional surgery is required in a second operation.

- Carcinoma remnants that have not been completely removed in the initial operation often are difficult to identify macroscopically, making their removal in a second operation more difficult.
- Although the frozen section diagnosis of surgical margins is extremely accurate, it is not entirely reliable in eliminating positive margins in the final diagnostic report.

Definition of a “Positive” Margin (Fig. 7-3)

- Specimens in which no tumor or dysplasia is present at the surgical margins of resection are considered completely excised.

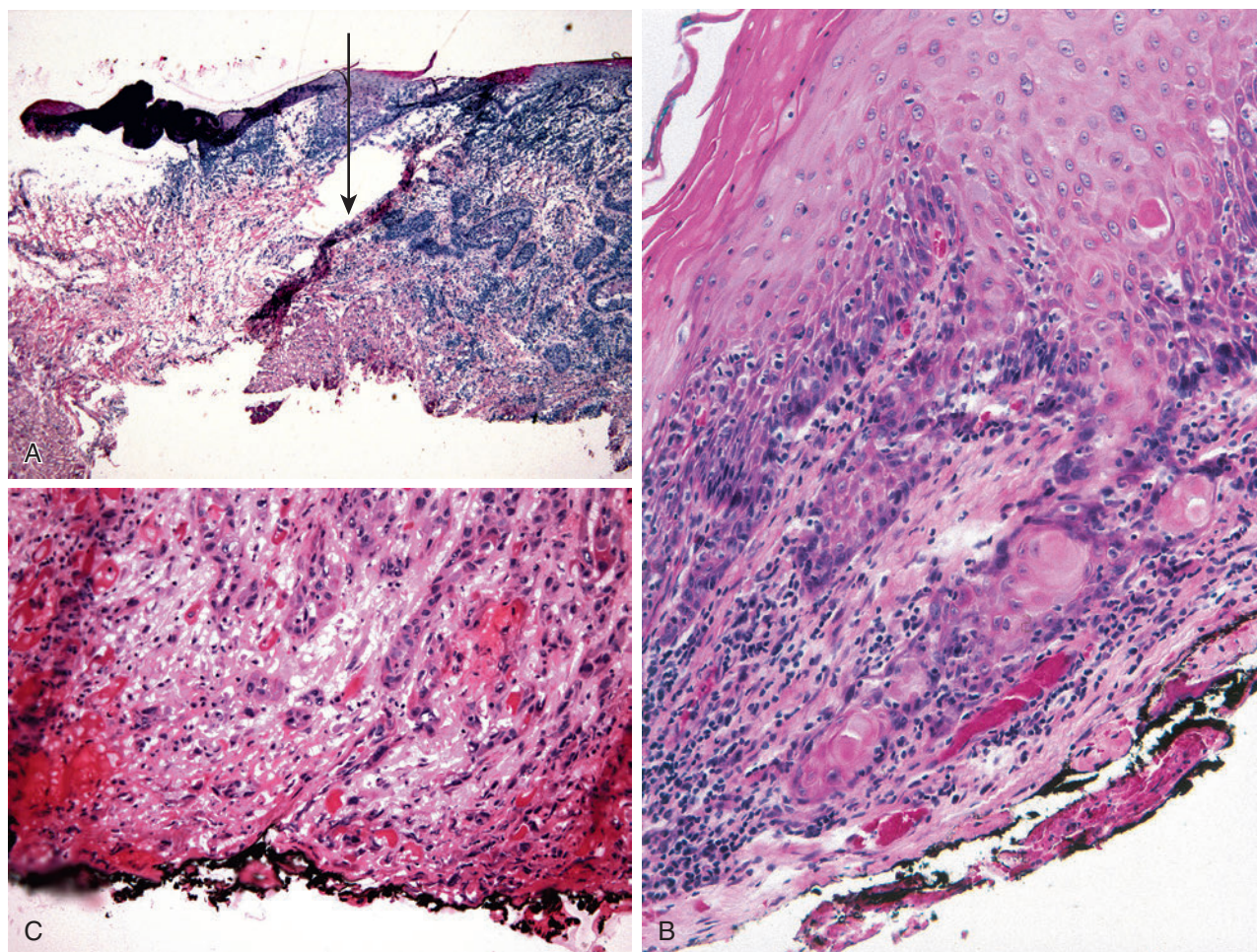


Fig. 7-3. Resection margins.

A, Lingual lesion showing carcinoma (*arrow*) lying within 5 mm of the resection margin (*left*) requiring additional surgical clearance of this margin. **B**, Laryngeal carcinoma lying 2 mm from the deep resection (black ink); in the larynx this amount of “clearance” is usually considered acceptable as to not require additional surgical clearance. **C**, Invasive squamous carcinoma involving the deep margin of resection (i.e., carcinoma at inked edge) in this tongue resection; additional surgical resection was required to “clear” this margin.

- “At the margin of resection” means that the neoplastic cells are seen in contact with or lie within millimeters of the pigment that was painted along the margin prior to sectioning (i.e., tumor across or up to the resection margin):
 - In this situation, the specimen is considered incompletely excised, requiring a wider excision to be assured that all viable tumor cells have been adequately removed.
- Sole reliance of margins as assessed on the resected specimen should be discouraged and, when feasible, the intraoperative evaluation of tissue surrounding the specimen should be made and regarded as the “true margin.”
- Histologic definition of what constitutes a “positive” margin should be uniformly accepted and applied:
 - Discrepancy in the literature as to what constitutes a positive or negative resection margin
 - Some authorities only include invasive carcinoma at the margin as positive, excluding carcinoma in situ, dysplasia, and gross residual disease.
 - Most pathologists would agree with the classification of positive margins as defined by:
 - Presence of lesional tissue within 0.5 mm of the surgical margin (so-called close margins) with the exception of laryngeal lesions (see later)
 - Significant dysplastic epithelium at the margin (see later)
 - Carcinoma in situ at the margin
 - Invasive carcinoma at the margin
- and often of minimal concern to head and neck surgeons.
- Given the previous statements, a two-tiered classification system can be advocated for keratinizing dysplastic lesions of the UADT, including:
 - Low-grade squamous intraepithelial lesion encompassing mild dysplasia
 - High-grade squamous intraepithelial lesion encompassing moderate dysplasia and severe dysplasia
- Relative to intraoperative consultation of mucosal dysplasia:
 - Presence of keratinizing mild dysplasia at a margin can be diagnosed as a negative margin.
 - Presence of keratinizing moderate dysplasia or keratinizing severe dysplasia at a margin is considered a positive margin.

Adequacy of Resection Margins

- Presence of invasive carcinoma and/or high-grade dysplasia within 5 mm of the inked surgical margin increases risk for local recurrence:
 - These margins are associated with approximately 80% incidence of recurrent disease so that failure of local control is not inevitable with such positive margins.
 - Absence of positive margins does not guarantee local control of disease nor is it a reliable guide to the biologic behavior of a tumor.
 - Presence of positive margins increases the likelihood of local recurrence but does not affect survival because subsequent surgery and/or irradiation may control tumor recurrence in some patients.
- Question of how wide a tumor should be excised is the responsibility of the surgeon:
 - For some specimens, such as the larynx, free margins up to 5 mm may be sufficient.
 - For a similar tumor at another extralaryngeal site, such as the oral cavity and pharynx (oropharynx, hypopharynx), wider margins (1.0 cm) are optimal.

Dysplastic Epithelium (Fig. 7-4)

- Evaluation of dysplasia under optimal circumstances (i.e., permanent sections) can be subjective, let alone at the time of frozen section, where tissue distortion and artifact create additional diagnostic difficulties potentially resulting in misdiagnoses, including overdiagnosis and underdiagnosis.
- In the upper aerodigestive tract (UADT), especially the oral cavity and larynx, the most common type of intraepithelial dysplasia is keratinizing dysplasia:
 - See Section 5, Larynx, for a discussion on keratinizing severe dysplasia.
 - In brief, keratinizing moderate dysplasia and keratinizing severe dysplasia share a similar statistical risk of progression to invasive carcinoma.
 - Therapeutic approach is similar for keratinizing moderate and severe dysplasia.
 - For all intents and purposes, keratinizing severe dysplasia is synonymous with carcinoma in situ.
 - Progression of keratinizing mild dysplasia to higher grade epithelial lesions is so low as to make this diagnosis of little clinical significance

Factors Affecting Margin Status and Prognosis (Fig. 7-5)

- More recent evidence suggests that resection margin status alone is not an independent predictor of local recurrence nor should resection margin status alone be used as the sole variable in deciding whether adjunctive radiation therapy is required; rather the need to give adjunctive radiation is suggested to be based on a variety of other parameters:
- Factors that may affect whether a margin is positive or negative, as well as in prognosis (control of

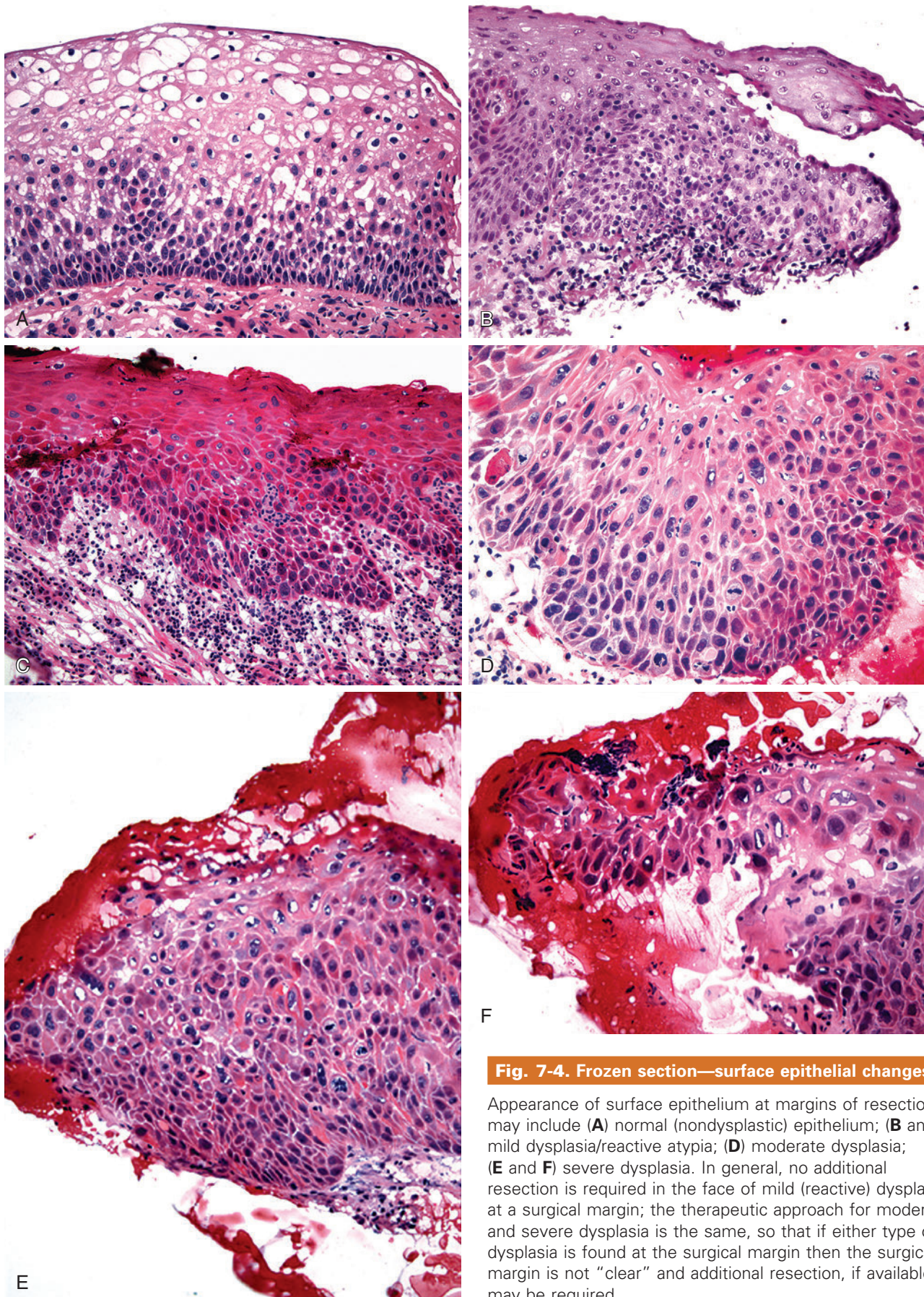


Fig. 7-4. Frozen section—surface epithelial changes.

Appearance of surface epithelium at margins of resection may include (A) normal (nondysplastic) epithelium; (B and C) mild dysplasia/reactive atypia; (D) moderate dysplasia; (E and F) severe dysplasia. In general, no additional resection is required in the face of mild (reactive) dysplasia at a surgical margin; the therapeutic approach for moderate and severe dysplasia is the same, so that if either type of dysplasia is found at the surgical margin then the surgical margin is not “clear” and additional resection, if available, may be required.

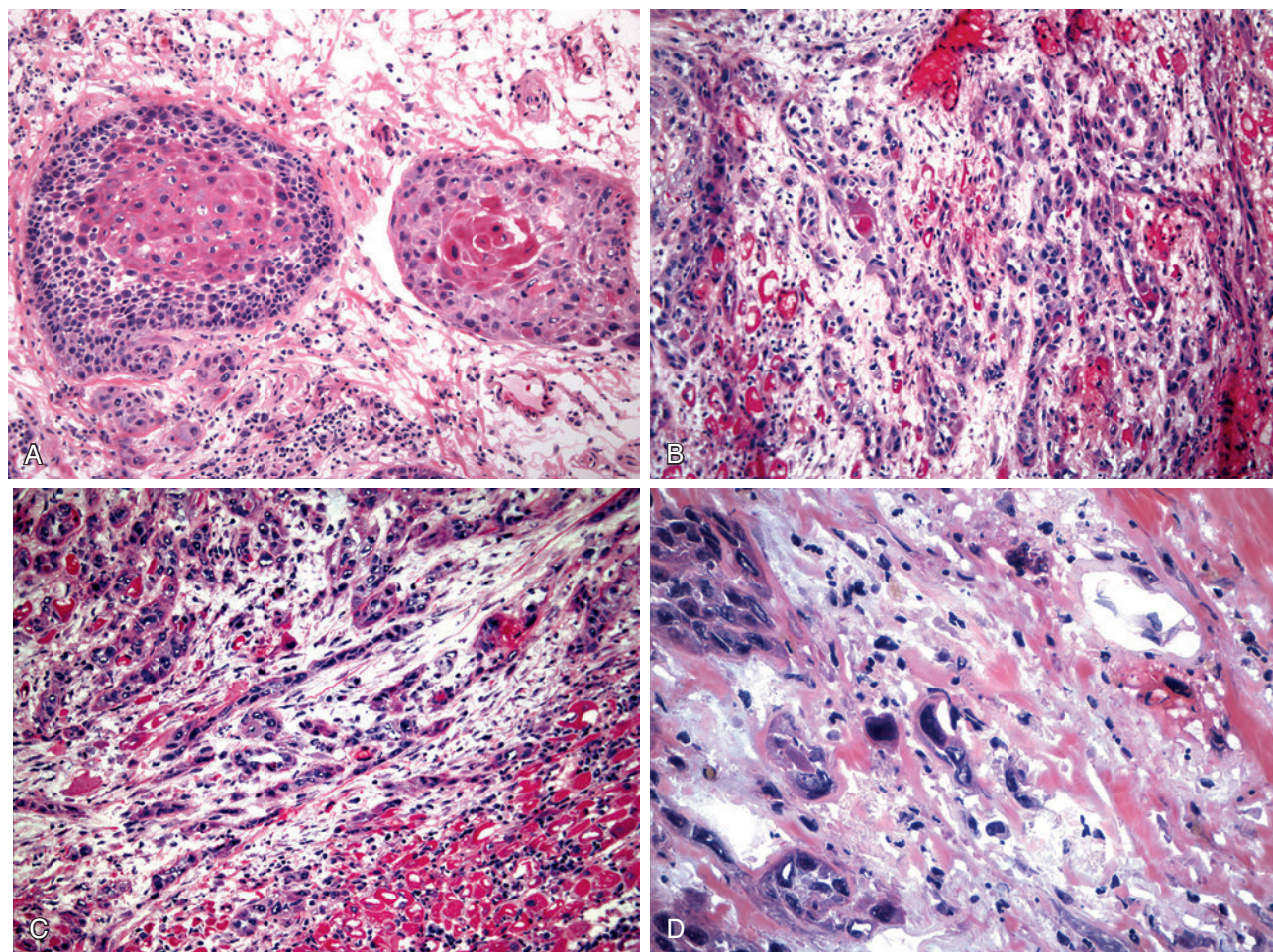


Fig. 7-5. Squamous cell carcinoma, invasive patterns.

Invasive patterns of growth in squamous cell carcinoma may include (A) invasion in well-delineated nests; (B) invasion along the advancing edge in solid cords, bands, or strands; (C) invasion in small groups or cords of infiltrating cells; (D) cellular dissociation in small groups and/or single cells.

disease) include (for more complete discussion on the following topics see previously in Chapter 6):

- Clinical stage
- Tumor size
- Positive margins:
 - Mucosal margins
 - Soft tissue margins (Fig. 7-6)
 - Mucosal margins are not the only tissue margins.
 - Surgical margins of resection may include all soft tissue components, including adipose tissue, skeletal muscle, bone, and neural structures.
 - Intraoperative assessment of osseous margins is difficult given the inherent difficulties in performing frozen section on bone.
 - Touch preparations or imprints of the cancellous bone of the stump or frozen sections of curetted material can be

performed and have shown varying degree of success.

- Alternatively, a portion of the soft tissue immediately adjacent to the periosteum may be submitted for frozen section. If negative this might indicate that there is sparing of the bone and if positive would indicate that there is bone involvement. However, the evaluation of the nonosseous soft tissue is not a reliable indicator vis-à-vis osseous involvement; in irradiated mandibles it may not be possible to separate the periosteum.
- Histologic risk assessment that includes score based on:
 - Pattern of invasion:
 - Histologic assessment results in stratification of patients into low-risk, intermediate-risk, and high-risk categories that define

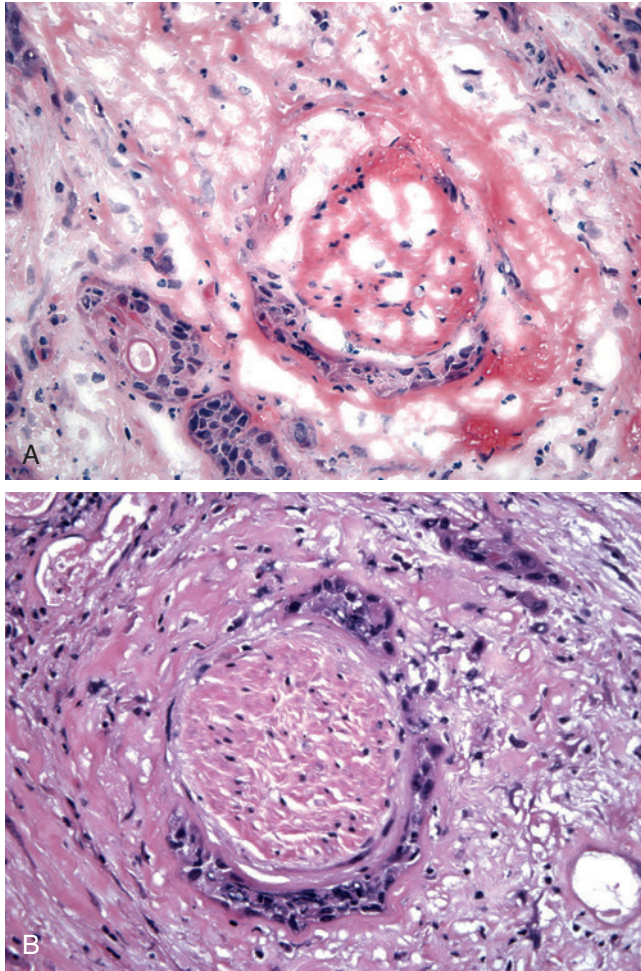


Fig. 7-6. Perineural invasion.

A, Frozen section showing perineural invasion, which may alter the intraoperative surgical approach and necessitate excision of additional nerves. **B**, Permanent section confirming the intraoperative diagnosis of neurotropism.

recommendations for adjuvant radiotherapy (see Table 6-4):

NOTE: In practice, the histologic assessment of the patterns of invasion is not considered a standard of practice and most pathologists do not render such an evaluation on intraoperative consultation or even in permanent sections.

Tissue Shrinkage and Surgical Margins

- Reliability of measuring the resection margins is affected by postremoval changes especially related to tissue shrinkage.

- It is obvious that obtaining adequate tumor-free surgical margins is critical for the successful management of the cancer patient.
- Disparate surgical margin lengths of resected specimens between the in vivo measurements by the surgeon and the in vitro measurements by the pathologist occur in head and neck resection specimens:
 - Mean tissue shrinkage of 31% from the initial in situ measurement by the surgeon to the final microscopic assessment of oral cavity and lingual surface mucosal margins by the pathologist has been reported.
 - To obtain 5 mm of histopathologically clear margin, an in situ margin of resection of at least 8 to 10 mm must be taken.
 - Relative to oral squamous cell carcinomas a reduction of 46% from the planned surgical margin before resection to the microscopically measured margin after pathologic preparation has been reported:
 - Minimum of 10-mm measured in situ surgical margin and average of 5.8 mm margin after fixation
 - Significant differences in the longitudinal diameter of the whole specimen from in situ to fresh states and in the diameter of the tumor from the fresh state to fixed states with the most significant shrinkage reported from the fresh state to the fixed state with a mean shrinkage of 4.82 mm.
- It is apparent that a significant amount of tissue shrinkage occurs from the moment the tissue is excised to the time the pathologist reviews the histologic preparation of the excised tissues; such tissue shrinkage should be taken into account and accommodated for by the surgeon at the time of the operation.

DIFFERENTIAL DIAGNOSIS OR PITFALLS IN THE INTRAOPERATIVE ASSESSMENT OF SQUAMOUS CELL CARCINOMA, INCLUDING INTRAEPITHELIAL DYSPLASIA AND INVASIVE CARCINOMA

- Frozen section consultations on mucosal surface lesions can be useful, especially in differentiating inflammatory and neoplastic lesions.
- Histologic grading of a mucosal malignancy (i.e., squamous cell carcinoma) may be problematic and is not advocated by frozen section.

- Artfactual distortion and sampling limitations may lead to erroneous conclusions relative to the histologic differentiation of the carcinoma.
- Lookalike lesions of squamous cell carcinoma and/or dysplasia may include reactive epithelial changes, postirradiation changes, and the juxtaoral organ of Chievitz.

Reactive Epithelial Changes

- Reactive, infectious, and neoplastic lesions (e.g., granular cell tumor) may be associated with an exuberant epithelial response (pseudoepitheliomatous hyperplasia [PEH]) that may be mistaken for squamous cell carcinoma.
- Despite this marked epithelial proliferation, there typically is an absence of significant cytomorphic atypia and evidence of invasion with associated

tissue response (i.e., desmoplasia), allowing for differentiating PEH from squamous carcinoma.

Postirradiation Changes

(Figs. 7-7 through 7-9)

- See Section 5, Larynx, for additional discussion and images.
- Postirradiation alterations may lead to false-positive diagnosis due to the presence of bizarre cytologic alterations in the epithelium, minor salivary glands, fibroblasts, skeletal muscle, and endothelial cells.
- Distinguishing invasive squamous cell carcinoma from radiation change is challenging.
- Knowledge of prior radiation treatment is imperative in the evaluation of a given specimen:

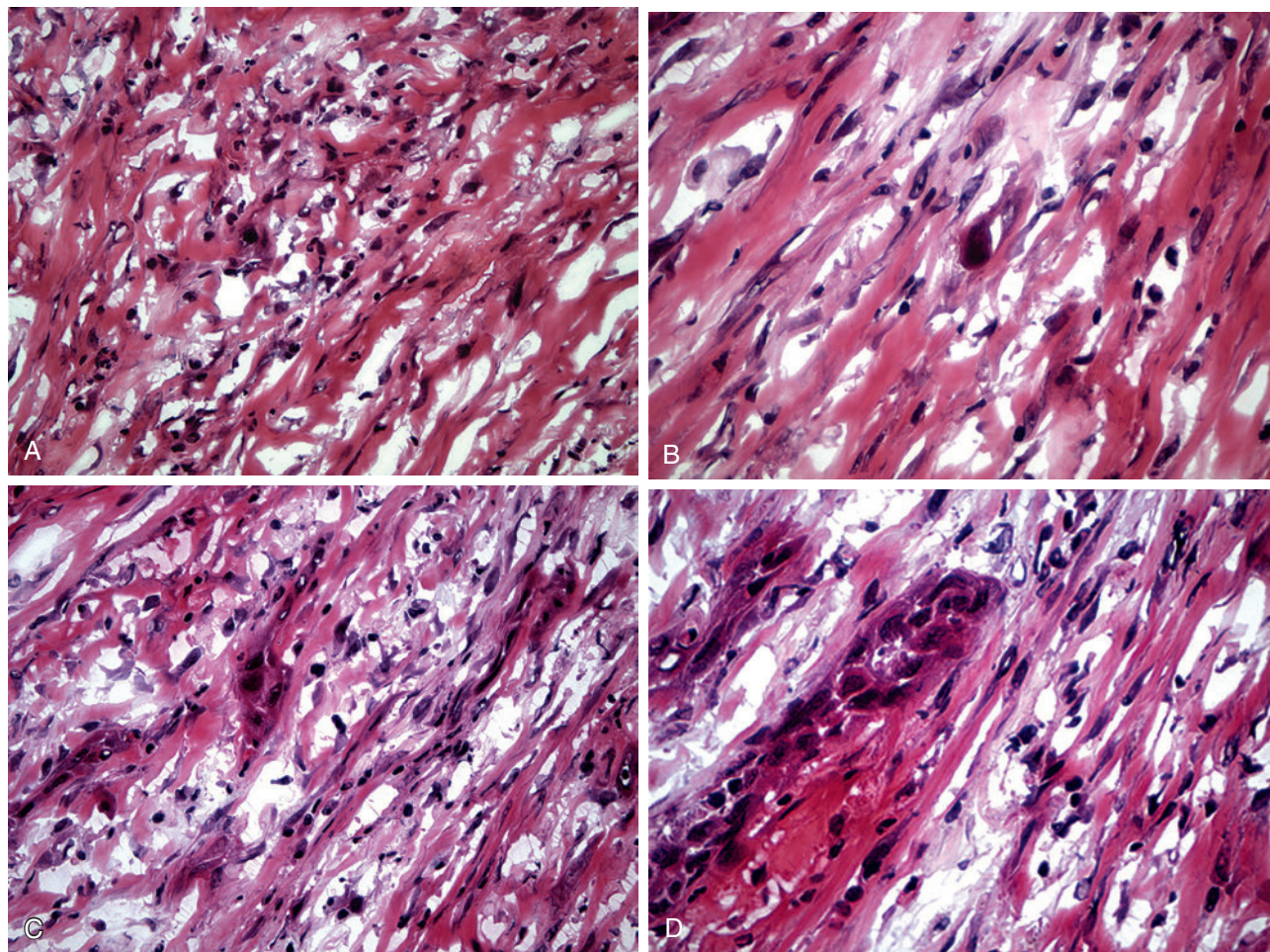


Fig. 7-7. Postirradiation atypical fibroblasts.

A and B, May appear as individual cells in scar formation or inflammatory tissue with “smudged”-appearing nuclei lacking cohesive cellular groupings. **C and D,** In contrast, foci of squamous cell carcinoma typically appear in cohesive cellular groupings.

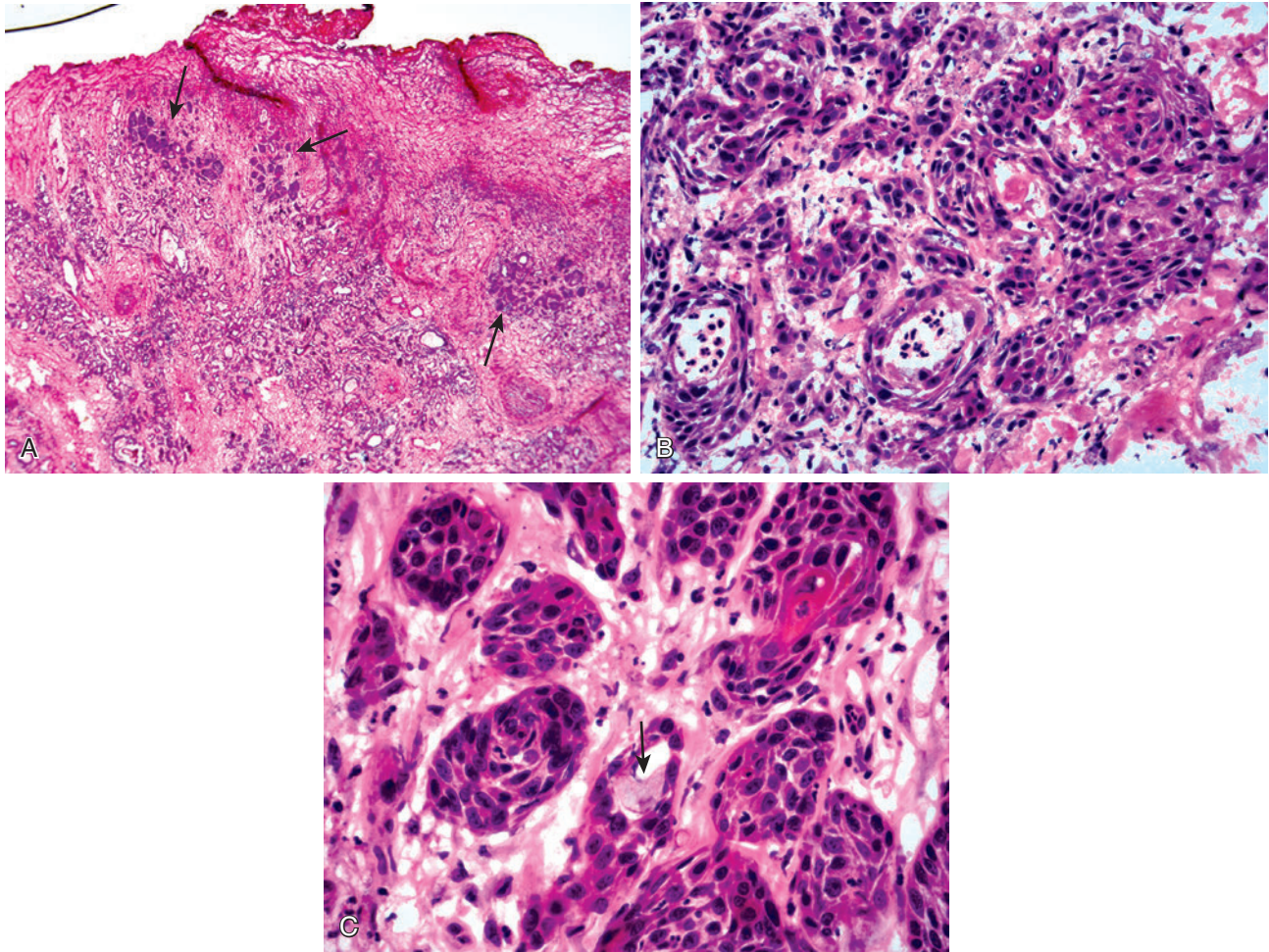


Fig. 7-8. Postirradiation squamous metaplasia of minor salivary glands (sialometaplasia).

A, At low magnification a key feature of sialometaplasia is the retention of the lobular architecture of the involved minor salivary glands (*arrows*). **B** and **C**, At higher magnification the features of the metaplastic foci may potentially be confused with invasive squamous cell carcinoma, making the low magnification features showing retention of lobular architecture a key diagnostic feature in rendering the correct interpretation; note residual mucocyte in panel **C** (*arrow*).

- Such information should routinely be provided by the clinical team to the pathologist(s) performing the intraoperative consultation.
- If this information is known prior to surgery and the intraoperative consultation, comparison of any previous material (e.g., biopsy) with the frozen section under review would be beneficial.
- Differentiation of radiation effect versus squamous cell carcinoma is based on histologic review.
- Postirradiation changes can be divided into acute and chronic alterations:
 - Acute postirradiation phase:
 - Days to weeks after radiation
 - Biopsies are seldom obtained
 - Later postirradiation period:
 - 6 to 7 weeks after therapy to years later
 - Show variable histologic changes, including:
 - Thinner than normal surface epithelium
 - Surface ulceration
 - Squamous epithelial atypia
 - Atrophy of minor salivary gland acini
 - Pseudoepitheliomatous proliferation of the surface epithelium
 - (Atypical) squamous metaplasia (sialometaplasia) of minor salivary glands:
 - Retention of lobular architecture/configuration of minor salivary glands supports benign (reactive) changes and not presence of invasive carcinoma irrespective of the cytologic atypia.
 - Conversely, effacement of the lobular architecture would support a diagnosis of carcinoma.

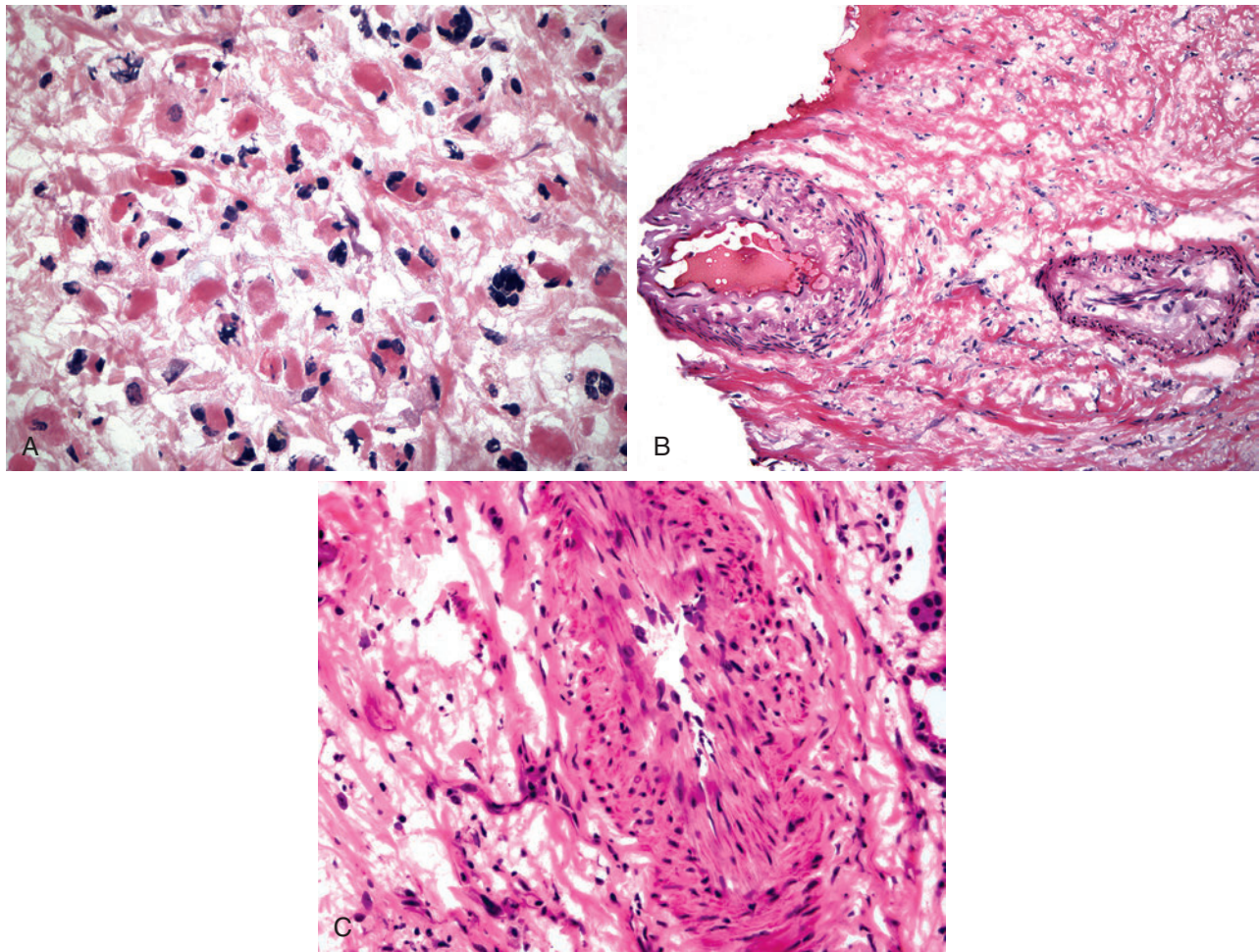


Fig. 7-9. Postirradiation soft tissue changes.

Additional postirradiation changes may include (**A**) bizarre-appearing skeletal muscle, which can be confused with invasive squamous carcinoma; (**B** and **C**) vascular alterations, including myointimal proliferation with enlarged and atypical appearing endothelial cells.

- Submucosal fibrosis
- Vascular alterations characterized by telangiectatic capillaries often with prominent (plump) endothelial cells, myointimal proliferation, foamy histiocytes within the intima and thrombosis
- Atypical (bizarre) stromal fibroblasts:
 - Often appears as individual cells with “smudged”-appearing nuclei, supporting diagnosis of radiation-associated atypical fibroblasts in scar tissue or inflammatory tissue rather than the cohesive pattern of growth that can be seen in association with invasive carcinoma
- Bizarre striated muscle degeneration
 - Delayed radiation injury generally is not characterized by cellular inflammatory infiltrate.
- Familiarity with these findings should allow for their recognition and prevent misinterpretation.

Juxtaoral Organ of Chievitz (Fig. 7-10)

- See Chapter 4 in this section.
- Normal microscopic structure of unknown function located bilaterally at the angle of the mandible (in the retromolar trigone of the oral cavity) near the buccotemporalis fascia and intimately associated with branches of the buccal nerve
- Histologically, this structure is composed of nests or clusters of squamous cells with intercellular bridges surrounded by basaloid cells; the latter may show nuclear palisading:
 - Keratinization is not present, although duct-like lumina may be seen.
 - Cells are uniform with low nuclear-to-cytoplasmic ratio, minimal pleomorphism, and absent mitotic figures; desmoplasia is absent.

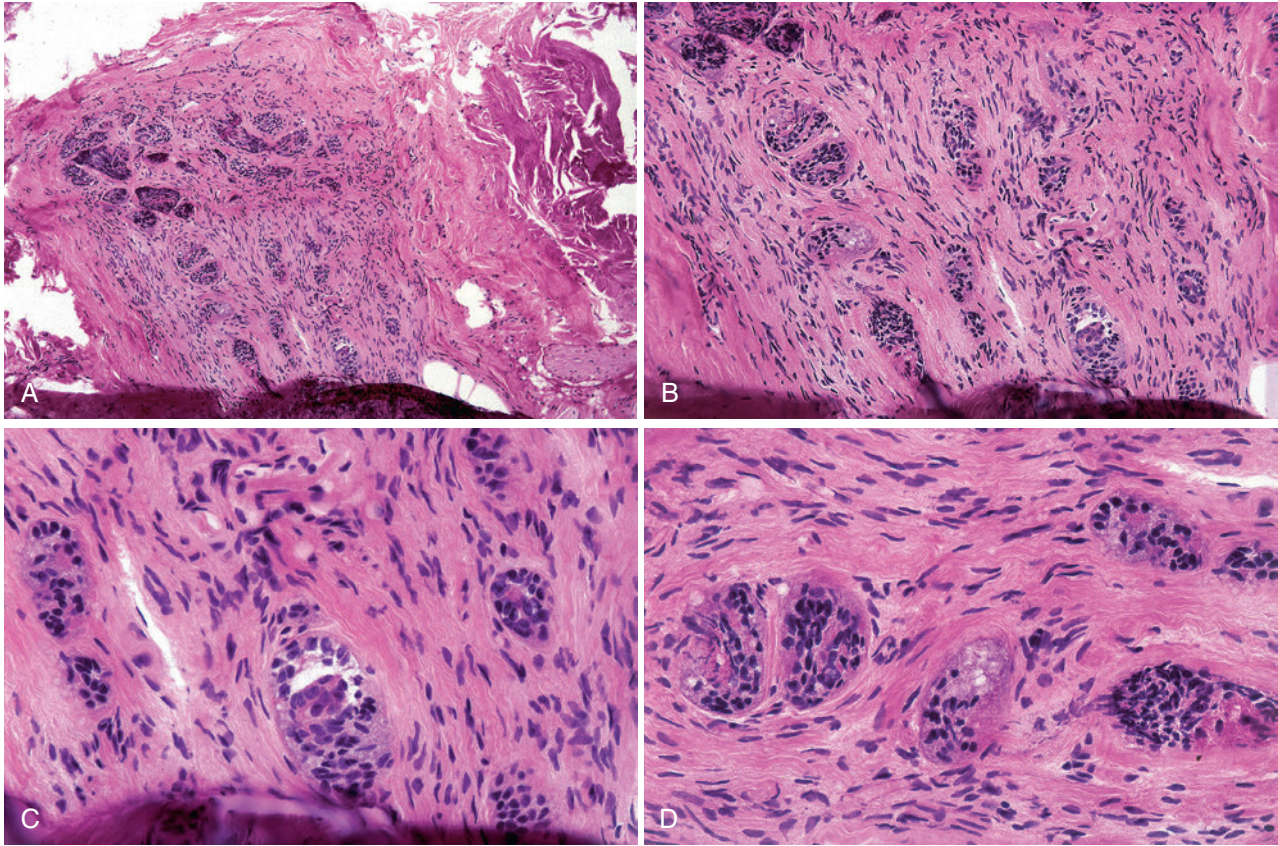


Fig. 7-10. Juxtaoral organ of Chievitz.

Juxtaoral organ of Chievitz is a normal microscopic structure of unknown function located bilaterally at the angle of the mandible (in the retromolar trigone of the oral cavity) near the buccotemporalis fascia and intimately associated with branches of the buccal nerve. **A-D**, Histologically, round nests of squamoid (epithelial) cells within a fibroconnective tissue stroma are identified; the cells are nonkeratinizing composed of uniform, bland-appearing nuclei with low nuclear-to-cytoplasmic ratio, minimal pleomorphism and absent mitotic figures; desmoplasia is absent. These structures represent an incidental finding at frozen section and normally may be intimately associated with small peripheral nerves (branches of the buccal nerve). Awareness of their presence and association with nerves allow for accurate interpretation and not misinterpretation as invasive neurotropic squamous cell carcinoma.

- These structures may easily be misinterpreted as invasive carcinoma with perineural invasion; familiarity with these structures, their characteristic location, and overall relatively bland histomorphology should allow for distinguishing these normal benign structures from invasive carcinoma.
- Communication with the surgeon would be imperative in identifying these structures and not misdiagnosing them as invasive carcinoma.

CONTRAINDICATIONS

- As with any surgical procedure, there are contraindications for the utilization of frozen sections (Fig. 7-11).
- Frozen section consultation should not be used:
 - When frozen section diagnosis will not have any impact on surgery and/or impact on additional (immediate) decision:
 - Contraindicated to satisfy curiosity of surgical team
 - If tissue specimen is small and additional sampling is not planned:
 - Findings in frozen section may be equivocal, and/or material is artifactually distorted by the frozen section technique, hampering histologic evaluation after routine (permanent) sections.
 - For heavily calcified or ossified tissue
 - For certain lesions such as small cutaneous melanocytic lesions and lymphoproliferative lesions requiring special handling or extensive histologic evaluation for diagnosis

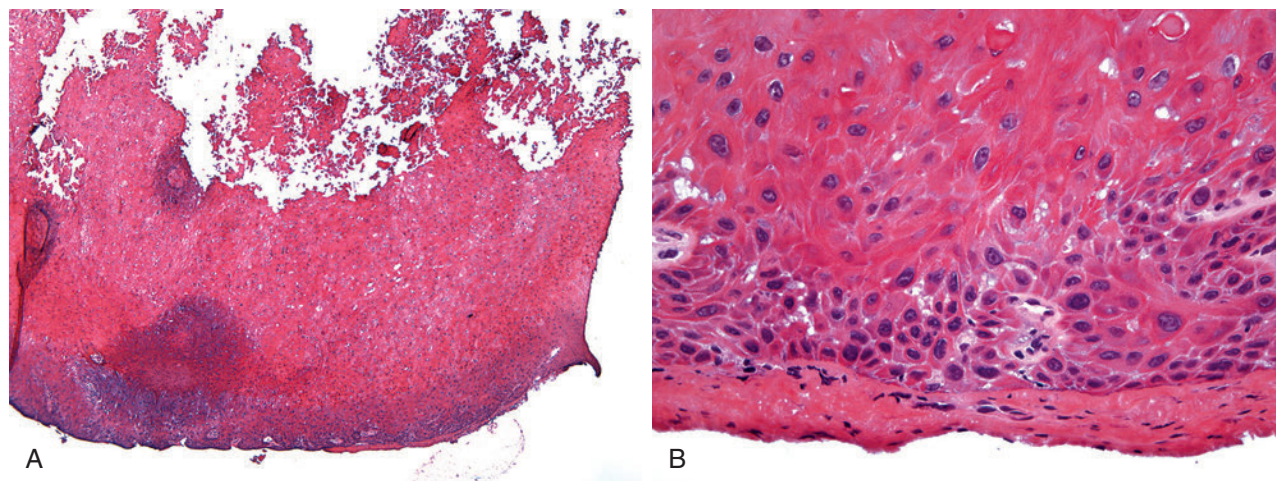


Fig. 7-11. Questionable use of frozen section.

Biopsy of a vocal cord keratotic lesion sent for frozen section. **A**, The tissue sample is small and includes the presence of an exophytic epithelial proliferation with marked keratosis. **B**, In the depth of the lesion there is a (focal) basal zone atypia with scant submucosa present. The request to perform a frozen section on this sort of lesion is of questionable utility; the specimen is inadequate for diagnosis given the limited stromal tissue, the surgeon had no intention of performing any additional resection based on the intraoperative consultation findings, and the freezing artifact potential compromises the ability to render a definitive diagnosis on permanent sections. This can be considered inappropriate use of frozen section and is a scenario that a frozen section should be declined in lieu of sending the tissue for routine (permanent) section.

INTRAOPERATIVE RAPID IMMUNOHISTOCHEMICAL ASSESSMENT

- Intraoperative immunohistochemical assessment consisting of touch smear cytologic preparations and cytokeratin staining in 20 minutes from the time of tissue sampling
- Not routinely used in setting of intraoperative consultations
- Limited studies to date in general and none relative to mucosal margins of the upper aerodigestive tract

MOLECULAR BIOLOGY IN THE ASSESSMENT OF SURGICAL MARGINS ("MOLECULAR MARGINS")

- Previous studies have shown some utility of molecular biologic markers in assessment of intraoperative consultation material including:
 - p53 mutations:
 - Presence of p53 mutations in surgical margins and in lymph nodes negative for tumor by light microscopic examination portended a substantially higher risk of local recurrent disease than those patients without p53 mutations in their surgical specimens

- Suggestion that molecular biologic studies may augment conventional light microscopy in identifying cancer at surgical margins and in lymph nodes and may improve the prediction of local tumor recurrence
- eIF4E is a translation initiation factor and powerful oncogene when overexpressed in model cell lines:
 - eIF4E reported to be elevated in head and neck squamous cell carcinoma (HNSCC) but not in benign lesions and overexpression of eIF4E may represent an early step in malignant transformation
 - Immunohistochemical analysis for eIF4E expression shown to be consistently elevated in patients with SCC:
 - In patients with laryngeal and hypopharyngeal carcinoma:
 - Absence of eIF4E in histologically negative surgical margins associated with absence of locoregional recurrences
 - Overexpression of eIF4E in the surgical margins associated with local recurrence; disease-free interval of 31.95 months
 - Significant differences in the Kaplan-Meier survival curves reported for eIF4E-positive and eIF4E-negative margins
- "Molecular margins" not presently used in setting of intraoperative consultations or in assessing histopathologic negative surgical margins and negative lymph nodes for patients with HNSCC nor has it

supplanted conventional methods of evaluating surgical resection margins

ACCURACY

- In general, the accuracy of frozen section diagnosis in head and neck surgery is high, and when deferred diagnoses are excluded, the reported accuracy ranges from 97% to 99%.
- Several errors and other factors may account for any potential discrepancies in the frozen section-to-permanent section diagnosis.
- Errors can be divided into four categories, including:
 - Sampling errors
 - Interpretative errors
 - Technical errors
 - Communication errors
- Other factors that may influence the result of a frozen section, including (but not limited to):
 - Cooperation between the surgeon and pathologist
 - Quality assurance program allowing for continuous analysis and critical overview of the frozen section standards
 - Availability of other pathologists for consultation in challenging cases
 - Availability of technically competent staff
 - Equipment

LYMPH NODES

- Frozen section diagnosis of lymph nodes is considered to be extremely accurate.
- An accuracy rate of approximately 99%, excluding deferred diagnoses, reported with a 0.1% false-positive rate and a 1% false negative rate.
- Lymph nodes represent the most frequently deferred specimen in frozen section diagnosis, especially in the diagnosis of a lymphoma.
- In general, the diagnosis of a carcinoma in a lymph node is not problematic at frozen section.
- Lymph node frozen section has also been used for accurate staging of the head and neck patient.

Sentinel Lymph Nodes in Head and Neck Squamous Cell Carcinoma

- There is increasing literature documenting the efficacy of sentinel lymph node evaluation in patients clinically staged as T1/T2,N0,M0 with diagnostic accuracy of more than 90% and with few reported false negatives.
- Elective treatment of cN0 necks by surgery and/or irradiation is controversial; some authorities

advocate a conservative (watch-and-wait) approach and other authorities advocate treatment.

- Overall risk of occult metastases or neck recurrence in cN0 necks ranges from 10% to 30%, prompting arguments for and against elective treatment.
- Majority of patients with cN0 necks likely do not harbor occult metastases, but patients with undetected and untreated metastases will experience high failure rates with increased morbidity and mortality; for this reason, sentinel lymph node procedure is gaining more support in the treatment of cN0 necks.
- Studies of sentinel lymph node procedure in head and neck squamous cell carcinoma have shown:
 - A sensitivity of greater than 90% in identifying at least one sentinel lymph node
 - False-negative rate of less than 10% (mean, 3.2%)
 - Clinical significance of identifying micrometastatic disease (i.e., isolated tumor cells and/or clusters of tumor cells measuring less than 0.2 mm as defined in breast cancer) relative to HNSCC remains to be clarified but likely is significant in its prognostic import.
 - Suggest that both the number and position of positive sentinel nodes may identify different prognostic groups that may allow further tailoring of management plans
- Conceptually, lymphatic drainage from a specific anatomic site is assumed to be predictable in the lymphatic drainage; therefore metastatic tumor cells from a specific location will become deposited into the first (sentinel) node in a lymph node chain.
- Pathologic work-up, including handling of the gross resection specimen, number of histologic sections, use of special stains (i.e., immunohistochemistry) for the sentinel lymph node procedure for head and neck squamous cell carcinoma has not to date been standardized.
- Application of sentinel lymph node procedure to head and neck squamous cell carcinoma has not as yet reached the level of standard of patient care.
- Further studies are warranted before considering this technique to be the “gold standard” in patients with oral squamous cell carcinoma and a negative neck by clinical examination and imaging studies.

FURTHER READING

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Embryology, Anatomy, and Histology of the Pharynx

PHARYNX

- 12- to 14-cm long musculomembranous tube shaped like an inverted cone
- Extends from the cranial base to the lower border of the cricoid cartilage (level of the sixth cervical vertebra)
- Limited superiorly by the posterior part of the body of the sphenoid and basilar part of the occipital bone and inferiorly with the esophagus, to which it is continuous
- Lies behind and communicates with the nasal, oral, and laryngeal cavities via the nasopharynx, oropharynx, and hypopharynx (laryngopharynx),

respectively; on this basis the pharynx is divided into three anatomic divisions including (from superior to inferior): (Fig. 8-1)

- Nasopharynx
- Oropharynx
- Hypopharynx:
 - Often included as part of the larynx but given differences in embryology from the larynx (see Section 5) and the inclusion of hypopharyngeal cancers in the AJCC staging of pharyngeal cancers and not laryngeal cancers, the hypopharynx including the piriform sinus is included in this section on the Pharynx rather than in Section 5, Larynx.

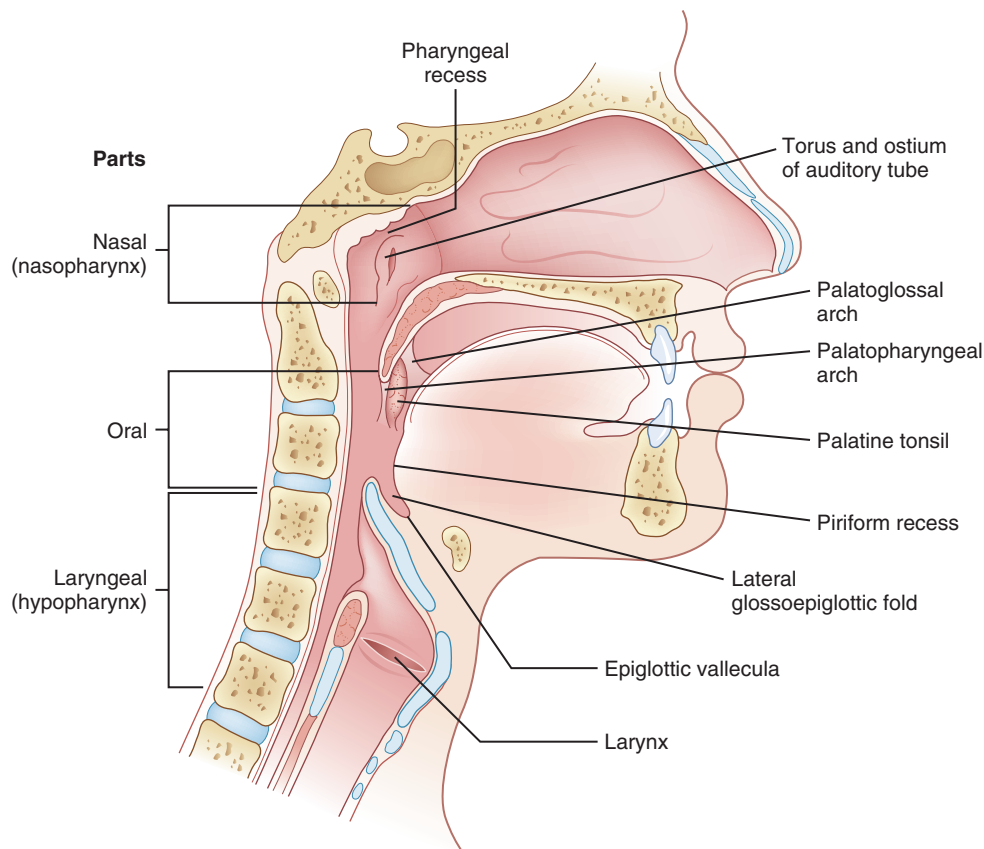


Fig. 8-1. Regions of the pharynx.

- Pharyngeal lining mucosa is continuous with the mucosa lining the nasal cavity, oral cavity, pharyngotympanic (eustachian) tubes, and larynx.

EMBRYOLOGY OF THE PHARYNX

- Primitive pharynx is derived from the foregut developing from the branchial arches and pharyngeal pouches:
 - Epithelium and glands are of endodermal derivation.
 - Tonsils develop from the second pharyngeal pouch.
 - Tubotympanic recess (forms the eustachian tube and tympanic cavity) develops from the first pharyngeal pouch.
 - Lymphoid tissues of the pharynx, including adenoids (pharyngeal tonsil), lateral pharyngeal lymphoid bands, and lingual and palatine tonsils, arise from pharyngeal endoderm.
 - Constrictor muscles derived from the fourth and sixth branchial arch

CONTENTS OF THE PHARYNX

Nasopharynx

- Nasopharyngeal tonsils (adenoids) lie along the posterior and lateral aspects of the nasopharynx.
- Orifice of eustachian tube lies along the lateral aspects of the nasopharyngeal wall.

Oropharynx

- Soft palate
- Base of tongue, including the lingual tonsils
- Tonsillar pillars
- Palatine tonsils
- Posterior tonsillar pillars
- Uvula
- Waldeyer tonsillar ring (Fig. 8-2) is formed by a ring or group of extranodal lymphoid tissues about the upper end of the pharynx, which consists of the:
 - Palatine tonsils
 - Pharyngeal tonsils (adenoids)
 - Base of tongue/lingual tonsils
 - Adjacent submucosal lymphatics

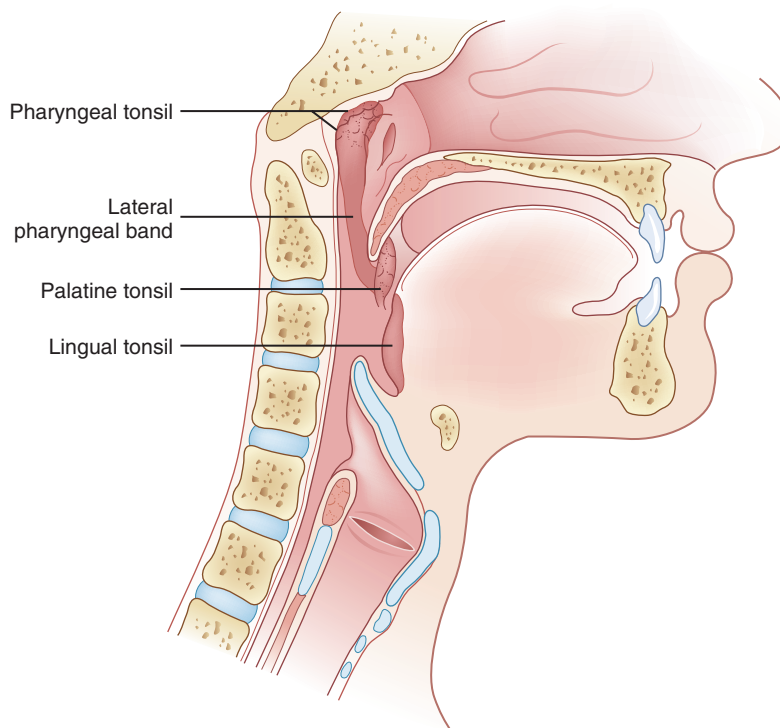


Fig. 8-2. Waldeyer tonsillar ring.

ANATOMIC BORDERS OF THE PHARYNX

Nasopharynx

- Situated behind the nasal cavity and above the soft palate, it begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate.
- Anterior: continuous with the nasal cavities through the choanae
- Posterior: continuous with the roof and is further supported by first cervical vertebra (anterior arch of the atlas)
- Superior (roof): base of skull (occipital bone) and posterior part of the body of the sphenoid bone
- Inferior (floor): continuous with the oropharynx; during swallowing, the palate and uvula provide a functional floor
- Lateral: each side contains the pharyngeal orifice of the eustachian tube, which in the posterior portion has a submucosal cartilaginous elevation called the torus tubarius, behind which is a shallow depression called the fossa of Rosenmüller.

Oropharynx

- Portion of continuity with the pharynx extending from the plane of the superior surface of the soft palate to the superior surface of the hyoid bone (or floor of the ventricle)
- Anterior: continuous with the mouth through the oropharyngeal isthmus
- Posterior: on a level with the second and third cervical vertebrae
- Superior: horizontal plane of the palate
- Inferior: horizontal plane of the hyoid bone (upper border of the epiglottis)
- Lateral: palatopharyngeal arch

HYPOPHARYNX

Anatomic Borders

- Superior border: just above the level of the hyoid bone
- Inferior border: lower border of the cricoid cartilage
- Anterior border: mucosa on the medial surface of the thyroid cartilage
- Posterior and lateral border: no markings; lateral walls attach to the hyoid bone and thyroid cartilage
- Medial border: larynx and its appendages
- Piriform sinus: (Fig. 8-3)

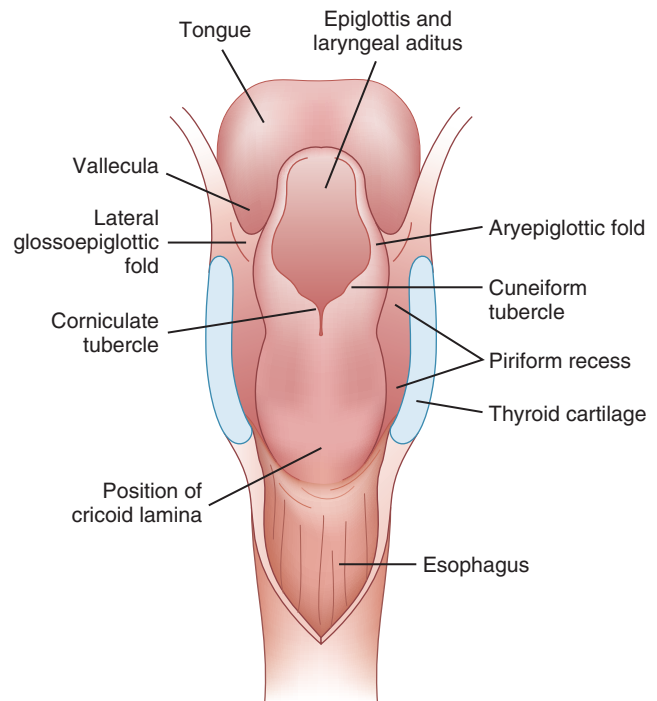


Fig. 8-3. Hypopharynx including the piriform sinus.

- Represents part of the hypopharynx that expands bilaterally and forward around the sides of the larynx and lies between the larynx and the thyroid cartilage
- Synonymous with piriform recess and piriform fossa
- Piriform means pear-shaped from Latin *pirum*, “pear,” and *forma*, “shape.”
- Pyriform means flame-shaped from Greek *pyra*, “fire.”
- Piriform sinus is pear shaped and not flame shaped; although both spellings have been used for this anatomic site, the correct spelling based on anatomic shape is piriform.

Innervation

- Both motor and sensory innervation are primarily supplied from the pharyngeal plexus formed by branches of cranial nerves IX (glossopharyngeal) and X (vagus).

Vascular Supply and Lymphatic Drainage

- Arteries and veins:
 - Naso- and oropharynx:
 - Arterial supply comes from branches of the external carotid artery, including the ascending pharyngeal, facial, lingual, maxillary, and superior thyroid arteries.

- Veins form a plexus that drains into the internal jugular and facial veins directly or via a communication with the pterygoid venous plexus.
- Hypopharynx:
 - Arterial supply from branches of the superior and inferior thyroid artery branches of the carotid artery and the subclavian artery, respectively
 - Venous plexus communicates with the pterygoid plexus above and the superior thyroid and lingual veins below or directly with the facial vein or the internal jugular vein.
- Lymphatics:
 - Nasopharynx:
 - Directly to the upper deep cervical lymph nodes
 - Oropharynx, including the tonsil and base of tongue:
 - Upper deep cervical lymph nodes particularly to the jugulodigastric and jugulo-omohyoid group of lymph nodes
 - Hypopharynx:
 - Drain to the lymph nodes of the deep cervical chain

HISTOLOGY OF THE PHARYNX

Nasopharynx (Fig. 8-4)

- Epithelium varies from stratified squamous in the lower and posterior regions to ciliated pseudostratified (respiratory) columnar type near the choanae and adjacent roof of the nasopharynx to intermediate (“transitional”) type in the junctional zones in the roof and lateral walls:
 - Intermediate (“transitional”) epithelium seen at junction between squamous and respiratory type epithelium (similar epithelium identified in the larynx)
 - Basaloid nuclei with minimal cytoplasm may raise concern for intraepithelial dysplasia:
 - Presence of smooth rather than coarse nuclear chromatin, smooth rather than irregular nuclear contours, and generally limited nuclear pleomorphism and absence of increased mitotic activity should allow distinction from intraepithelial dysplasia.
 - Isolated focus or foci of intraepithelial dysplasia occurring in the absence of an invasive carcinoma is rarely seen:
 - Unlike the oral cavity and glottic portion of the larynx, where intraepithelial dysplastic lesions may result in clinical symptoms warranting biopsy, intraepithelial dysplasia(s) of the pharynx typically does not engender clinical symptoms, so it is extremely uncommon

for the pathologist to identify isolated intraepithelial dysplastic alterations of the pharynx without its being seen in association with invasive carcinoma.

- More likely, when confronted with histologically suspicious foci for intraepithelial dysplasia in a routine specimen from a structure in the nasopharynx, it is likely intermediate (“transitional”) epithelium.
- Although these types of epithelia may be associated with a specific part of the nasopharyngeal region, this is not constant so that any site may be covered by any type of epithelium.
- Submucosa contains minor salivary glands as well as a prominent lymphoid component.
- Nasopharyngeal tonsils, also known as the adenoids, represent extranodal lymphoid tissues characterized by:
 - Epithelium infiltrated by many small lymphoid cells (so-called lymphoepithelium, Fig. 8-5) expanding and disrupting the epithelium to produce a reticulated pattern:
 - Blurred interface between epithelium and submucosa, including lymphoid cells
 - Basaloid-appearing cells with uniform, vesicular nuclei
 - Typically lack keratinization but abrupt areas of keratinization may be present
 - Epithelial component is cytokeratin positive
 - In nonendemic populations, normal nasopharyngeal mucosa is typically negative for the presence of Epstein-Barr virus
 - Presence of germinal centers but absence of a capsule, sinusoids, or epithelial crypts

Oropharynx (Figs. 8-6 and 8-7)

- Epithelium throughout is a stratified squamous epithelium, which normally does not have a keratin layer.
- Submucosa contains:
 - Minor salivary glands, which are mixed seromucous glands but are predominantly mucous
 - Scattered lymphoid component
- Palatine and lingual tonsils, like the adenoids, contain:
 - A prominent lymphoid component, including germinal centers but does not have a capsule or sinusoids
 - Unlike the adenoids, the palatine and lingual tonsils have 10 to 20 (tonsillar) crypts formed by invagination of the free surface mucosa, are narrow tubular epithelial diverticuli branching within the tonsils, and are frequently packed with plugs of shed epithelial cells, lymphocytes, and bacteria, which may calcify:

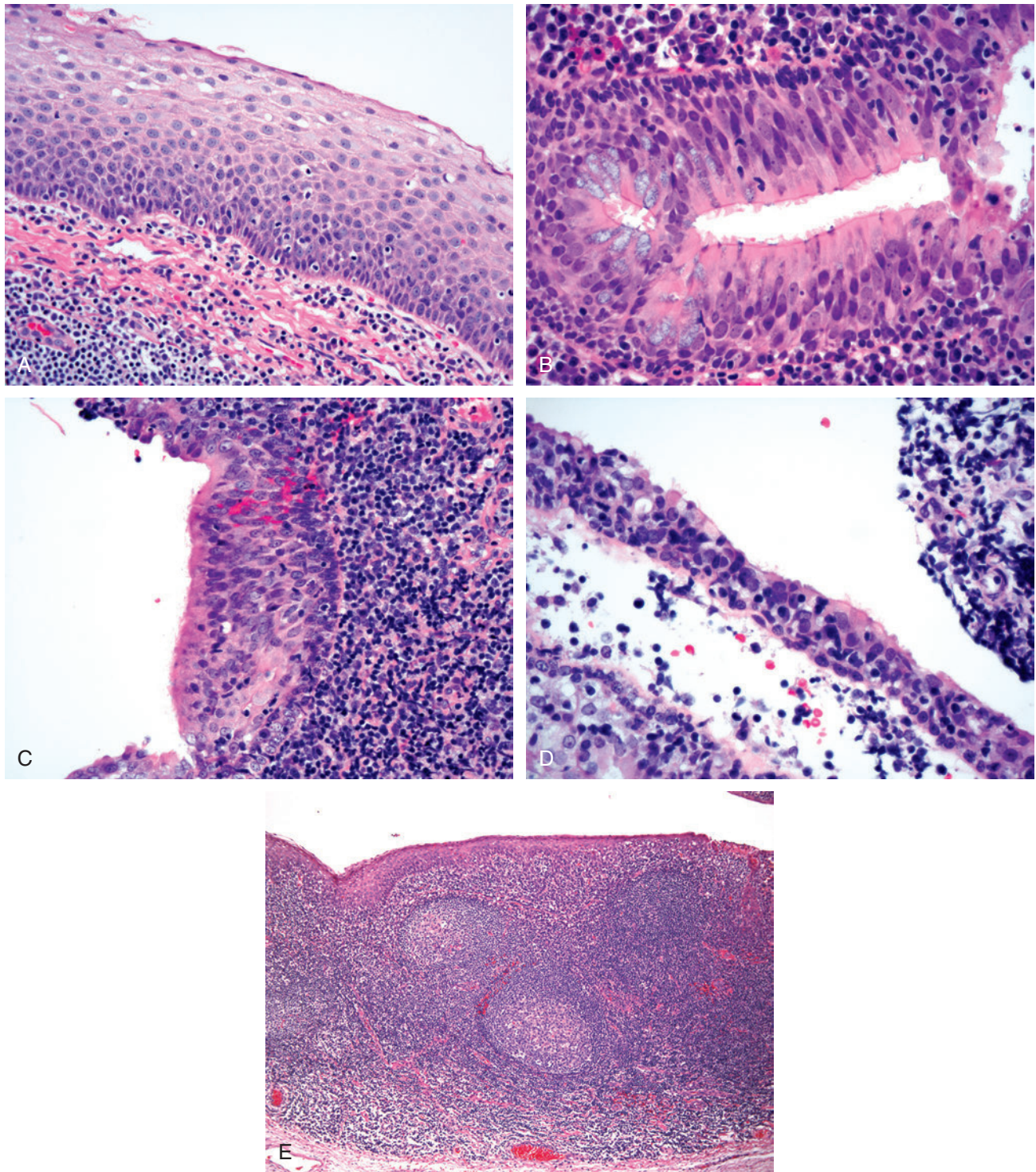


Fig. 8-4. Normal nasopharyngeal histology. Nasopharyngeal “lymphoepithelium.”

Areas of the nasopharynx are lined by (A) nonkeratinizing stratified squamous epithelium or (B) ciliated columnar (respiratory) type epithelium; mucocytes are present. C and D, Intermediate (“transitional”) epithelium lying between squamous and respiratory type epithelium characterized by cells with basaloid nuclei, smooth nuclear contours, and limited nuclear pleomorphism with absent increased mitotic activity. Note preservation of surface cilia. Such features should allow for distinction from intraepithelial dysplasia, the latter rarely seen as an isolated finding in nasopharyngeal biopsies in the absence of an invasive carcinoma. E, Nasopharyngeal tonsils also referred to as adenoids represent extranodal lymphoid tissues lined by squamous epithelium and submucosal lymphoid cell population including germinal centers; there is polar distribution of mantle lymphocytes with orientation toward the surface epithelium.

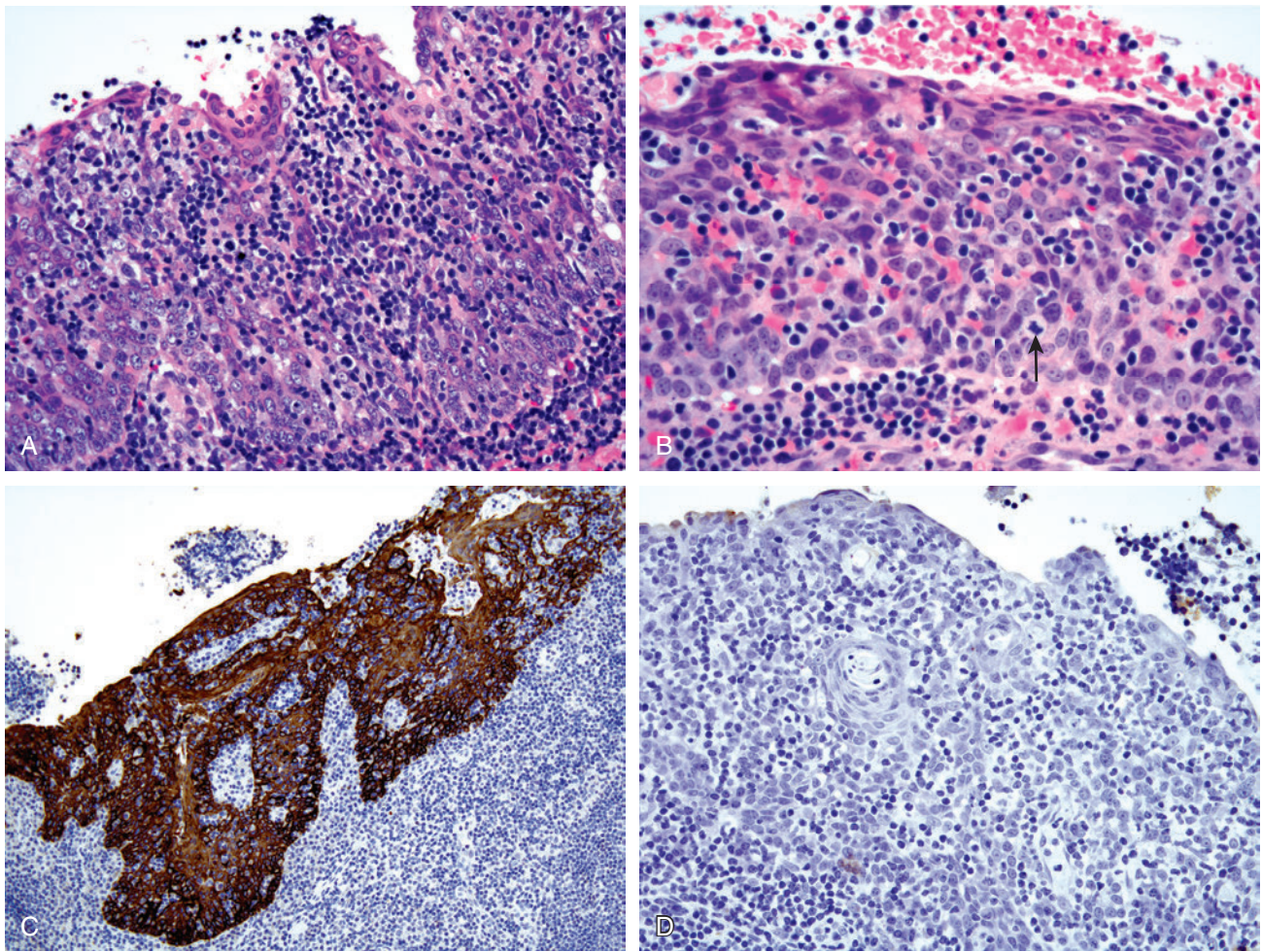


Fig. 8-5.

A, Nasopharyngeal “lymphoepithelium” characterized by basaloid appearing cells with uniform, vesicular nuclei infiltrated by small lymphoid cells expanding and disrupting the epithelium and producing a reticulated pattern. **B**, At higher magnification the epithelial cells are composed of uniform, vesicular nuclei and small eosinophilic nucleoli; rare mitotic figures can be identified (*arrow*). **C**, Cytokeratin (AE1/AE3) staining highlights the epithelial cells, whereas the lymphoid cells lack cytokeratin staining. **D**, In nonendemic populations, the nasopharyngeal mucosa is negative for the Epstein-Barr virus (in situ hybridization for Epstein-Barr encoded RNA).

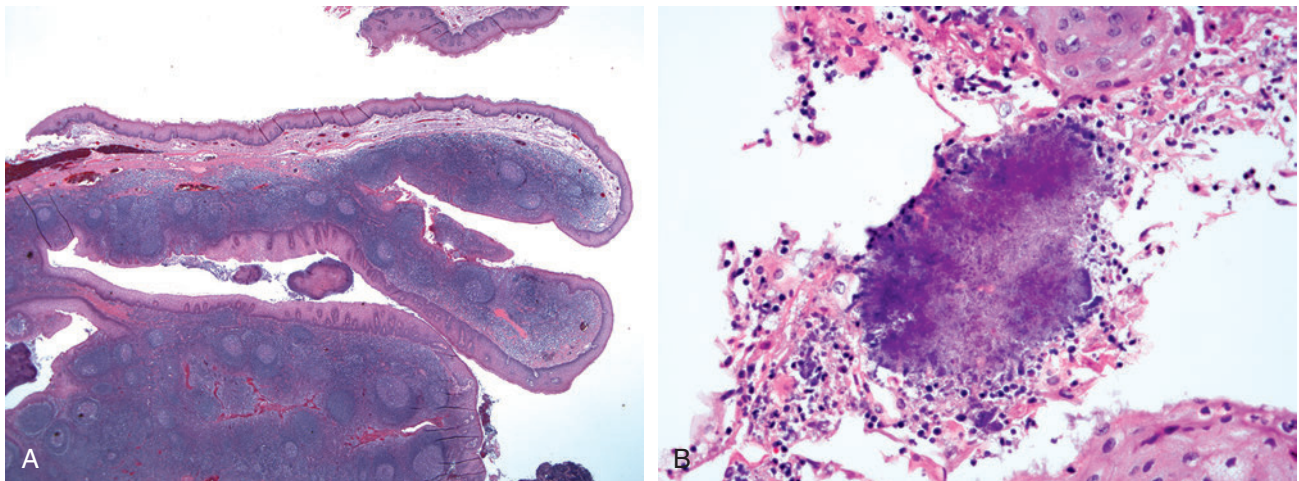


Fig. 8-6. Oropharyngeal tonsils.

A, At low magnification the nasopharyngeal tonsils (adenoids) are lined by a surface nonkeratinizing squamous epithelium that, unlike the nasopharyngeal tonsils (adenoids), include tonsillar crypts formed by invagination of the surface mucosa appearing as narrow tubular epithelial diverticuli branching within the tonsils frequently containing actinomycotic colonies (*center of image*). **B**, Higher magnification of the actinomycotic colonies (so-called sulfur granules) representing commensal microorganisms normally found within tonsillar crypts. Surrounding the bacterial colonies are shed epithelial cells and lymphocytes.

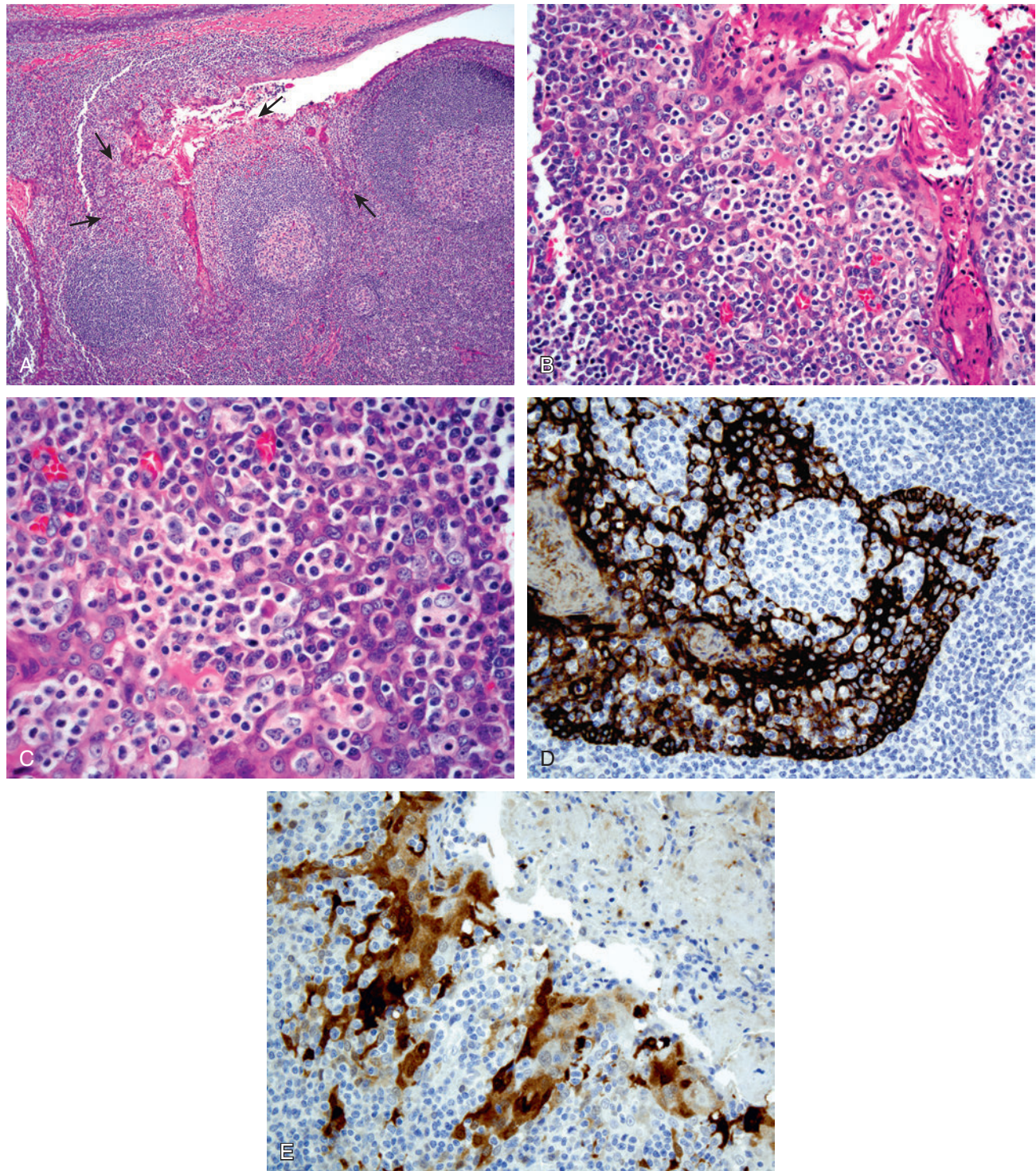


Fig. 8-7. Tonsillar crypt reticulated epithelium.

A, As the stratified squamous epithelium of the tonsillar surface (*upper right*) extends into the tonsillar crypts, a dense lymphoid infiltrate penetrates the reticulated epithelium (*arrows*), obscuring the junction between epithelial and lymphoid components; like the adenoids, the palatine and lingual tonsils contain a submucosal prominent lymphoid component, including germinal centers with orientation of the mantle lymphocytes toward the surface epithelium. **B**, The basal lamina of reticulated epithelium is discontinuous and porous, facilitating migration of mature lymphocytes and plasma cells (and dendritic cells) penetrating the reticulated epithelium obscuring the junction between epithelial and lymphoplasmacytic components. **C**, Reticulated epithelial cells are basaloid appearing with vesicular nuclei, increased nuclear-to-cytoplasmic ratio, absence of keratinization, absence of intercellular bridges, and loss of distinct cytoplasmic border. **D**, Cytokeratin (AE1/AE3) staining highlights the epithelial cells, whereas the lymphoplasmacytic cell infiltrate lacks cytokeratin staining. **E**, p16 immunoreactivity seen in normal (non-neoplastic) tonsillar crypt epithelium is not evidence for the presence of HPV-associated intraepithelial dysplasia and/or carcinoma.

- Actinomycotic colonies (*Actinomyces israelii*) are commensal microorganisms that may be found within tonsillar crypts.
- Tonsillar crypts are lined by specialized stratified squamous epithelia known as reticulated epithelia, which:
 - Lack the orderly laminar structure of the surface-stratified squamous epithelia of the tonsils, including loss of cellular polarity and surface maturation
 - As stratified squamous epithelium of the tonsillar surface extends into the tonsillar crypts a dense lymphoid infiltrate, as well as macrophages, penetrates the reticulated epithelium obscuring junction between epithelial and lymphoid components:
 - Basal lamina of reticulated epithelium is discontinuous and therefore porous, facilitating migration of lymphocytes and dendritic cells, the latter representing potent antigen processing cells.
 - Intimate association of epithelial cells and lymphocytes facilitates direct transport of antigen (e.g., HPV, HIV) from external environment to the tonsillar lymphoid cells:
 - Reticulated epithelial cells are functionally similar to microfold (M) cells of the gut.
 - Lymphoid tissue elsewhere depends on direct antigen delivery through afferent lymphatic vessels but such afferent vessels are absent from the tonsils.
 - Total surface area of the reticulated epithelium is very large owing to the complex branched nature of the tonsillar crypts.
 - Reticulated epithelium is characterized by numerous (intraepithelial) blood vessels that can be further delineated by vascular endothelial cell immunomarkers (e.g., CD31, others).
- Metastatic carcinomas to the cervical neck may originate from very small crypt carcinomas that histologically appear to be wholly confined to the crypt epithelium without apparent evidence of invasion into the submucosa.
 - Reticulated epithelial cells are basaloid appearing with vesicular nuclei, increased nuclear-to-cytoplasmic ratio, absence of keratinization, absence of intercellular bridges, and loss of distinct cytoplasmic border.
 - HPV-associated squamous cell carcinomas originating from tonsillar crypt epithelium are nonkeratinizing and may be viewed as “poorly differentiated”; however, such cancers are in fact differentiated, originating and recapitulating the features of its cell of origin being that of the specialized tonsillar crypt reticulated epithelium.
 - p16 immunoreactivity may be seen in normal (non-neoplastic) tonsillar crypt epithelium and is not evidence for the presence of HPV-associated intraepithelial dysplasia and/or carcinoma.
- Minor salivary glands of the palatine tonsils (as well as the uvula and soft palate) are mixed seromucous but are predominantly mucous and can be seen embedded in the underlying muscle.
- Minor salivary glands at the lingual tonsils/base of the tongue are pure mucous type.

NOTE: The discontinuous basal lamina of the reticulated epithelium coupled to the numerous intraepithelial blood vessels assist in explaining the facts that:

- Any carcinoma arising from the crypt epithelium should be interpreted as invasive carcinoma rather than carcinoma in situ.

Hypopharynx

- Epithelium is nonkeratinizing stratified squamous epithelium.
- Seromucous glands are seen throughout the submucosa.
- Not characterized by “lymphoepithelium” or reticulated epithelium

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Neoplasms of the Sinonasal Tract

CLASSIFICATION OF NEOPLASMS OF THE NASAL CAVITY AND PARANASAL SINUS (Table 3-1)

BOX 3-1 Classification of Neoplasms of the Sinonasal Tract

Benign Neoplasms

Epithelial

- Schneiderian papillomas
- Squamous papilloma (nasal vestibule)
- Minor salivary gland neoplasms

Mesenchymal/Neuroectodermal

- Lobular capillary hemangioma (pyogenic granuloma)
- Sinonasal glomangiopericytoma (formerly sinonasal-type hemangiopericytoma)
- Sinonasal tract meningioma
- Ectopic pituitary adenoma
- Solitary fibrous tumor
- Benign peripheral nerve sheath tumor
- Benign fibrous histiocytoma
- Leiomyoma
- Rhabdomyoma
- Osteoma
- Fibro-osseous lesions (ossifying fibroma, juvenile active ossifying fibroma)
- Chondroma
- Myxoma/fibromyxoma/chondromyxoid fibroma
- Ossifying and nonossifying fibromyxoid tumor
- Ameloblastoma
- Others

Malignant Neoplasms

Epithelial

- Squamous cell carcinoma:
 - Keratinizing squamous cell carcinoma
 - Nonkeratinizing squamous cell carcinoma

- Variants of squamous cell carcinoma (verrucous carcinoma, papillary squamous cell carcinoma, spindle cell squamous carcinoma, basaloid squamous cell carcinoma, lymphoepithelial carcinoma, adenosquamous carcinoma)
- Sinonasal undifferentiated carcinoma
- *SMARCB1* (INI1)-deficient carcinoma
- NUT midline carcinoma
- HPV-associated adenoid cystic-like carcinoma
- Adenocarcinoma:
 - Salivary gland types
 - Intestinal types
 - Nonsalivary, nonintestinal types

Mesenchymal/Neuroectodermal

- Olfactory neuroblastoma
- Neuroendocrine carcinomas
- Mucosal malignant melanoma
- Non-Hodgkin malignant lymphomas
- Ewing family of tumors
- Undifferentiated pleomorphic sarcoma
- Fibrosarcoma
- Leiomyosarcoma
- Malignant schwannoma
- Angiosarcoma
- Matrix-forming malignant tumors (osteosarcoma, chondrosarcoma)
- Low-grade sarcoma with neural and myogenic differentiation (LGSSNMF)
- Teratocarcinosarcoma
- Secondary tumors

GENERAL CONSIDERATIONS

- The sinonasal tract is the location for a wide variety of benign and malignant tumors.
- The more common tumor types are of epithelial origin and include:
 - Benign neoplasms: Schneiderian papillomas
 - Malignant neoplasms: squamous cell carcinoma and variants thereof
- Whether benign or malignant, neoplasms of the sinonasal tract often present with nasal obstruction,

which may also be the clinical presentation for non-neoplastic lesions:

- Presence of pain and/or manifestations of cranial nerve dysfunction is an indicator of a malignancy until proven otherwise.
- Clinical information is paramount for the pathologist to evaluate any given case.
- Carcinomas of the sinonasal tract account for less than 1% of all malignant neoplasms.
- Carcinomas of the sinonasal tract account for approximately 3% of head and neck malignant neoplasms.

- Based on the entire sinonasal tract, malignant neoplasms originate (in descending order of occurrence) from:
 - Maxillary sinus (60%)
 - Nasal cavity (20% to 30%)
 - Ethmoid sinus (10% to 15%)
 - Sphenoid and frontal sinuses (1%)
- Based on the entire paranasal sinuses alone, malignant neoplasms originate (in descending order of occurrence) from:
 - Maxillary sinus (77%)
 - Ethmoid sinus (22%)
 - Sphenoid and frontal sinuses (1%)
- Cause of sinonasal malignant neoplasms include:
 - Occupational exposure to wood dust is linked to the development of sinonasal adenocarcinomas, intestinal types, and to a lesser extent squamous cell carcinoma.
 - Occupational exposure to nickel refining and chromate pigment manufacture is linked to an increased risk of sinonasal carcinoma.
 - Epstein-Barr virus (EBV) present in association with some sinonasal tract neoplasms including:
 - NK/T-cell lymphoma
 - Lymphoepithelial-like carcinoma
 - Human papillomavirus (HPV), mainly high-risk types, may be present in association with some sinonasal tract neoplasms, including:
 - Schneiderian papilloma (include low- and high-risk HPV)
 - As many as 20% of sinonasal carcinomas may harbor transcriptionally active high-risk HPV:
 - Almost always nonkeratinizing squamous cell carcinoma (SCC)
 - Less commonly with other morphologic types including:
 - keratinizing SCC (de novo or in association with Schneiderian papilloma)
 - basaloid SCC
 - papillary SC
 - adenosquamous carcinoma
 - other morphologic types
 - Prognostic significance of transcriptionally active HPV in sinonasal SCC remains uncertain; unclear whether ameliorating prognostic effect as may occur in association with HPV-associated carcinomas of oropharynx also applicable to HPV-associated sinonasal carcinomas
- Premalignant lesions:
 - Unlike other upper aerodigestive tract sites, in particular the oral cavity and larynx, isolated premalignant lesions of the sinonasal tract (i.e., high-grade intraepithelial dysplasia and carcinoma in situ) are rarely seen unless associated with another neoplasm:
 - Often seen in association with an invasive squamous cell carcinoma, including conventional keratinizing type, nonkeratinizing carcinoma, basaloid squamous cell carcinoma, others
 - May be seen in association with a carcinoma arising in association with a benign neoplasm (e.g., malignant transformation of Schneiderian papilloma)
 - Although an extremely rare occurrence, sinonasal high-grade intraepithelial dysplasia can be seen in association with non-neoplastic sinonasal tract lesions, such as inflammatory polyps.
 - Squamous cell carcinoma and variants thereof may develop from inverted and oncocytic types of Schneiderian papillomas:
 - HPV can be found in these types of Schneiderian papillomas, but there is no definitive link between the presence of HPV and the development of sinonasal squamous cell carcinoma.
 - No known association between the presence of squamous metaplasia of the sinonasal epithelium and the development of squamous cell carcinoma
- Cytogenetics and molecular genetics:
 - For the majority of patients with head and neck squamous cell carcinoma and its variants, there are genetic alterations at the short arm of chromosome 9 regions.
 - Specific types of squamous cell carcinoma demonstrate distinctive molecular alterations.
 - These findings support the early involvement of these chromosomal loci in squamous epithelial carcinogenesis and support their temporal occurrence prior to the phenotypic diversion.
- Not infrequently, sinonasal neoplasms are removed in pieces lacking orientation.
- Partial maxillectomy:
 - Usually performed for tumors situated in the inferior portion of the maxilla (e.g., hard palate and alveolar recess)
 - The specimen includes a portion of the maxilla that may include the alveolar process, palate, and nasal turbinates.
 - For certain tumor types the incision may be extended to include the ethmoid complex and lateral nose.
- Radical maxillectomy includes:
 - The entire maxillary wall, ethmoid labyrinth, with or without the orbital content
 - Anterior portion: anterior maxilla, anterolateral portion of the zygomatic process of the frontal bone, frontal processes of the maxilla, medial and inferior walls of the orbit:
 - Skin and soft tissue overlying the anterior maxilla may be removed.

- Posterior margin: pterygoid muscle
 - If the orbit is resected, then the optic nerve and orbital content are the posterior margin.
- Medial margin: transected hard palate and maxilla
- Lateral margin: zygomatic arch
- Superior margin:
 - If orbit removed, exposed orbital soft tissue
 - If orbit not removed, floor of orbit

TNM Classification for Sinonasal Tract Neoplasms (Table 3-1)

Anatomic Site

- For staging purposes the sites of inclusion include:
 - Maxillary sinus
 - The nasoethmoid complex, which includes:
 - Nasal cavity
 - Ethmoid sinuses

Nasal Cavity

- The nasal cavity is subdivided into four subsites:
 - Septum
 - Floor
 - Lateral wall
 - Vestibule

Maxillary Sinus (Fig. 3-1)

- The maxillary sinus is divided into right and left.
- Ohngren line connecting the medial canthus of the eye to the angle of the mandible dividing the maxillary sinus into an anteroinferior portion (infrastructure) and superoposterior portion (suprastructure) structures (see Fig. 3-1):
 - Carcinomas of the infrastructure are associated with a good prognosis.
 - Carcinomas of the suprastructure are associated with a poor prognosis:
 - The poorer prognosis with carcinomas of the suprastructure reflects early access of these tumors to critical structures, including the eye, skull base, pterygoids, and infratemporal fossa.

TABLE 3-1 TNM Classification of Sinonasal Tract Neoplasms

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Maxillary Sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease Tumor invades the anterior orbital contents, skin of the cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V ₂), nasopharynx, or clivus
Nasal Cavity and Ethmoid Sinuses	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or ethmoid sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V ₂), nasopharynx, or clivus

Continued

TABLE 3-1 TNM Classification of Sinonasal Tract Neoplasms—cont'd

Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Clinical Stage	
Stage 0	TisN0M0
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0 T1N1M0 T2N1M0 T3N1M0
Stage IVA	T4aN0M0 T4aN1M0 T1N2M0 T2N2M0 T3N2M0 T4aN2M0
Stage IVB	T4b AnyN M0 Any T N3M0
Stage IVC	Any T Any N M1

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BENIGN NEOPLASMS

SCHNEIDERIAN PAPILLOMAS

(Table 3-2, Figs. 3-2 through 3-10)

Definition: Group of benign neoplasms arising from the sinonasal (Schneiderian) mucosa and composed of a squamous or columnar epithelial proliferation with associated mucous cells.

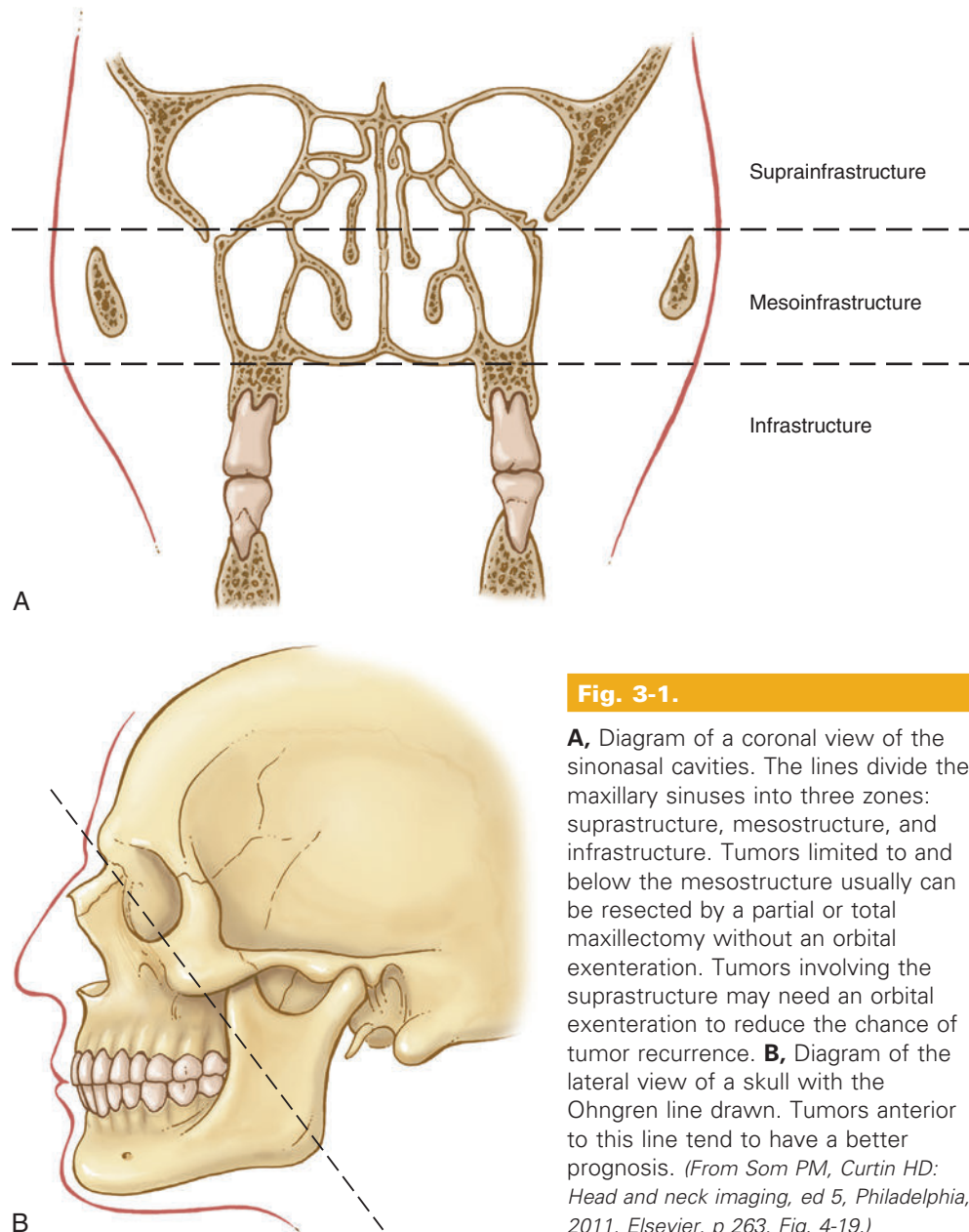
Synonym: Sinonasal-type papillomas

Clinical

- Ectodermally derived lining of the sinonasal tract, termed the Schneiderian membrane, may give rise to three morphologically distinct benign papillomas

collectively referred to as Schneiderian or sinonasal-type papillomas. The three morphologic types are:

- Inverted
- Oncocytic (cylindric or columnar cell)
- Exophytic (fungiform, septal) papillomas
- Collectively, Schneiderian papillomas represent less than 5% of all sinonasal tract tumors.
- As reported in the literature, among sinonasal-type papillomas, the exophytic (septal) papilloma is the most common type; however, practical experience indicates that the inverted type is the most common subtype; the oncocytic type is the least common.

**Fig. 3-1.**

A, Diagram of a coronal view of the sinonasal cavities. The lines divide the maxillary sinuses into three zones: suprastructure, mesostructure, and infrastructure. Tumors limited to and below the mesostructure usually can be resected by a partial or total maxillectomy without an orbital exenteration. Tumors involving the suprastructure may need an orbital exenteration to reduce the chance of tumor recurrence. **B**, Diagram of the lateral view of a skull with the Ohngren line drawn. Tumors anterior to this line tend to have a better prognosis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 263, Fig. 4-19.)

- In general, the sinonasal-type papillomas occur over a wide age range but are rare in children:
 - Inverted papillomas are most common in the fifth to eighth decades.
 - Oncocytic papillomas occur in a somewhat older age range (greater than 50 years) and are uncommon in patients younger than the fourth decade of life.
 - Exophytic (septal) papillomas tend to occur in a younger age group.
- Localization:
 - Exophytic papillomas almost invariably are limited to the nasal septum.
 - Inverted papillomas occur along the lateral nasal wall (middle turbinate or ethmoid recesses) with secondary extension into the paranasal sinuses (maxillary and ethmoid, and less often sphenoid and frontal); less frequently, inverted papillomas may originate in a paranasal sinus.
 - Oncocytic papillomas also are most often seen along the lateral nasal wall but may originate within a paranasal sinus (maxillary or ethmoid).
 - Inverted and oncocytic subtypes rarely occur on the nasal septum.
 - Inverted papillomas may occur in a paranasal sinus without involvement of the nasal cavity.
 - Schneiderian papillomas have a tendency to spread along the mucosa into adjacent areas.
 - Although uncommon, the sinonasal-type (Schneiderian) papillomas may originate in the

TABLE 3-2 Sinonasal (Schneiderian) Papillomas: Clinicopathologic Features

	Exophytic	Inverted	Oncocytic
Percentage	18% to 50%	47% to 79%	3% to 8%
Gender/Age	M > F; 20-50 yrs	M > F; 40-70 yrs	M = F; >50 yrs
Location	Nasal septum	Lateral nasal wall in region of middle turbinates with extension into sinuses (maxillary or ethmoid)	Lateral nasal wall and sinuses (maxillary or ethmoid)
Focality	Unilateral	Typically unilateral; rarely, bilateral (up to 10%); bilateral disease should prompt possibility of septal perforation from unilateral disease	Unilateral
Histology	Papillary fronds composed of a predominantly squamous (epidermoid) epithelium; mucocytes (goblet cells) and intraepithelial mucous cysts are present; delicate fibrovascular cores	Endophytic or “inverted” growth consisting of thickened squamous epithelium composed of squamous, transitional, and columnar cells (all three may be present in a given lesion) with admixed mucocytes (goblet cells) and intraepithelial mucous cysts; mixed chronic inflammatory cell infiltrate characteristically is seen within all layers of the surface epithelium	Multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm; outer surface of the epithelial proliferation may demonstrate cilia; intraepithelial mucous cysts, often containing polymorphonuclear leukocytes
Incidence of human papillomavirus	Approximately 50% positive; HPV 6 and 11 most common; rarely HPV 16 and 57b	Approximately 38% positive; HPV 6 and 11; less frequently HPV 16, 18; rarely HPV 57	Typically absent
Treatment	Complete surgical excision	Complete surgical excision; may require lateral rhinotomy or medial maxillectomy with en bloc excision	Complete surgical excision; may require lateral rhinotomy or medial maxillectomy with en bloc excision
Prognosis	Good following complete surgical excision; will recur if incompletely resected	Good following complete surgical excision; will recur if incompletely resected	Good following complete surgical excision; will recur if incompletely resected
Incidence malignant transformation	Rare	Approximately 10% (range reported of 2% to 27%); most commonly SCC and NKSCC; less common types including VC, MEC, SCSC, adenocarcinoma; synchronous (61%) > metachronous (39%)	4% to 17%; most commonly SCC; less common types include MEC, SCUNC, SNUC

HPV, Human papillomavirus; MEC, mucoepidermoid carcinoma; NKSCC, nonkeratinizing squamous cell carcinoma; SCC, (keratinizing) squamous cell carcinoma; SCSC, spindle cell squamous carcinoma; SCUNC, small cell undifferentiated neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; VC, verrucous carcinoma.

nonsinonasal tract sites, including the nasopharynx or the ear:

- Typically in such situations there is no connection to the sinonasal tract and/or to a Schneiderian papilloma extending from the sinonasal tract to these locations.
- In all likelihood such Schneiderian-type papillomas occurring in nonsinonasal tract sites arise from misplaced ectodermal-derived epithelial rests from the sinonasal tract.
- Typically, Schneiderian papillomas are unilateral; bilateral papillomas, in particular the inverted subtype, may occur with reported incidence of up to 10%:
 - In the presence of bilaterality, clinical evaluation to exclude the possibility of extension from unilateral disease (i.e., septal perforation) should be undertaken.
- Symptoms vary according to site of occurrence and include airway obstruction, epistaxis, asymptomatic mass, and pain.
- Schneiderian papillomas may occur simultaneously with nasal inflammatory polyps or other lesion types including (but not limited to) sinonasal hamartomas.
- Radiology: appearance varies with extent of disease:
 - A soft tissue density is seen early in the disease.

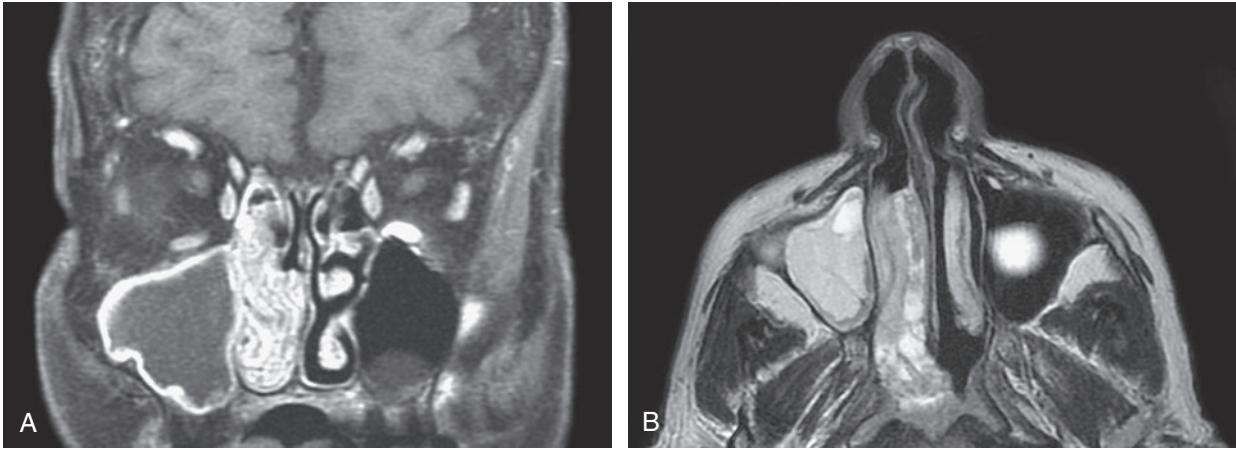


Fig. 3-2. Schneiderian papilloma, inverted type.

Coronal (**A**) T1-weighted, fat-suppressed, contrast-enhanced MR image shows a nonhomogeneously enhancing right nasal cavity mass that extends into the right ethmoid complex and obstructs the right maxillary sinus. Axial (**B**) T2-weighted MR image on the same patient again shows the nonhomogeneous nature of the right polypoid nasal mass that obstructs the right antrum. A small retention cyst or polyp is in the floor of the left antrum. This patient had an inverted papilloma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 260, Fig. 4-14.)

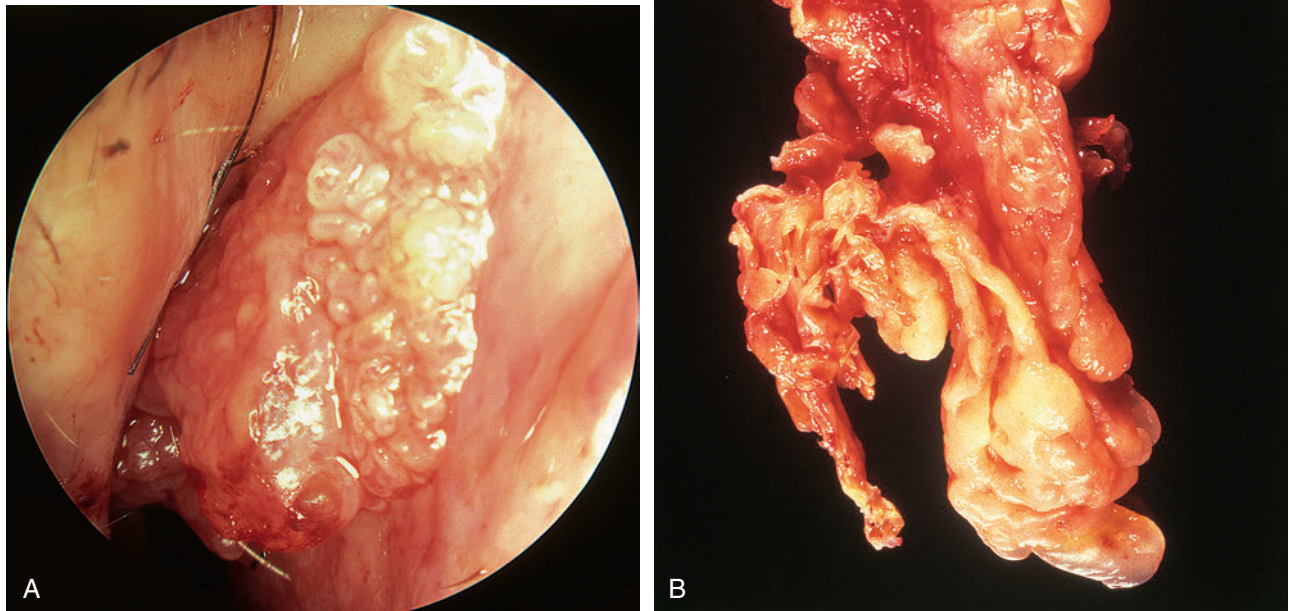


Fig. 3-3. Schneiderian papilloma, inverted type.

A, Endoscopic appearance of the lesion seen along the floor and lateral wall of the nasal cavity; the tumor appears as a sessile, tan-white mucosal lesion. **B**, Resection specimen showing the tumor arising along the surface (*top*) as a flat, tan-white thickened area with an endophytic or inverted growth into the submucosal compartment (*top right*).

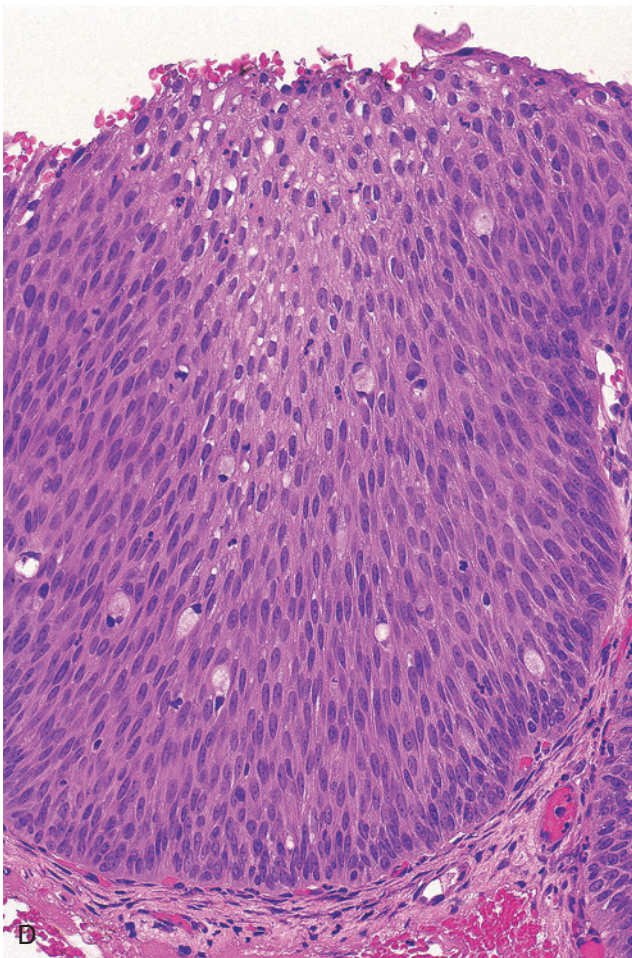
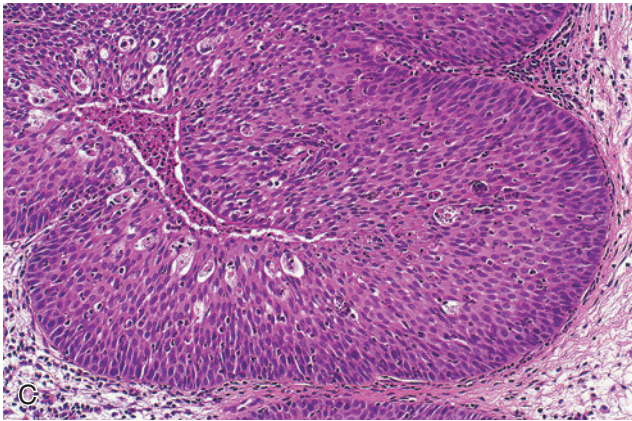
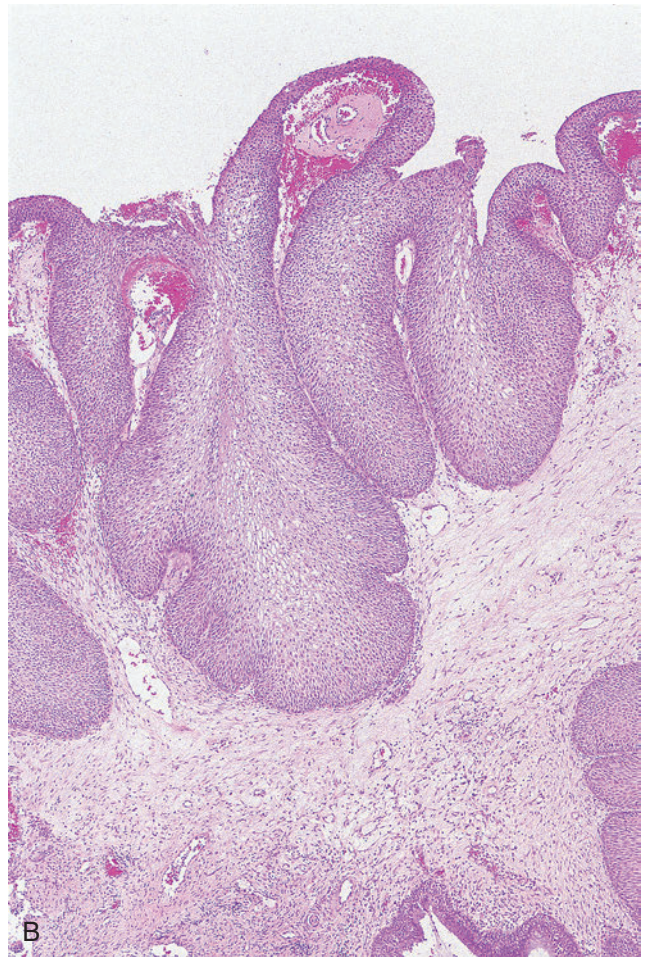
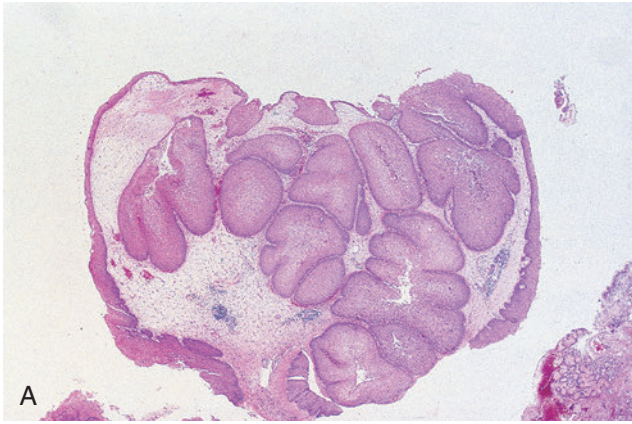
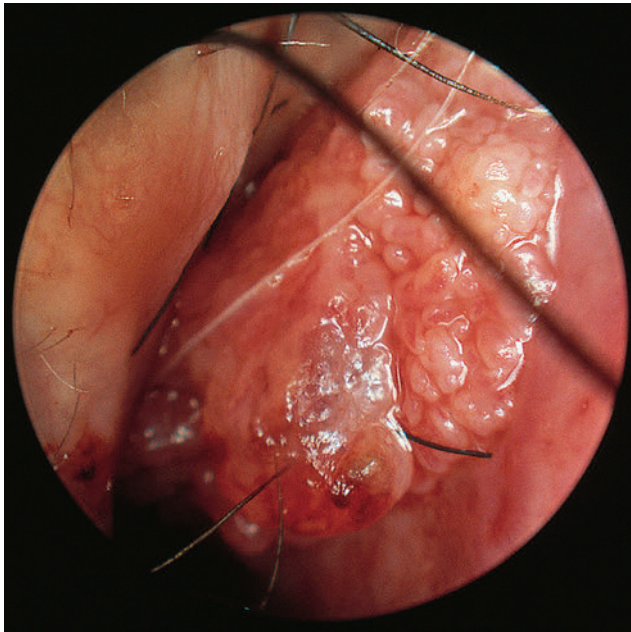


Fig. 3-4. Schneiderian papilloma, inverted type.

A, Endophytic or “inverted” growth pattern consisting of thickened epithelial nests arising from the surface and growing down into the stroma; the surface epithelium has undergone squamous metaplasia, and the stroma is composed of a myxomatous to fibrous tissue with admixed chronic inflammatory cells. **B**, Slightly higher magnification showing the endophytic pattern of growth of benign nonkeratinizing squamous epithelium. **C**, The epithelial proliferation is noteworthy for uniformity of nuclei maintaining consistency in polarity, absence of cytologic atypia, scattered mucous cysts, and the presence of neutrophils throughout the epithelium. **D**, Scattered intraepithelial mucocytes are present and assist in defining the papilloma as being of Schneiderian (mucosal) origin and not a squamous papilloma of cutaneous origin, which lacks intraepithelial mucocytes. **E**, Schneiderian papilloma, inverted type with “early” changes including epithelial proliferation with expansion and downward projection.

**Fig. 3-5. Schneiderian papilloma, exophytic (septal) type.**

This lesion on the septum is an exophytic, tan-white lesion with a cauliflower-like appearance.

- Opacification and mucosal thickening are present with more extensive disease.
- Evidence of pressure erosion of bone may be seen.
- Human papillomavirus (HPV) types 6/11, less often 16, and rarely other HPV types (e.g., HPV57), have been found in septal and inverted papillomas by various molecular biologic analyses (in situ hybridization and/or polymerase chain reaction):
 - Strong association identified between HPV and exophytic papillomas
 - Association between HPV and inverted papillomas less well defined:
 - Approximately 38% of inverted papillomas reported to be positive for HPV by molecular biologic evaluation

- To date, molecular biologic analysis of oncogenic papillomas has not identified the presence of HPV.
- Whether there is a cause and effect between the presence of HPV and the development of Schneiderian papillomas remains to be determined.
- p16(INK4a) not considered a useful surrogate marker for HPV detection across the various types of Schneiderian papillomas.
- HPV detection rates increase in inverted papillomas with epithelial dysplasia and malignant transformation (i.e., carcinoma) of inverted papillomas:
 - Increasing ratio of high-risk to low-risk HR HPV types as compared with “conventional” inverted papillomas (i.e., without dysplastic epithelium)
- Epstein-Barr virus has not been found to be associated with Schneiderian papillomas.

Pathology

Schneiderian Papilloma, Inverted Type

Gross

- Large, bulky, translucent masses with a red to gray color, varying from firm to friable in consistency

Histology

- Endophytic or “inverted” growth pattern consisting of markedly thickened squamous epithelial proliferation growing downward into the underlying stroma:
 - Exophytic growth, in addition to endophytic growth, may be present.
- Epithelium varies in cellularity and is composed of squamous, transitional, and columnar cells (all three may be present in a given lesion) with admixed mucocytes (goblet cells) and intraepithelial mucous cysts.
- Cells are generally bland in appearance with uniform nuclei and no piling up; however, pleomorphism and cytologic atypia may be present.
- Mixed chronic inflammatory cell infiltrate characteristically is seen within all layers of the surface epithelium.

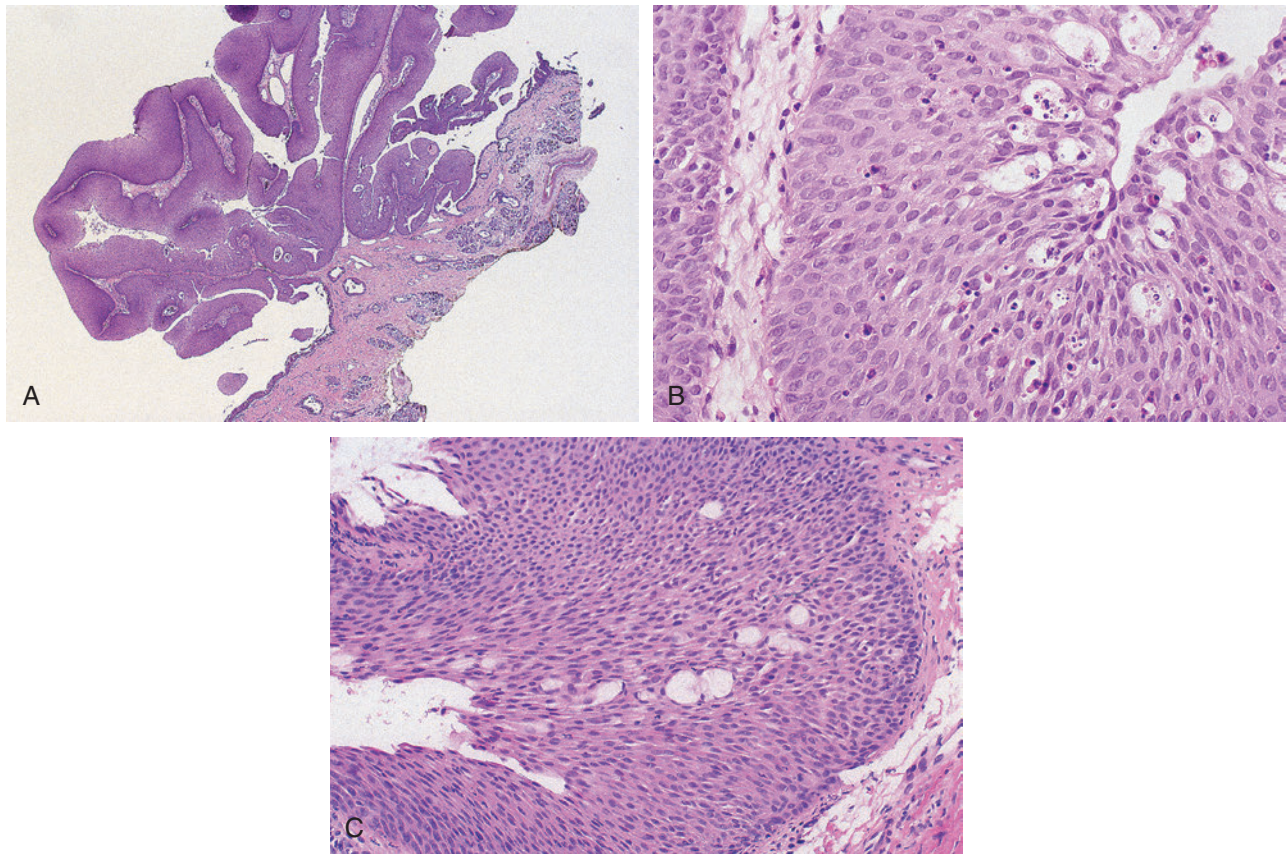


Fig. 3-6. Schneiderian papilloma, exophytic (septal) type.

A, The tumor has a papillary growth protruding from the surface respiratory epithelium and composed of a thickened nonkeratinized squamous (epidermoid) epithelium. **B,** At higher magnification the epithelium shows cytomorphic uniformity, retention of cellular polarity, absence of cytologic atypia, presence of scattered mucous cysts, and intraepithelial inflammatory cells. **C,** Scattered intraepithelial mucocytes are present and assist in defining the papilloma as being of Schneiderian (mucosal) origin and not a squamous papilloma of cutaneous origin, which lacks intraepithelial mucocytes.

- Epithelial component may demonstrate extensive clear cell features indicative of abundant glycogen content (diastase-sensitive, PAS-positive).
- Mitotic figures may be seen in the basal and parabasal layers, but atypical mitotic figures are not seen.
- Surface keratinization may be present.
- Stromal component varies from myxoid to fibrous with admixed chronic inflammatory cells and variable vascularity.
- Histochemistry:
 - Intraepithelial mucocytes show intracytoplasmic mucin-positive material (mucicarmin-positive; diastase-resistant, PAS-positive).

Differential Diagnosis

- Sinonasal inflammatory polyps
- Nonkeratinizing respiratory (“transitional”) carcinoma
- Verrucous carcinoma

Schneiderian Papilloma, Exophytic (Septal) Type

Gross

- Septal papillomas are papillary, exophytic, verrucoid lesions with a pink to tan appearance and a firm to rubbery consistency; they are often attached to the mucosa by a narrow or broad-based stalk.

Histology

- Papillary fronds are seen and are composed of a thick epithelium, which is predominantly squamous (epidermoid) and, less frequently, respiratory type.
- Surface keratinization is uncommon.
- Mucocytes (goblet cells) and intraepithelial mucous cysts are present.
- Stromal component is composed of delicate fibrovascular cores.



Fig. 3-7. Schneiderian papilloma, oncocytic type appearing as an intranasal dark red to brown mass.

- Histochemistry:
 - Intraepithelial mucocytes will show intracytoplasmic mucin positive material (mucicarmine positive; diastase-resistant, PAS-positive).

Differential Diagnosis

- Verruca vulgaris
- Squamous papilloma:
 - In contrast to all of the sinonasal-type papillomas, squamous papilloma of the nasal vestibule does not have mucocytes as a part of the neoplastic proliferation.

Schneiderian Papilloma, Oncocytic Type

Gross

- Oncocytic papillomas are dark red to brown, papillary, or polypoid lesions.

Histology

- Multilayered epithelial proliferation composed of columnar cells with abundant eosinophilic and granular cytoplasm
- Nuclei vary from vesicular to hyperchromatic; nucleoli are usually indistinct.
- Outer surface of the epithelial proliferation may demonstrate cilia.
- Intraepithelial mucin cysts, often containing polymorphonuclear leukocytes are seen; cysts are not identified in the submucosa.
- Stromal component varies from myxoid to fibrous with admixed chronic inflammatory cells and variable vascularity.

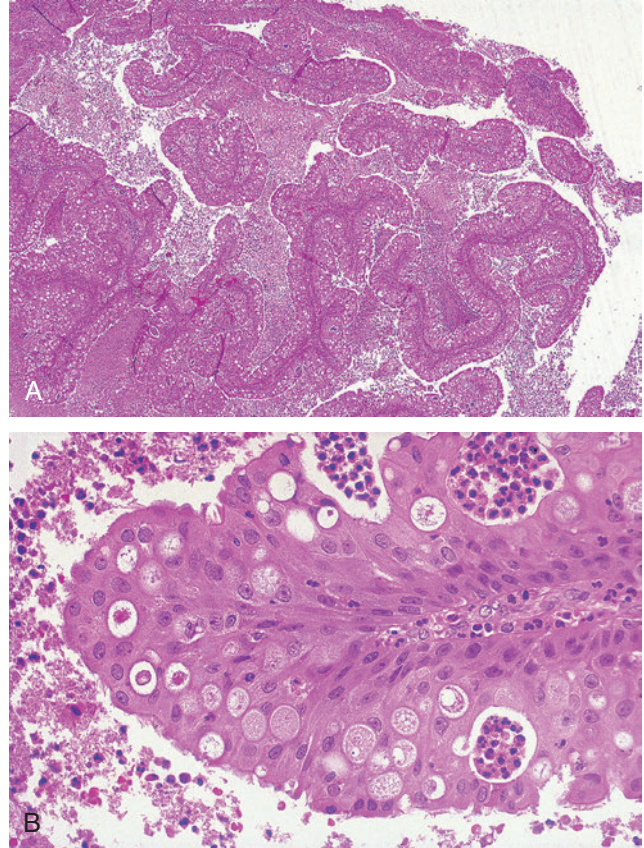


Fig. 3-8. Schneiderian papilloma, oncocytic type.

A, Histologically this lesion is characterized by a multilayered papillary epithelial proliferation with multiple intraepithelial mucin cysts; cysts are not identified in the submucosal compartment. **B**, The cells consist of an eosinophilic to granular cytoplasm (oncocytes) with uniform, round nuclei and intraepithelial mucin cysts containing amorphous pink material and/or neutrophils; cilia can be seen at the outer surface of the epithelial proliferation.

- Histochemistry:
 - Intraepithelial mucocytes will show intracytoplasmic mucin-positive material (mucicarmine-positive; diastase-resistant, PAS-positive).

Differential Diagnosis

- Rhinosporidiosis
- Low-grade papillary adenocarcinoma

Treatment and Prognosis (for All Papilloma Types)

- Treatment for all sinonasal-type papillomas is complete surgical excision, including adjacent uninvolved mucosa; the latter is necessary because growth and extension along the mucosa results from the

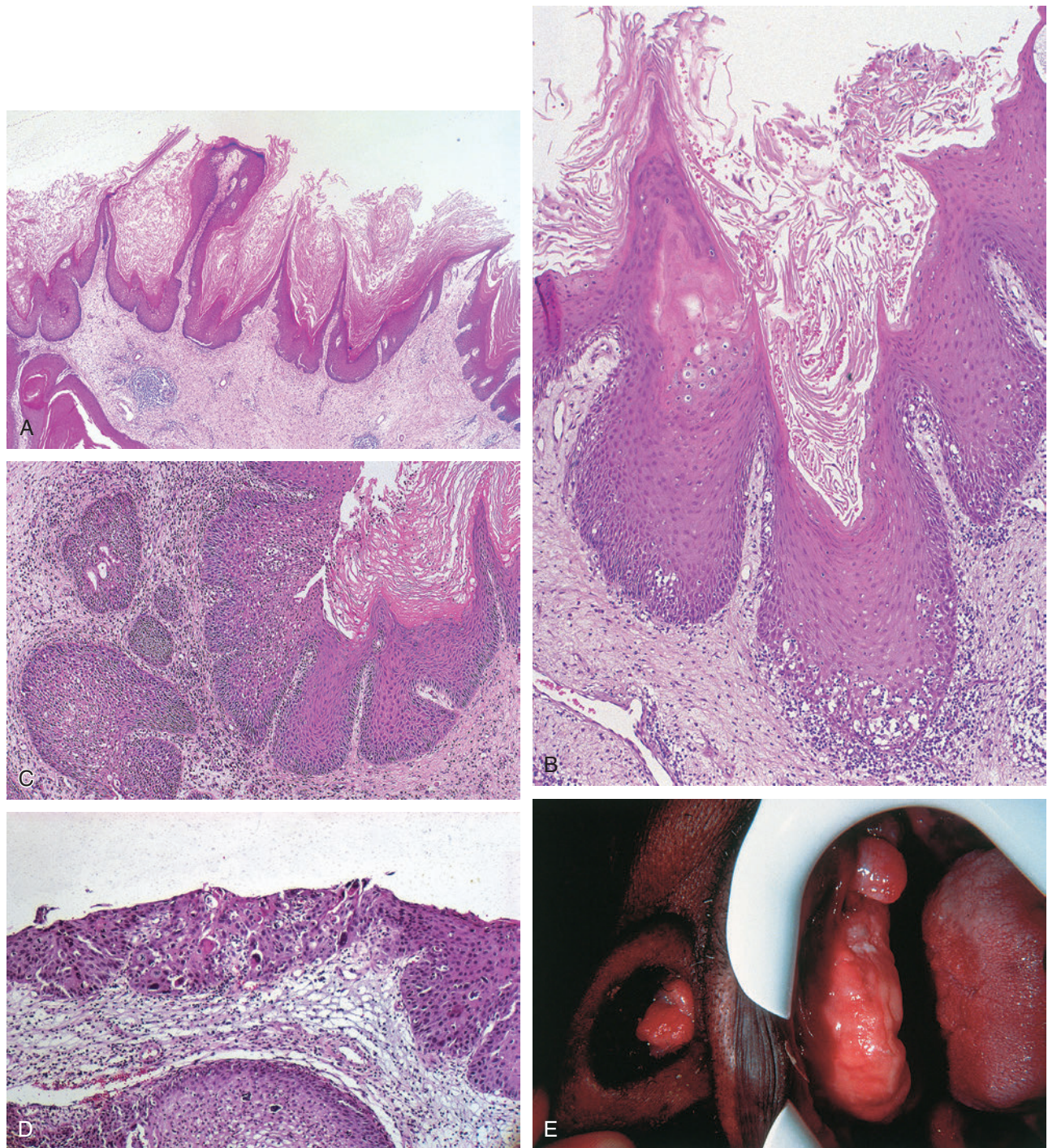


Fig. 3-9. Schneiderian papilloma, inverted type.

A, Typically these tumors lack keratinization and when present, as seen in this illustration, some concern for the possibility of a coexisting squamous cell carcinoma or the development into a squamous cell carcinoma should be raised. **B**, Higher magnification shows the epithelium to be bland without evidence to suggest malignant transformation. **C**, In this example, more worrisome features of malignancy (i.e., squamous cell carcinoma) are present, including nests of tumor with cytologic atypia within the submucosa and **(D)** foci of severe dysplasia (carcinoma in situ). **E**, The patient did have a malignancy that was invasive, extending from one nasal cavity with destruction of the septum and extension to the other nasal cavity.

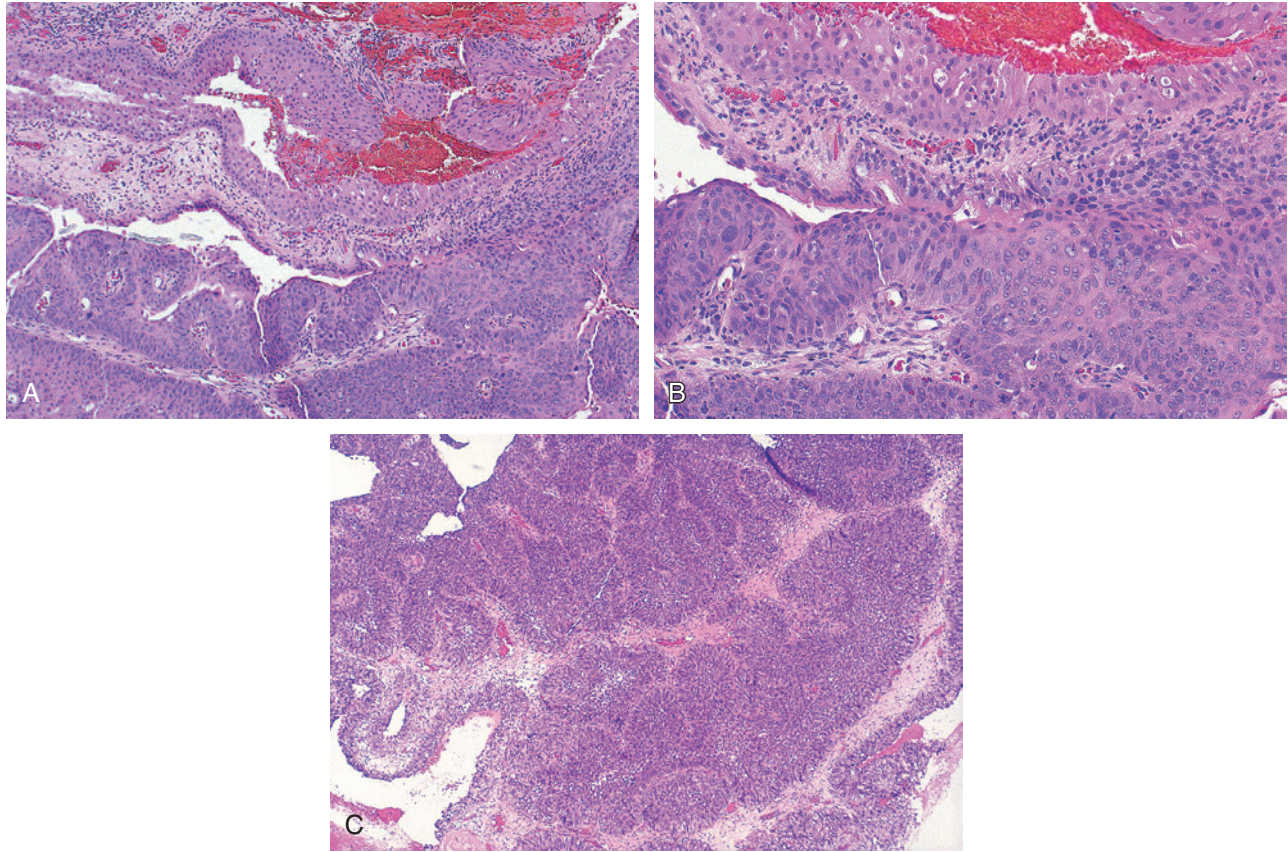


Fig. 3-10. Schneiderian papilloma, oncocytic type may also undergo malignant transformation.

A and **B**, Residual papilloma with oncocytic features are seen (top portion of images) with associated intraepithelial severe dysplasia and (**C**) areas of invasive growth. The carcinoma is nonkeratinizing, characterized by broad interconnecting cords of tumor, a pattern not typically seen in benign Schneiderian papillomas.

- induction of squamous metaplasia in the adjacent sinonasal mucosa:
 - Adequate surgery includes a lateral rhinotomy or medial maxillectomy with en bloc excision.
- Schneiderian papillomas of all histologic types will recur if incompletely resected; recurrence probably represents persistence of disease instead of multicentricity of the neoplasm.
- In general, prognosis is good following complete surgical excision; however, if left unchecked, these neoplasms have the capability of continued growth with extension along the mucosal surface with destruction of bone and invasion of vital structures (e.g., central nervous system, others).
- Adjuvant therapy (chemo- and radiotherapy) has not been demonstrated to be beneficial in sinonasal papilloma:
 - Radiation may prove beneficial in a select population of patients with unresectable tumors due to locally advanced disease.
- Complications associated with Schneiderian papillomas include recurrence and malignant transformation:
 - Inverted papillomas and oncocytic papillomas can undergo malignant transformation.
 - Incidence of malignant transformation varies per subtype:
 - Malignant transformation reported for the inverted subtype ranges from 2% to 27% but is more likely around 11%.
 - Malignant transformation reported for the oncocytic subtype ranges from 4% to 17%.
 - Malignant transformation relative to exophytic (septal) papilloma rarely, if ever, occurs.
 - Majority of the malignancies occurring in association with Schneiderian papillomas are squamous cell carcinomas (keratinizing and nonkeratinizing), varying in appearance from well to poorly differentiated; less frequently, other carcinomas may occur, including verrucous

carcinoma, mucoepidermoid carcinoma, spindle cell squamous carcinoma, small cell carcinoma, adenocarcinoma, and sinonasal undifferentiated carcinoma.

- Carcinoma may occur synchronously or metachronously with the papilloma:
 - Metachronous carcinomas develop with a mean interval of 63 months (range 6 months to 13 years) from the onset of the papilloma to the development of the carcinoma.
- Carcinomatous foci may be limited or extensive and may show epithelial dysplasia as well as carcinoma in situ or invasive carcinoma.
- Evidence of a pre-existing papilloma may be present with obvious transition from benign papilloma to overt carcinoma; other possibilities include a tumor that is predominantly benign (papilloma) with only limited foci of malignancy or a tumor that is predominantly a carcinoma with very limited residual papilloma.
- In some cases, there may be no residual evidence of a pre-existing benign tumor and only by history was the patient known to have had a previous benign sinonasal papilloma.
- There are no reliable histologic features that predict which papillomas are likely to become malignant:
 - Papillomas with increased cellularity, pleomorphism, and increased mitotic activity do not necessarily become malignant.
 - Presence of moderate to severe intraepithelial dysplasia is a potential indicator of malignant transformation.
 - Dysplastic epithelium will have increased p16, p53, and Ki67 expression.
 - Surface keratinization and dyskeratosis have anecdotally been considered as possible predictors of malignant transformation.
 - Any sinonasal papilloma that shows moderate to severe intraepithelial dysplasia or has surface keratinization should prompt thorough histologic examination of all resected tissue to exclude the presence of malignancy.
- There is no correlation between the number of recurrences and the development of carcinoma.
- Treatment for malignant transformation of a sinonasal papilloma includes surgery and radiotherapy.
- Prognosis for patients with malignant transformation varies:
 - In some patients the carcinomas are only locally invasive with favorable prognosis following treatment.
 - In other patients there may be extensive invasion with involvement of vital structures and/or metastatic disease; these patients generally have

a poor clinical outcome irrespective of therapeutic intervention.

SQUAMOUS PAPILLOMA OF THE NASAL VESTIBULE

Clinical

- Squamous papillomas represent the most common benign neoplasms of the upper aerodigestive tract mucosa and are commonly seen in the oral cavity and larynx; less often, squamous papillomas occur in the nasopharynx and nasal vestibule.
- For a more complete discussion on squamous papillomas see Section 2, Oral Cavity, and Section 5, Larynx.
- Nasal vestibular squamous papillomas are of cutaneous origin.
- In contrast to the sinonasal-type papillomas, squamous papillomas of the nasopharynx are endodermally derived.
- Squamous papillomas are exophytic, warty, or cauliflower-like tumors ranging in size from a few millimeters up to 3.0 cm in greatest dimension.
- Histologically, these tumors are composed of benign squamous epithelium arranged in multiple finger-like projections with prominent fibrovascular cores.
- In contrast to the sinonasal-type papillomas, cutaneous squamous papillomas lack intraepithelial mucocytes.
- In squamous papillomas the squamous epithelium is free of dysplastic change.
- In general, these tumors lack surface keratin, but in any tumor there may be (hyper)keratosis, as well as para- and orthokeratosis:
 - Presence of surface keratin carries no additional risk for the development of carcinoma.
- Surgical excision is the treatment of choice and is curative.
- Recurrences occur infrequently and relate to inadequate excision.
- Malignant transformation does not occur.

BENIGN MINOR SALIVARY GLAND NEOPLASMS

- Benign salivary gland tumors of the sinonasal region are uncommon.
- For a more complete discussion on benign salivary gland tumors see Section 6, Salivary Glands.
- In general, minor salivary gland tumors occur most often in the nasal cavity and rarely in the paranasal sinuses.

- Pleomorphic adenoma is the dominant histologic type seen; less often, monomorphic adenomas such as myoepithelioma and oncocytoma occur:
 - Pleomorphic adenomas of the sinonasal tract may be hypercellular, dominated by the presence of epithelial cells or myoepithelial cells or both cellular components.
 - Not infrequently, such neoplasms are myoepithelial-predominant pleomorphic adenomas.
 - There may be a limited amount of chondromyxoid stroma.
- Pleomorphic adenomas tend to originate along the nasal septum (bony or cartilaginous component) more than any other site.
- Although these tumors may arise from within the paranasal sinus, more often paranasal sinus involvement occurs secondary to extension from an intranasal lesion.
- These tumors appear as polypoid or exophytic growths, usually covered by an intact mucosa, and vary in size from 1 to 7 cm.
- As is true of all upper aerodigestive tract minor salivary gland tumors (benign or malignant), the pleomorphic adenomas are unencapsulated; however, in contrast to malignant minor salivary gland tumors, these tumors are relatively circumscribed without invasive growth; involvement of surface epithelium does not constitute invasion:
 - Diagnostic caution should be exercised when confronted with biopsy material that essentially includes lesional tissue with limited to absent surrounding tissues; in such biopsy material, although lesional cells appear bland, lacking cytomorphic features of malignancy, there are histologic features shared by benign salivary gland neoplasms and malignant salivary gland neoplasms (e.g., growth patterns, cell types) such that differentiation may be predicated solely on the basis of the presence or absence of invasive growth.
 - In the above scenario, although the findings may suggest a diagnosis of a benign minor salivary gland neoplasm, a diagnosis of “minor salivary gland neoplasm, not further specified” or “minor salivary gland neoplasm, favor benign neoplasm” may be prudent, with the recommendation for conservative but complete surgical excision.
- Histologically, these tumors are identical to those of major salivary glands, including an admixture of ductular or tubular structures, spindle-shaped or plasmacytoid-appearing myoepithelial cells, and a chondromyxoid stroma.
- There is a tendency for pleomorphic adenomas of the nasal cavity to be cellular, showing a predominant myoepithelial component:
 - Myoepithelial cells usually are in the form of plasmacytoid (hyaline cell) rather than spindle-shaped myoepithelial cells.
 - Given the presence of ductular or tubular structures and chondromyxoid stroma, these tumors would not be considered as myoepitheliomas.
 - Myoepithelial differentiation can be shown by immunoreactivity for cytokeratins as well as p63, p40, calponin, S100 protein, smooth muscle actin, glial fibrillary acidic protein, and vimentin.
 - Rarely, skeletal muscle differentiation can be seen.
- Surgical excision is the preferred treatment for all types of benign minor salivary gland tumors.
- Surgery is usually curative, with local recurrence seen in less than 10% of patients.

LOBULAR CAPILLARY HEMANGIOMA (LCH)

(Figs. 3-11 and 3-12)

Definition: Benign polypoid form of capillary hemangioma occurring primarily on skin and mucous membranes.

Synonyms: Pyogenic granuloma; pregnancy tumor; epulis gravidarum. The term pyogenic granuloma is a misnomer in that this lesion is neither an infectious process nor granulomatous.

Clinical

- No gender predilection; wide age range commonly seen in the fourth and fifth decades of life but uncommon under 16 years of age

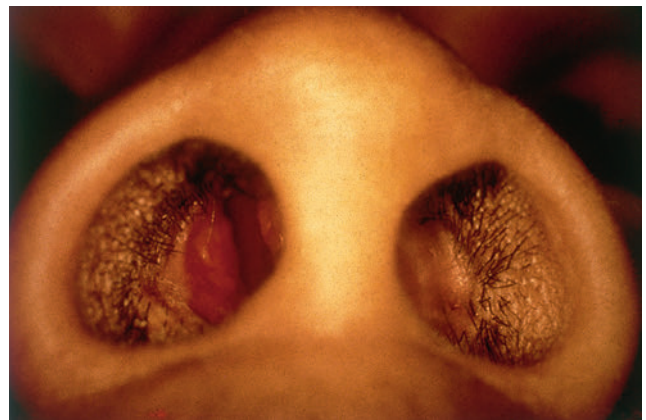


Fig. 3-11. Intranasal lobular capillary hemangioma characterized by a smooth lobulated, polypoid red mass.

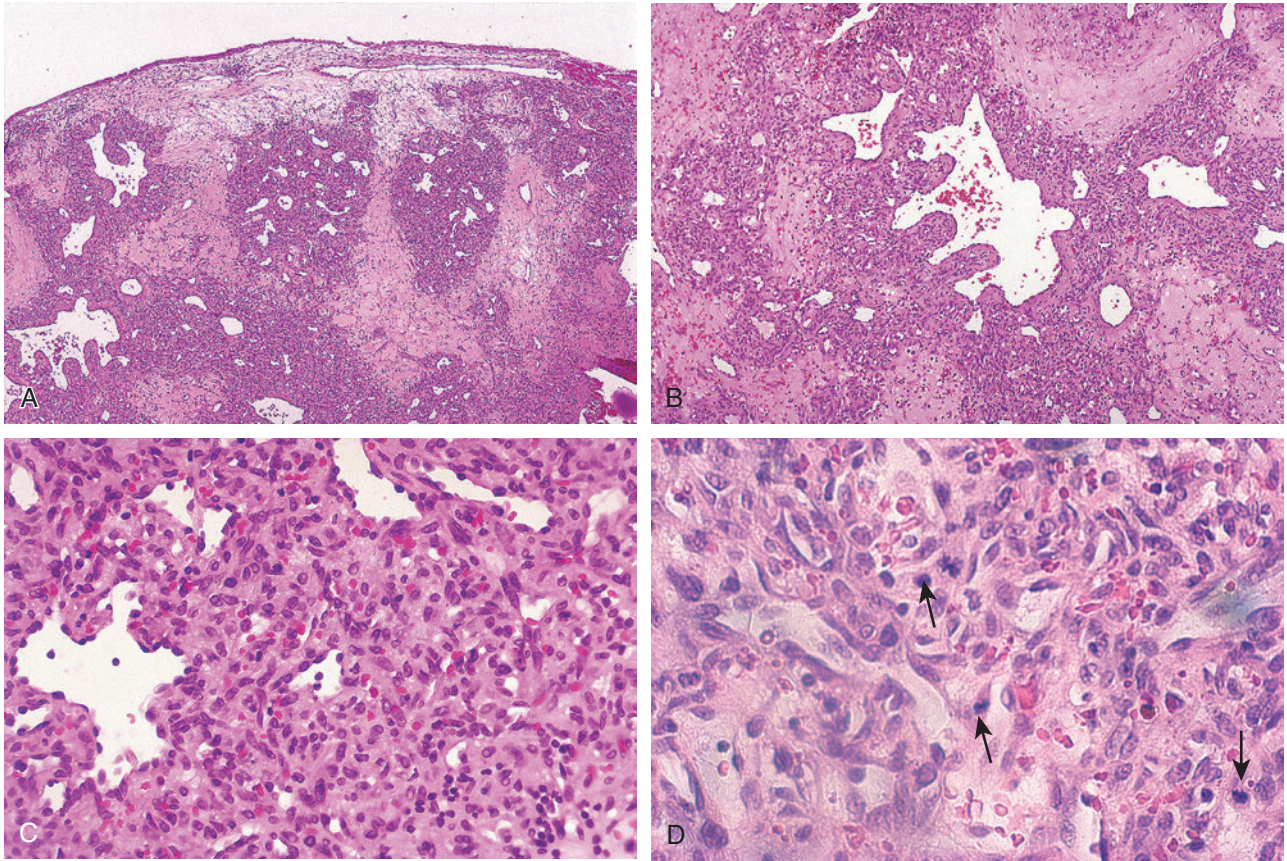


Fig. 3-12. Intranasal lobular capillary hemangioma.

A, The lesion is submucosal and composed of cellular lobules consisting of dilated, irregularly shaped vascular spaces and surrounded by a cellular proliferation. **B** and **C,** The blood vessels may ramify with a “staghorn” appearance, but there is no intercommunicating of the vascular channels; the vessels are lined by flattened endothelial cells and are surrounded by granulation tissue with a chronic inflammatory cell infiltrate. The lobular pattern and admixture of cell types contrasts to sinonasal glomangiopericytoma, which is characterized by a diffuse growth composed of single cell type. **D,** Increased mitotic figures may be present (*arrows*) and have been referred to as “active” lobular capillary hemangiomas. This finding does not portend adverse behavior to the lesion.

- Most often identified in the anterior portion of the nasal septum referred to as Little’s area or Kisselbach’s triangle; next most common sinonasal location is the tip of the turbinates.
- Hemangiomas of the sinonasal tract tend to be mucosally based but also may arise from within the osseous components of this region (intraosseous hemangiomas).
- Aside from the lobular capillary hemangioma, other types of hemangiomas of the sinonasal cavity and nasopharynx are rare.
- Most common clinical complaint is epistaxis; an obstructive painless mass may be present.
- Pathogenesis remains unclear:
 - A minority of cases may be associated with prior trauma.
 - LCH may occur in association with pregnancy and in association with oral contraceptive use, suggesting that hormonal factors may be involved.
 - A hormonal role is further supported by the regression of these tumors following parturition; however, immunohistochemical evaluation failed to identify estrogen or progesterone receptors in any of these tumors.
 - The mechanism for the regression of pregnancy-related pyogenic granuloma after parturition remains unclear; proposed mechanisms for regression include the absence of vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2), causing blood vessels to regress:
 - Amount of VEGF has been found to be high in the LCH in pregnancy and almost undetectable after parturition, suggesting that a lack of

VEGF is associated with apoptosis of endothelial cells and regression of these tumors.

- No role for Ang-2 alone in regression has been found.

Pathology

Gross

- Smooth, lobulated, polypoid red mass measuring up to 1.5 cm in diameter

Histology

- Characterized by a submucosal vascular proliferation arranged in lobules or clusters composed of central capillaries and smaller ramifying tributaries:
 - Central capillaries vary in caliber, as well as in shape, and in more “mature” lesions may show a “staghorn” appearance.
- Endothelial cell lining may be prominent and may display endothelial tufting, as well as mitoses, but atypical mitoses are not identified:
 - Designation of “active” LCH can be used in conjunction with those tumors showing an increase of mitotic activity, but these “active” lesions carry no additional risk of aggressive behavior or of transformation to an angiosarcoma.
- There is no intercommunication of vascular spaces as seen in angiosarcomas nor is there true cytologic atypia or atypical mitoses.
- Surrounding and intimately associated with the vascular component is granulation tissue and a mixed chronic inflammatory cell infiltrate.
- Surface epithelium is often ulcerated with associated (fibrinoid) necrosis but may show squamous metaplasia with or without hyperplastic changes.
- Immunohistochemistry:
 - Lesional cells are reactive for CD31, CD34, and Factor VIII-related antigen; androgen receptor (nuclear) reactivity may be present.
 - No immunoreactivity is present for glucose transporter 1 (GLUT1), human herpesvirus 8 (HHV-8).

Differential Diagnosis

- Sinonasal-type hemangiopericytoma-like tumor:
 - Diffuse growth pattern composed of a single cell type and presence of perivascular hyalinization contrast to the findings seen in LCH
- Angiofibroma
- Infantile hemangiomas:
 - GLUT1 positive
 - See Section 6, Salivary Gland for more detailed discussion.
- Angiosarcoma

Treatment and Prognosis

- Treatment includes conservative but complete surgical excision of the lesion.

- Prognosis following excision is excellent.
- Recurrences are relatively infrequent.

OTHER BENIGN VASCULAR TUMORS

- Cavernous hemangiomas occur less frequently in the upper respiratory tract when compared with the capillary hemangioma.
- In general, cavernous hemangiomas have a similar clinical presentation to capillary hemangiomas but are more often identified in the turbinates, lateral nasal wall, or within bone (intraosseous) than in the nasal septum.
- Similar to histology of cavernous hemangiomas of other sites, those of the sinonasal tract are composed of multiple, variably sized, dilated and thin-walled, endothelial cell-lined vascular spaces.
- Surgical resection is curative.

SINONASAL HEMANGIOPERICYTOMA-LIKE TUMOR (GLOMANGIOPERICYTOMA) (Figs. 3-13 through 3-15)

Definition: Sinonasal tumor showing perivascular myoid differentiation, typically with indolent biologic behavior.

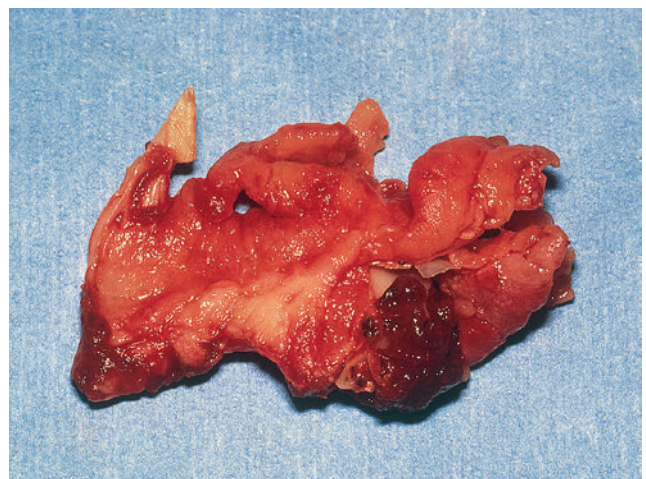


Fig. 3-13. Sinonasal hemangiopericytoma-like tumor.

The resection specimen shows the tumor to be a glistening, red polypoid mass (lower right of the tissue specimen).

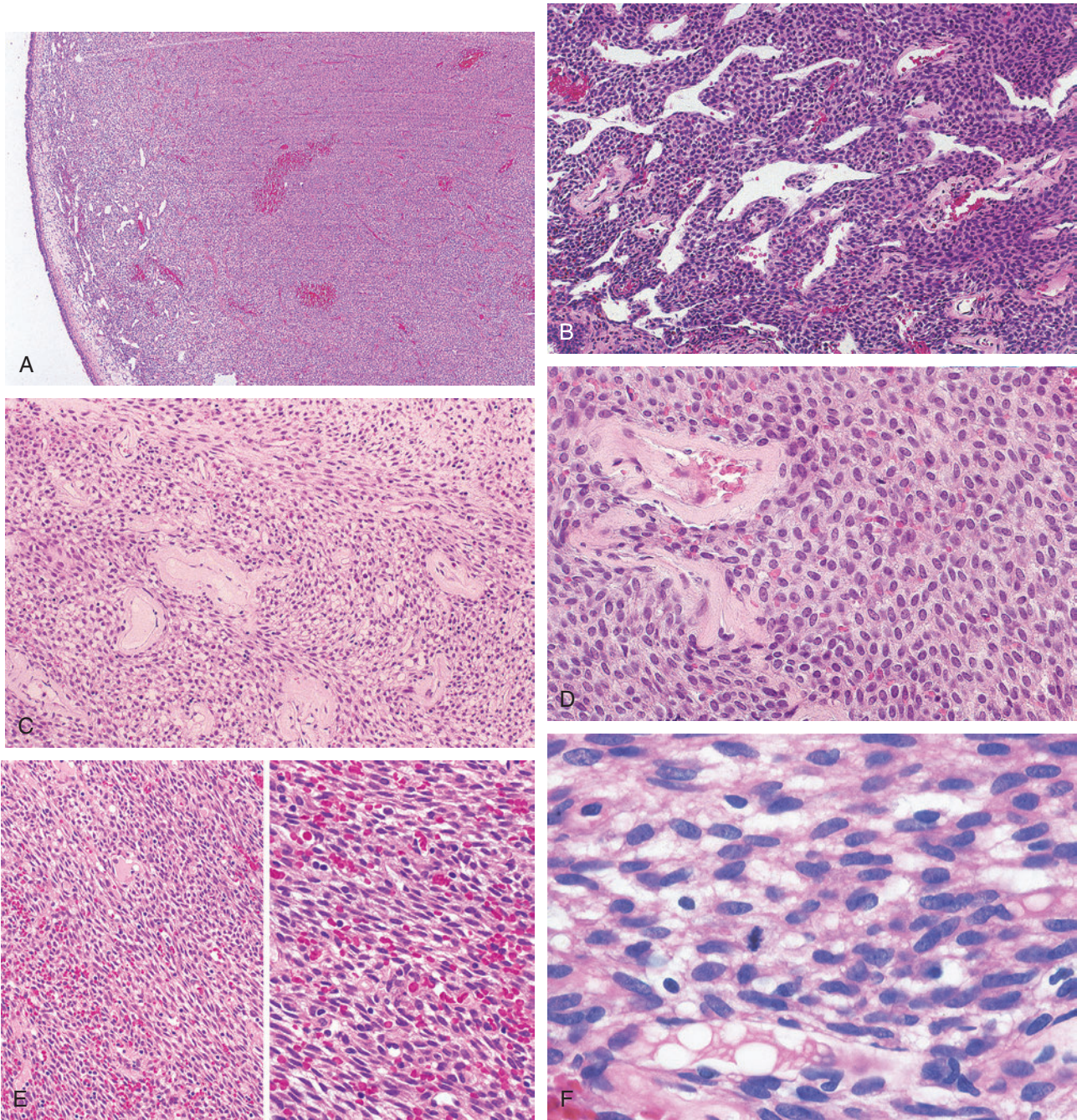


Fig. 3-14. Sinonasal hemangiopericytoma-like tumor.

A, The tumor characteristically is submucosal without involvement of the surface epithelium and is cellular, diffuse in its growth, and well vascularized; the vascular spaces toward the surface are readily apparent as compared with compressed vascular spaces within the depth of the lesion. **B,** The neoplastic cells are tightly packed with hyperchromatic nuclei and situated in and around endothelial-lined vascular spaces; the latter appear dilated and irregularly shaped, but there is no intercommunication of the vascular channels. **C,** A characteristic finding relative to the vascular spaces is the presence of perivascular (peritheliomatous) hyalinization that in conjunction with the cytomorphology assists in recognizing this tumor. **D,** The cells are uniform in size and shape and have round to oval nuclei with fine nuclear chromatin and an indistinct cytoplasm; perivascular hyalinization is present. **E,** In some tumors the cells are spindle-shaped; in this densely cellular tumor there is compression of vascular spaces, which appear slit-like instead of dilated and irregularly shaped; extravasation of erythrocytes is present. **F,** In any given tumor nuclear pleomorphism and scattered mitotic figures may be present, but usually marked pleomorphism, increased mitotic activity, necrosis, and invasive growth are not seen except for (multiply) recurrent tumors and/or in overtly malignant tumors.

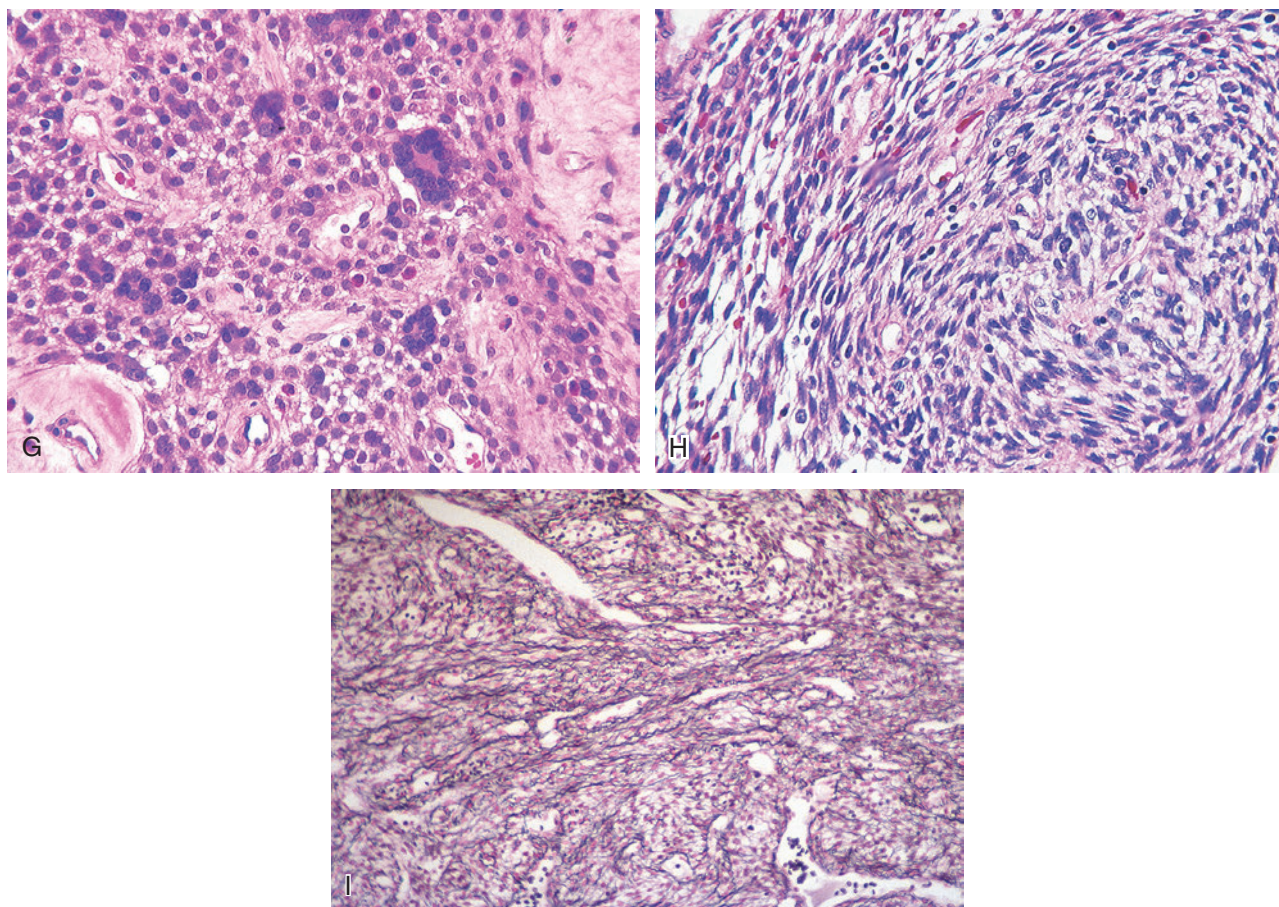


Fig. 3-14, cont'd

G, Multinucleated giant cells may focally be present. **H**, An unusual feature may include a whorling pattern of growth. **I**, Reticulin stain shows envelopment of individual pericytes by the black staining reticulin fibers.

Synonyms: Sinonasal-type hemangiopericytoma; sinonasal glomus tumor

NOTES:

- The classification of this sinonasal tumor has evolved from its designation for the last several decades as sinonasal hemangiopericytoma-like tumor, reflecting the uncertainty of its relationship to soft tissue hemangiopericytoma, to the current designation of sinonasal glomangiopericytoma, reflecting a perivascular myoid differentiation.
- The current classification of soft tissue hemangiopericytoma incorporates it within the spectrum solitary fibrous tumor (SFT) based on the presence of *NAB2-STAT6* gene fusion and STAT6 immunoreactivity.
- Limited studies to date have shown that sinonasal hemangiopericytoma-like tumors are negative for *NAB2-STAT6* gene fusion and/or STAT6 immunoreactivity, precluding classification within the spectrum of SFT and soft tissue hemangiopericytoma.

- Genetic abnormalities seen in association with glomus tumor and pericytoma include *miR143-NOTCH* fusions and *GLI1*, respectively, but neither NOTCH or GLI reported in sinonasal hemangiopericytoma-like tumor.
- Based on the limited genetic studies reported in the literature to date, it would appear that the sinonasal hemangiopericytoma-like tumor does not merit classification within the spectrum of SFT/soft tissue hemangiopericytoma or glomangiopericytoma but perhaps does merit the retention of the designation sinonasal hemangiopericytoma-like tumor, although its eventual classification based on more defining molecular findings may yet to be determined.

Clinical

- Represents less than 1% of all sinonasal tract tumors
- No gender predilection; occurs over a wide age range but is most commonly seen in the sixth to seventh decades of life

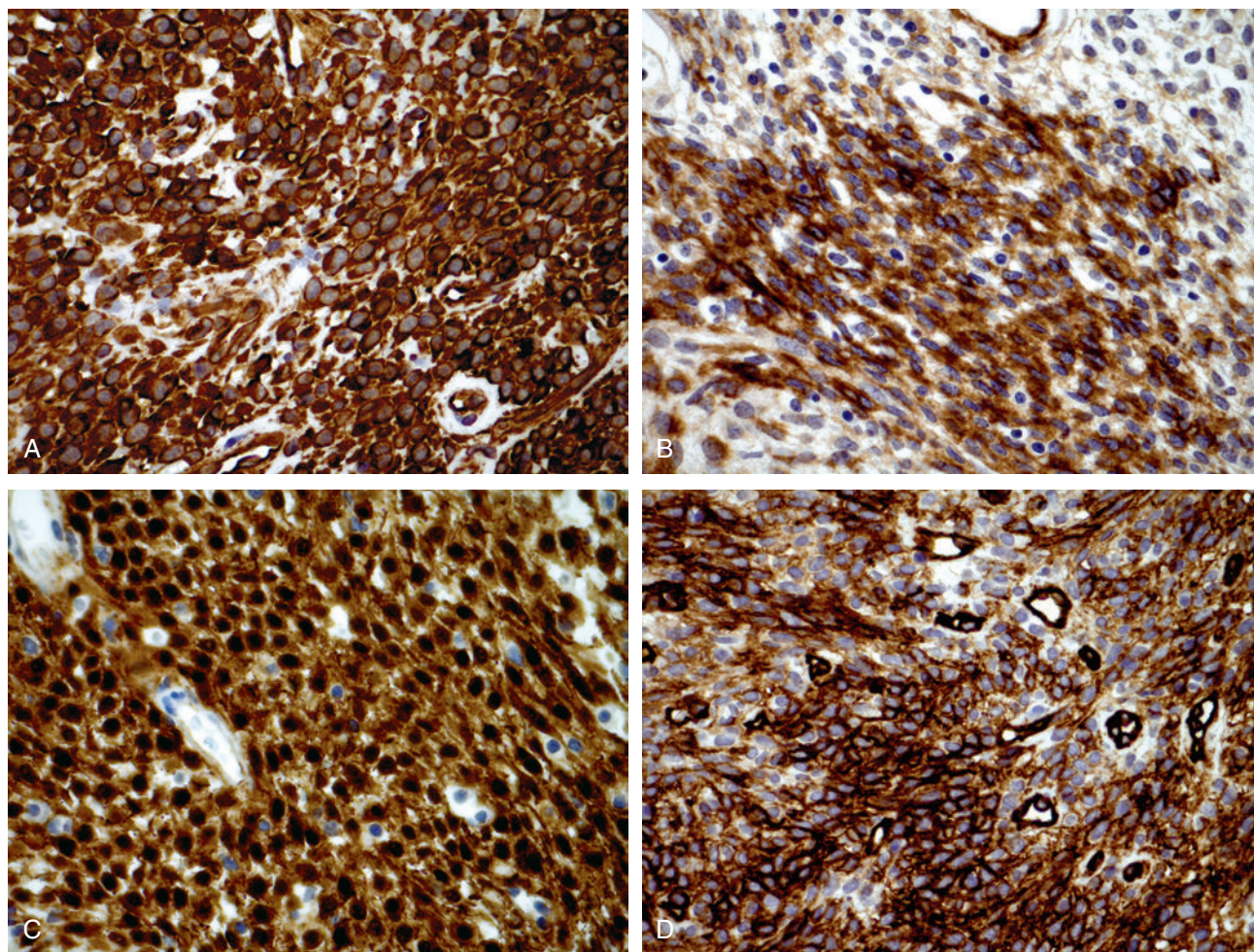


Fig. 3-15. Immunohistochemical staining in sinonasal-type hemangiopericytoma.

Immunohistochemical staining of sinonasal hemangiopericytoma-like tumor includes **A**, vimentin; **B**, muscle specific actin; **C**, β -catenin (nuclear); and **D**, CD34, which occasionally can be identified and does not exclude this diagnosis in a lesion with typical light microscopic features and absence of STAT6 immunostaining, the latter present in solitary fibrous tumors.

- Typically presents as a unilateral nasal mass with obstruction and epistaxis; extension into adjacent paranasal sinuses may occur, but isolated involvement to a paranasal sinus is uncommon.
- Radiology:
 - Opacification of the involved sinus
 - Bone erosion due to pressure may be seen.
 - Arteriographic findings reveal a richly vascular neoplasm.
- There are no known etiologic factors.
- May rarely cause oncogenic osteomalacia (OO):
 - OO is a rare paraneoplastic syndrome of osteomalacia due to phosphate wasting.
 - Phosphaturic mesenchymal tumor (mixed connective tissue variant) extremely rare, distinctive tumor frequently associated with OO
 - Overexpression of fibroblast growth factor-23 (FGF-23), a phosphaturic hormone, shown in phosphaturic mesenchymal tumor

- Phosphaturic mesenchymal tumor is a soft tissue tumor histologically characterized by:
 - Hemangiopericytoma-like areas and osteoclast-like giant cells with or without osseous and cartilaginous metaplasia
 - "Grungy" calcified matrix identified

Pathology

Gross

- Red to tan-gray, soft to firm polypoid mass of varying size

Histology

- Submucosal, circumscribed, but unencapsulated cellular tumor with effacement of seromucous glands, although seromucous glands may be retained although surrounded by lesional cells.
- Diffuse growth pattern composed of single cell type situated around endothelial-lined vascular spaces

- Lesional cells are usually arrayed in short fascicles, and less often may show storiform, whorled, or even palisaded growth patterns with little intervening stromal collagen.
- Lesional cells are usually uniform with round to oval nuclei, vesicular to hyperchromatic-appearing chromatin, and indistinct eosinophilic cytoplasm; occasionally, spindle-shaped cells are seen.
- Mild nuclear pleomorphism and an occasional mitotic figures can be seen, but typically there is an absence of increased mitotic activity, atypical mitoses, and necrosis.
- Vascular channels range from capillary size to large sinusoidal spaces that may have a “staghorn” or “antler-like” configuration.
- A characteristic but not pathognomonic feature is the presence of perivascular hyalinization.
- Cellular proliferation may compress and obscure blood vessels of smaller size.
- Extravasated erythrocytes are often identified.
- An inflammatory cell component usually including mast cells but also eosinophils is present scattered throughout the tumor.
- Multinucleated (tumor) giant cells can be seen in a minority of cases.
- Fibrosis or a myxoid stroma may be seen, especially in tumors undergoing degenerative change.
- Heterologous metaplastic elements, including bone and cartilage, may occasionally be seen; lipomatous change may also be present.
- Histochemistry:
 - Reticulin stain reveals a distinctive pattern characterized by envelopment of individual pericytes by reticulin fibers.
- Immunohistochemistry:
 - Consistent immunoreactivity for vimentin and smooth muscle actin
 - Majority of cases stain for Factor XIIIa, muscle-specific actin, β -catenin (nuclear) and cyclin D1 (nuclear):
 - Nuclear expression of β -catenin and cyclin D1 represent sign of oncogenic activation and demonstrate that mutational activation of β -catenin and associated cyclin D1 overexpression may be central events in pathogenesis.
- Negative for STAT6
- Typically negative for CD34, but in any given case CD34 staining may be present.
- Variably reactivity for S100 protein
- Typically do not stain for cytokeratins, CD31, Factor VIII-related antigen, desmin, neuron-specific enolase, EMA, CD68, bcl-2, CD99, TLE1, Fli1, and CD117
- Electron microscopy:
 - Pericellular basal lamina, pinocytotic vesicles, intracytoplasmic (thin) filaments, dense bodies, and membranous attachment plaques
- Cytogenetics and molecular biology:
 - Absence of *NAB2-STAT6* gene fusion (this gene fusion reported in solitary fibrous tumors/soft tissue hemangiopericytoma)
 - Absence of *miR143-NOTCH* fusions (these gene fusions reported in glomus tumor)
 - Absence of *GLI1* (this gene fusion seen in reported in pericytoma)

Differential Diagnosis

- Lobular capillary hemangioma
- Nasopharyngeal angiofibroma
- Glomus tumor (glomangioma)
- Solitary fibrous tumor (SFT):
 - In contrast to the solitary fibrous tumor, sinonasal hemangiopericytoma-like tumor lacks the presence of “ropey” keloidal-appearing collagen or amianthoid fibers and bcl-2 staining.
 - Sinonasal hemangiopericytoma-like tumor and SFT may show the presence of CD34 immunoreactivity; however, the extent of CD34 immunoreactivity varies:
 - In sinonasal hemangiopericytoma-like tumor CD34 staining if present is localized and not diffuse.
 - In solitary fibrous tumors CD34 tends to be diffuse and strong.
 - STAT6 immunoreactivity seen in SFT but not in sinonasal hemangiopericytoma-like tumor
 - *NAB2-STAT6* gene fusion seen in SFT but not in sinonasal hemangiopericytoma-like tumor
- Smooth muscle tumors (leiomyoma and leiomyosarcoma)
- Benign and malignant fibrohistiocytic neoplasms
- Synovial sarcoma
- Mesenchymal chondrosarcoma

Treatment and Prognosis

- Surgery is the preferred treatment and should include complete excision to include tumor-free margins.
- Considered radioresistant neoplasms
- Indolent behavior with overall 5-year survival rates of greater than 90%
- Local recurrence may occur in as high of 30% of cases and is likely due to inadequate surgical excision:
 - Recurrence can be anticipated over extended follow-up periods (1 to 2 decades).
- Aggressively behaving sinonasal hemangiopericytoma-like tumors are uncommon and include tumors that are locally destructive or are metastatic.
- Findings potentially linked to aggressive behavior include:
 - Large tumor size (greater than 5 cm)
 - Marked nuclear pleomorphism
 - Increased mitotic activity

- Necrosis
- Invasive growth (e.g., bone)
- Proliferation index of greater than 10%
- Metastatic tumor is uncommon; if it occurs, spread usually is to regional lymph nodes and lung and is preceded by (one or more) recurrent tumor.

SINONASAL TRACT MENINGIOMA (Fig. 3-16)

- Meningiomas are benign neoplasms of meningothe-
lial cells representing from 13% to 18% of all intra-
cranial tumors; occurrence outside the central
nervous system is considered ectopic; ectopic menin-
giomas are divided into:
 - Primary ectopic meningiomas representing those
tumors with no identifiable central nervous
system connection
 - Secondary ectopic meningiomas representing those
tumors with central nervous system connection
- For a more complete discussion see Section 7, Ear
and Temporal Bone.
- Most common sites of occurrence of the ectopic
meningiomas of the head and neck region include
the middle ear and temporal bone and sinonasal
cavity; less commonly, oral cavity and parotid gland.
- Sinonasal tract meningiomas most often involve the
nasal cavity, or a combination of nasal cavity and
paranasal sinuses; less frequently, involvement may
be isolated to the nasopharynx, frontal sinus, or
sphenoid sinus.
- In the sinonasal cavity, symptoms include nasal
obstruction, epistaxis, headache, pain, visual distur-
bances, and facial deformity.
- Tumors may erode the bones of the sinuses with
involvement of surrounding soft tissues, the orbit,
and occasionally the base of the skull.
- Grossly, these tumors appear as a polypoid mass;
often, the tumor is curetted out and received as frag-
ments of solid, white tissue; a gritty consistency may
be noted.
- Among the histologic subtypes of meningioma, the
meningotheliomatous type is the most common in
the sinonasal cavity:
 - Histologic features include a lobular growth
pattern with tumor nests separated by a variable
amount of fibrous tissue.
 - Cells have a whorled arrangement and have
round to oval or spindle-shaped nuclei with pale-
staining cytoplasm and indistinct cell borders.
 - Characteristically, the nuclei have a punched-out
or empty appearance resulting from intranuclear
cytoplasmic inclusions.
 - Psammoma bodies, typical and numerous in
intracranial meningothe-
lial meningiomas, may be

seen but are not as common in the ectopically
located meningiomas.

- Immunohistochemistry:
 - Reactivity with epithelial membrane antigen
(EMA) and vimentin
 - Cytokeratins can be positive:
 - As a whole may be positive in 20% of cases
 - May approach 40% positivity in epithelial
variants
 - No immunoreactivity with neuroendocrine markers
(chromogranin and synaptophysin, others)
- Surgical removal is the preferred treatment:
 - Complete surgical excision may be difficult to
achieve, resulting in recurrence; recurrence rates
range up to 30%.
- Following the histologic diagnosis, it is essential to
exclude spread from a primary intracranial neoplasm.

ECTOPIC PITUITARY ADENOMA (EPA) (Fig. 3-17)

Definition: Pituitary adenoma that arises in upper
aerodigestive tract mucosal sites from remnants of
Rathke's pouch without any continuity/connection with
the sella turcica.

NOTE: Pituitary neoplasms originating from their
usual origin in the sella turcica may occasionally extend
into the sinonasal tract or nasopharynx and appear to
present as a primary neoplasm of those regions. There-
fore, prior to rendering a possible diagnosis of EPA,
radiographic analysis is required to exclude derivation
from the normally situated pituitary gland within the
sella turcica.

Clinical Features

- No gender predilection; occurs in adults
- Clinical presentation may include airway obstruc-
tion, chronic sinusitis, visual field defects, cere-
brospinal fluid leakage, and endocrinopathic
manifestations (e.g., Cushing's syndrome, hirsutism).
- Most common ectopic sites of occurrence are the
sphenoid sinus followed by the nasopharynx:
 - Other less common sites include the nasal cavity
and ethmoid sinus; rarely, may involve the clivus.

Pathology

Gross

- Polypoid appearance

Histology

- Submucosal epithelioid neoplastic proliferation with
solid, organoid, and trabecular growth patterns:
 - Epithelioid cells have round nuclei with a
dispersed nuclear chromatin pattern and granular
eosinophilic-appearing cytoplasm.

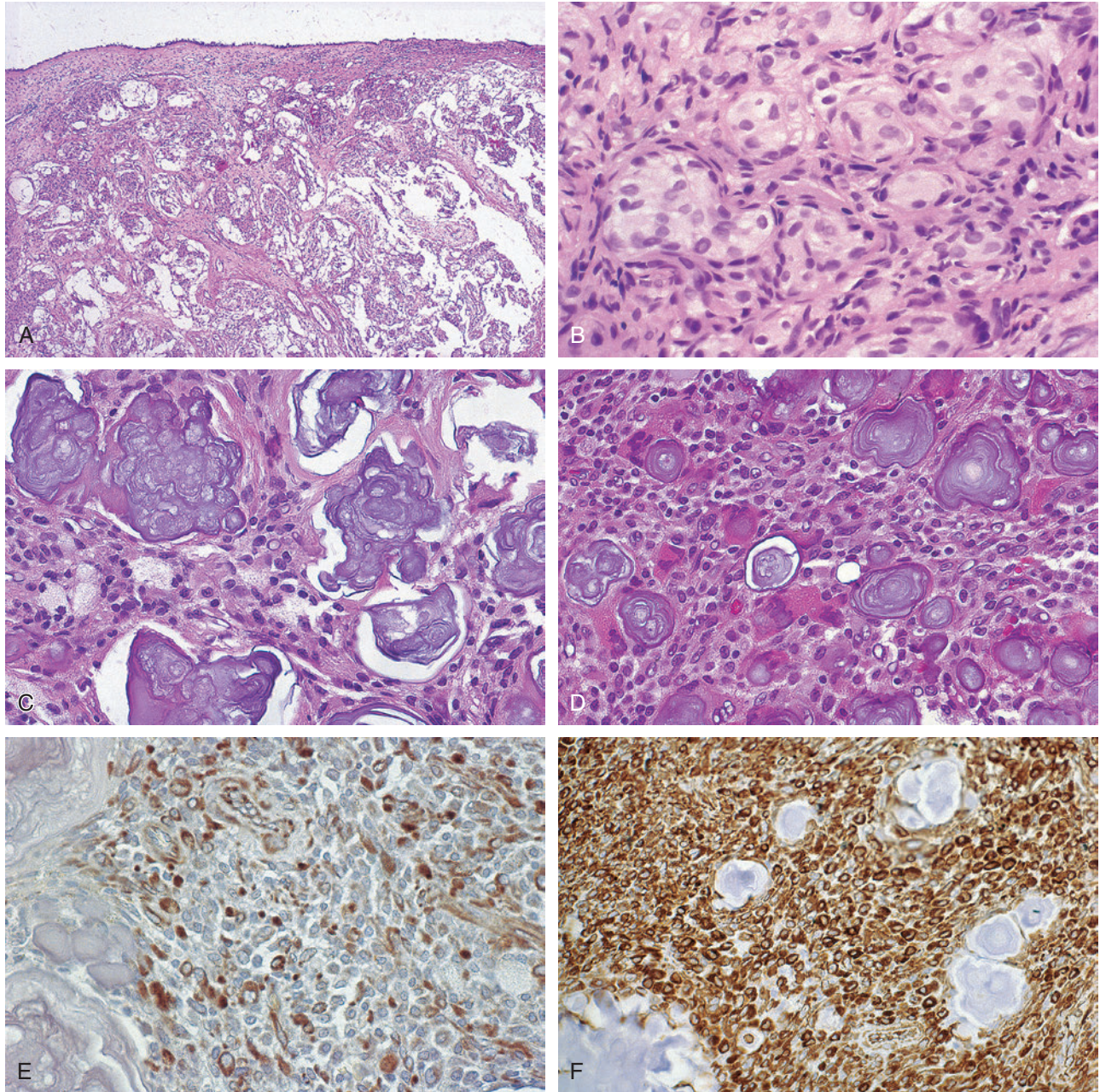


Fig. 3-16. Sinonasal meningioma.

A, Submucosal cellular proliferation with lobular growth pattern and tumor nests separated by a variable amount of fibrous tissue. **B**, At higher magnification the tumor nests have a whorled arrangement composed of cells with round to oval to spindle-shaped nuclei with pale-staining cytoplasm and indistinct cell borders; characteristically, the nuclei have a punched-out or empty appearance resulting from intranuclear cytoplasmic inclusions. **C**, Psammoma bodies as seen in this sinonasal meningioma tend to be less common in ectopically located meningiomas as compared to **D**, intracranial meningiomas; meningiomas are immunoreactive for **(E)** epithelial membrane antigen and **(F)** vimentin.

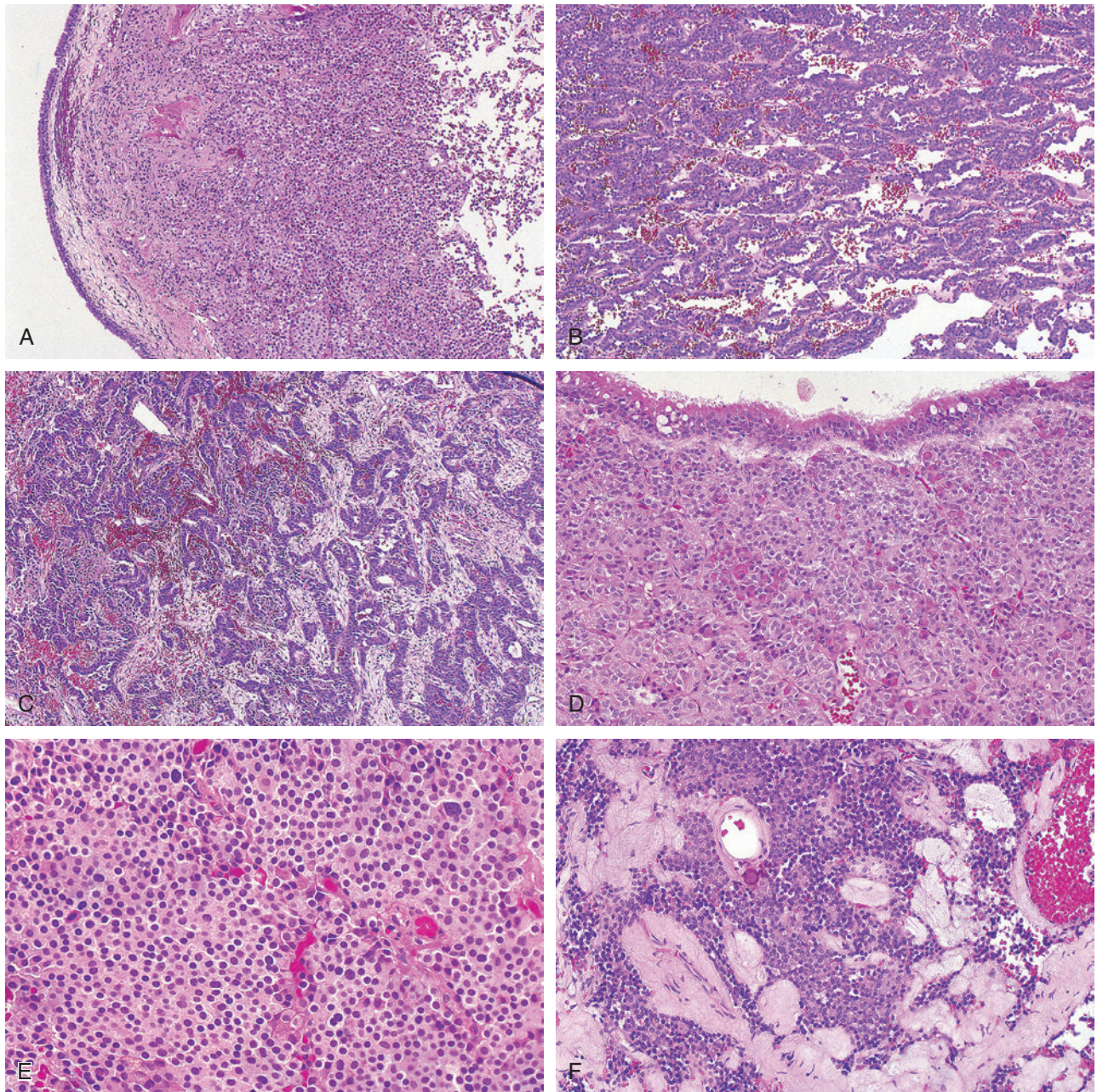
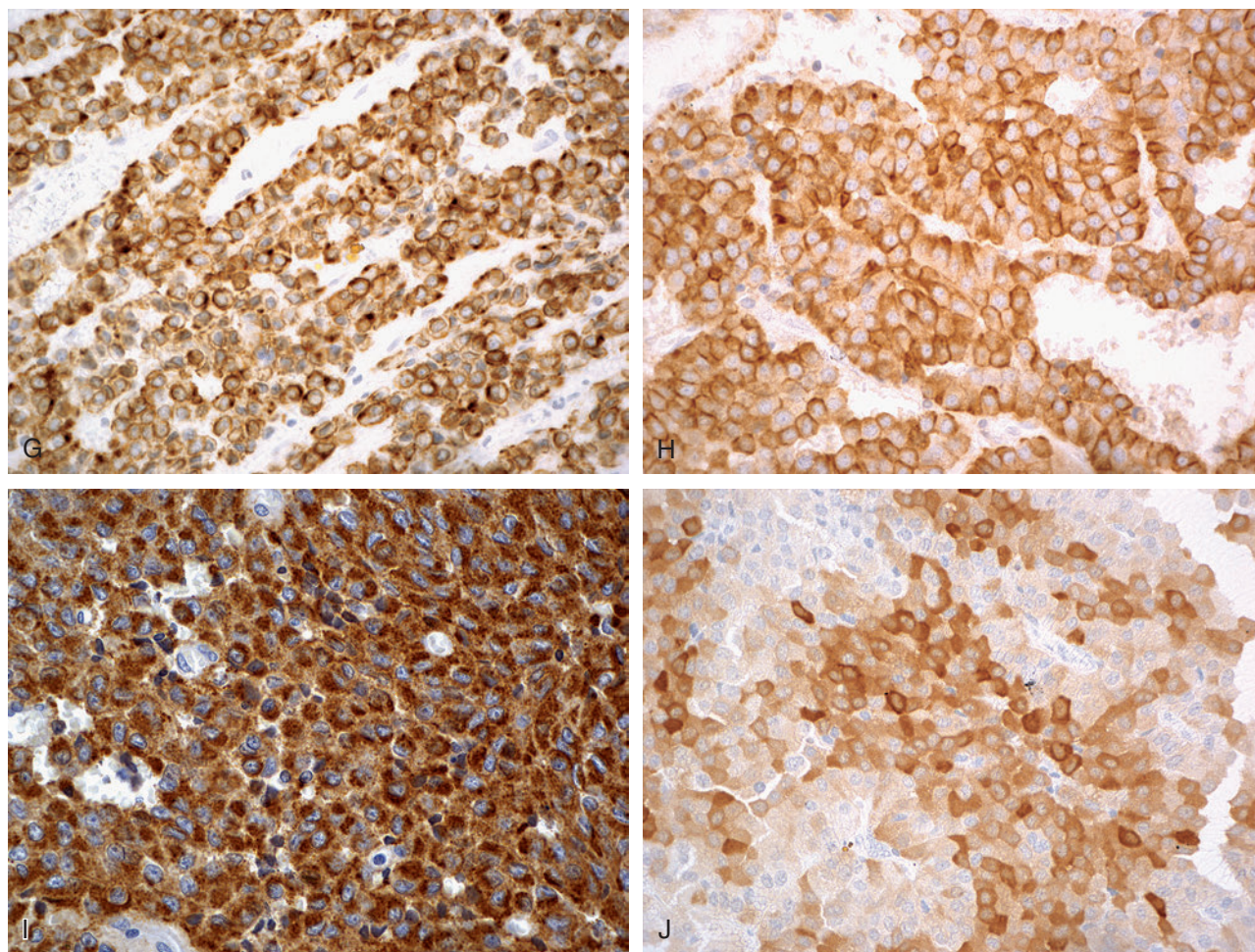


Fig. 3-17. Ectopic pituitary adenoma.

A, Submucosal neoplastic proliferation showing solid growth; additional growth patterns may include **(B)** trabecular; **(C)** ribbon-like; **(D and E)** uniform epithelioid cells with round nuclei and dispersed nuclear chromatin pattern; cells with granular eosinophilic-appearing cytoplasm and plasmacytoid-appearing cells are present. **F**, Extracellular hyalinization and calcifications, including psammoma body concretions, may be identified.

**Fig. 3-17, cont'd**

Immunoreactivity is present for **(G)** cytokeratin (focally with paranuclear punctuate staining), **(H)** chromogranin, as well as a variety of pituitary hormones, among the latter including **(I)** prolactin and **(J)** luteinizing hormone.

- Plasmacytoid-appearing cells may be present.
- Mild to moderate nuclear pleomorphism may be identified.
- Scattered mitotic figures may be present but atypical mitoses are not identified; necrosis is absent.
- Gland-like spaces may be seen; absence of squamous differentiation
- Calcifications and/or psammoma-like concretions may be identified.
- Infiltrative growth can be identified, including in and around residual seromucous glands as well as into bone.
- Immunohistochemistry:
 - Cytokeratin (AE1/AE3, CAM5.2, others) positive:
 - Tends to be diffuse and strong, and show paranuclear dot-like pattern
 - Neuroendocrine markers positive, including:
 - Chromogranin, synaptophysin, CD56, neuron-specific enolase
 - Vimentin and S100 protein positive:
 - S100 protein lacks peripheral sustentacular staining pattern seen in paragangliomas and olfactory neuroblastoma
 - Pituitary hormones, including growth hormone, adrenocorticotrophic hormone (ACTH), prolactin, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH):
 - Reactivity with two or more hormones, so-called plurihormonal pituitary adenoma, may be seen in up to approximately 50% of cases.
 - Approximately one third of cases express a single hormone:
 - Prolactin most common
 - In up to approximately 20% reactivity with pituitary hormone markers may be absent:
 - Referred to as null cell pituitary adenoma.

TABLE 3-3 Ectopic Pituitary Adenoma (EPA), Olfactory Neuroblastoma (ONB), Carcinoid and Paraganglioma: Comparison of Sites of Occurrence and Immunohistochemical Findings

	EPA	ONB	Carcinoid	Paraganglioma
Location	Sphenoid sinus » nasopharynx	Roof of nasal cavity	Uncommon in H&N; rarely occurs in SNT	Neck, ME; rarely if ever identified in SNT
Cytokeratins	Positive, diffuse/strong	Negative in majority of cases; may be positive in scattered lesional cells	Positive, diffuse/strong	Negative
NE markers	Positive	Positive	Positive	Positive
S100	Positive in lesional cells but not at periphery of lobules	Positive at periphery of lobules as well as in lesional cells	Positive in lesional cells but not at periphery of lobules	Positive at periphery of lobules
Pituitary markers	Positive in majority of cases; may be negative	Negative	Negative	Negative
Calretinin	Negative	Positive	Negative	Negative
Ki67	Low	Low: grades* 1, 2 High: grades* 3, 4	Low	Low

H&N, Head and neck; ME, middle ear; SNT, sinonasal tract.

Cytokeratins—AE1/AE3, CAM5.2, OSCAR; NE markers—neuroendocrine markers including synaptophysin, chromogranin, CD56.

*Refers to histologic grades.

- Low proliferation rates (less than 5%) by Ki67 (MIB1) staining
- Calretinin negative
- p53 negative

- Although benign, EPAs may be large and infiltrative, including into bone precluding surgical extirpation; in such cases radiation therapy can be used.
- Rarely, malignant transformation may occur.

Differential Diagnosis (Table 3-3)

- Paraganglioma
 - Rarely if ever occurs in the sinonasal tract
- Olfactory neuroblastoma (ONB)
 - ONBs predominantly arise in the superior aspect of the nasal cavity and rarely originate from the sphenoid sinus, the most common location for EPA.
 - Presence of diffuse and intense cytokeratin staining as seen in EPA essentially excludes a diagnosis of ONB, which is typically cytokeratin negative or at most only focally positive.
- Neuroendocrine carcinoma (e.g., carcinoid tumor):
 - Carcinoid tumor (well-differentiated neuroendocrine carcinoma) is so uncommon in the sinonasal tract as to be considered nonexistent.
- Malignant epithelial neoplasms (e.g., SNUC, other)

Treatment and Prognosis

- Wide surgical resection is the preferred treatment:
 - Complete removal may prove curative without recurrent or progressive tumor, and with resolution of endocrinopathic effects associated with the tumor.
 - Recurrence not uncommon especially for large tumors and/or incompletely excised tumors
- Medical therapy, bromocriptine (dopamine agonist) may be employed to control endocrinopathic effects of the tumor.

SOLITARY FIBROUS TUMOR (SFT), EXTRAPLEURAL (Fig. 3-18)

Definition: Solitary fibrous tumor (SFT) is a distinctive neoplasm composed of CD34-positive fibroblasts with hemangiopericytoma-like vascular pattern that are typically a (pleural) serosal-based proliferation but may occur in extrapleural sites.

NOTE: Current soft tissue classification of tumors links solitary fibrous tumor and hemangiopericytoma.

Clinical

- SFTs are rare but do occur in the upper aerodigestive tract, primarily involving the nasal cavity and paranasal sinuses.
- Patients with tumors in these sites present with nasal obstruction:
 - Usually, the symptoms have been present for an extended period of time (a year or more).

Pathology

- These tumors typically are polypoid.

Histology

- Unencapsulated tumor composed of a variably cellular proliferation of bland spindle-shaped cells lacking any pattern of growth and associated with

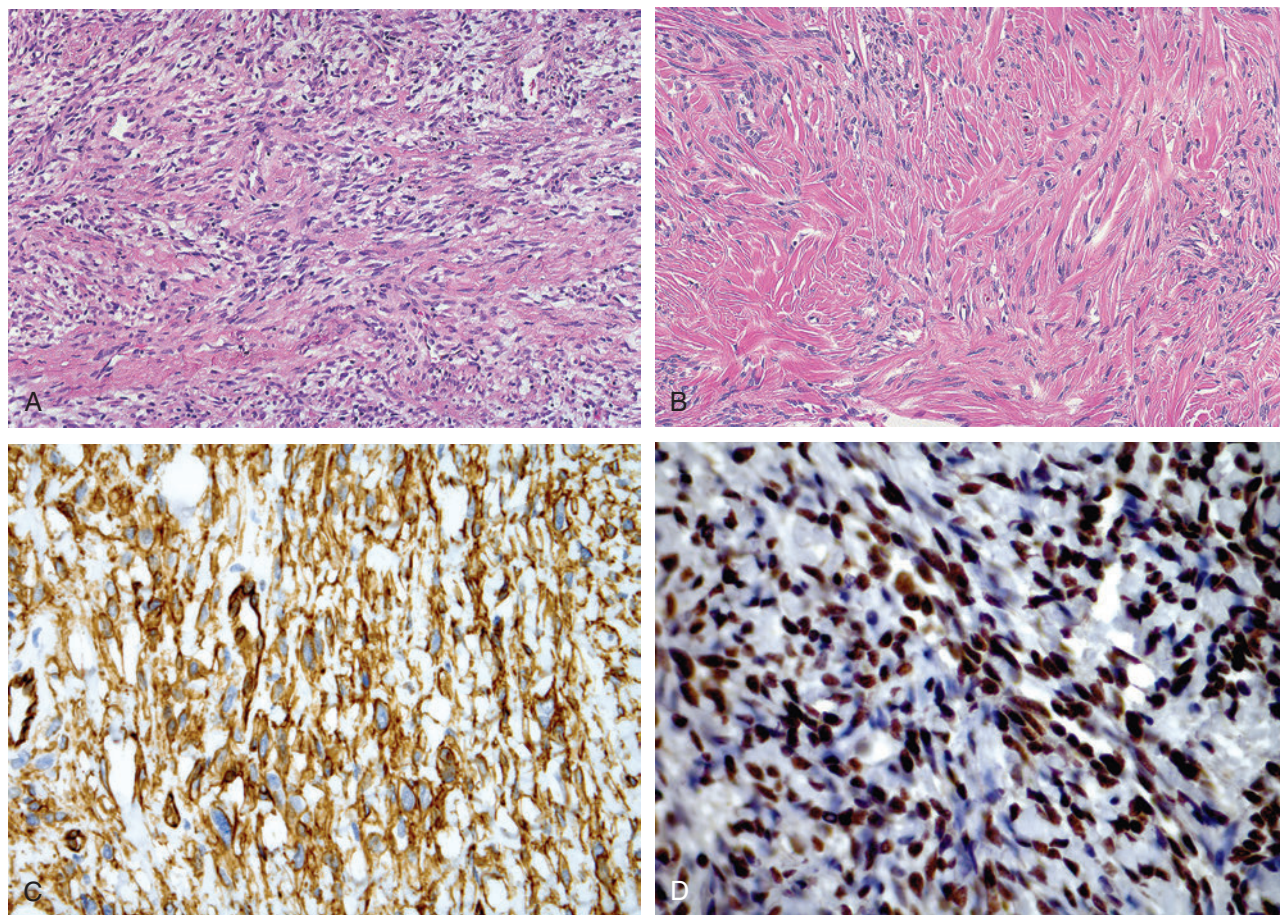


Fig. 3-18. Sinonasal solitary fibrous tumor.

A, Sinonasal unencapsulated tumor composed of a variably cellular proliferation of bland spindle-shaped cells lacking any pattern of growth with associated ropey collagen or **(B)** keloidal collagen bundles. **C**, The cells are immunoreactive for CD34 and **(D)** STAT6 (nuclear staining).

ropey, keloidal collagen bundles and associated thin-walled vascular spaces.

- Vascular spaces may be focally prominent and often have the branching appearance as seen in hemangiopericytomas.
- Rare mitoses may be seen, but the mitotic rate is not excessive; atypical mitoses are absent and necrosis is absent.
- Histologic variants include:
 - Lipomatous SFT:
 - Rare variant that consists of histologically benign SFT admixed with areas of mature fat
 - SFT with giant cells (giant cell angiofibroma):
 - Giant cell-rich form of SFT
- Immunohistochemistry:
 - Reactivity for CD34 (80% to 90%), CD99 (70%) and bcl-2 (30%), EMA (30%) and actin (20%):
 - CD34 reactivity tends to be diffuse and strong.
 - STAT6 immunoreactivity (nuclear)

- Absence of S100 protein, desmin, and cytokeratins

- Cytogenetics and molecular genetics:
 - Overexpression of *NAB2-STAT6* gene fusion:
 - Establish *NAB2-STAT6* as the defining driver mutation of SFT
 - Rearrangements of long arm of chromosome 12

Differential Diagnosis

- Sinonasal hemangiopericytoma-like tumor
- Smooth muscle tumors (leiomyoma)
- Peripheral nerve sheath tumors
- Fibrohistiocytic tumors
- Fibromatosis
- Nasopharyngeal angiofibroma

Treatment and Prognosis

- Given their tendency to be polypoid, solitary fibrous tumors of the sinonasal tract are amenable to complete surgical resection.

- Complete surgical resection is usually curative:
 - Recurrences generally a function of incomplete excision
 - SFTs of the nasopharynx may be more difficult to completely excise; despite incomplete resection, these tumors are not generally associated with adverse biologic behavior at this anatomic location.
 - Malignant transformation of SFT may occur in particular for intrathoracic or soft tissue but rarely for those of head and neck sites; histologic features associated with malignancy include:
 - Increased cellularity, pleomorphism, and increased mitotic activity ($>4/10$ high-power fields)
- BENIGN PERIPHERAL NERVE SHEATH TUMORS (BENIGN SCHWANNOMA AND NEUROFIBROMA) (Fig. 3-19)**
- This category of tumors includes benign schwannoma and neurofibroma.
 - For a more complete discussion of these tumor types see Section 2, Oral Cavity; 4, Neck; and 7, Ear and Temporal Bone.
 - Benign peripheral nerve sheath tumors of the head and neck are common, perhaps accounting for as many as 45% of all cases; benign peripheral nerve sheath tumors of the sinonasal tract (and nasopharynx) are uncommon, accounting for less than 4%.
 - In the sinonasal tract, schwannomas are substantially more common than neurofibromas.
 - Adults are most commonly affected, with no gender predilection.
 - Patients present with symptoms related to nasal obstruction and epistaxis:
 - Visual disturbances due to intracranial extension of the tumor may occur.
 - These tumors may cause pressure erosion of bone.
 - Nasopharyngeal involvement may result in unilateral serous otitis media.
 - There is no association with neurofibromatosis.

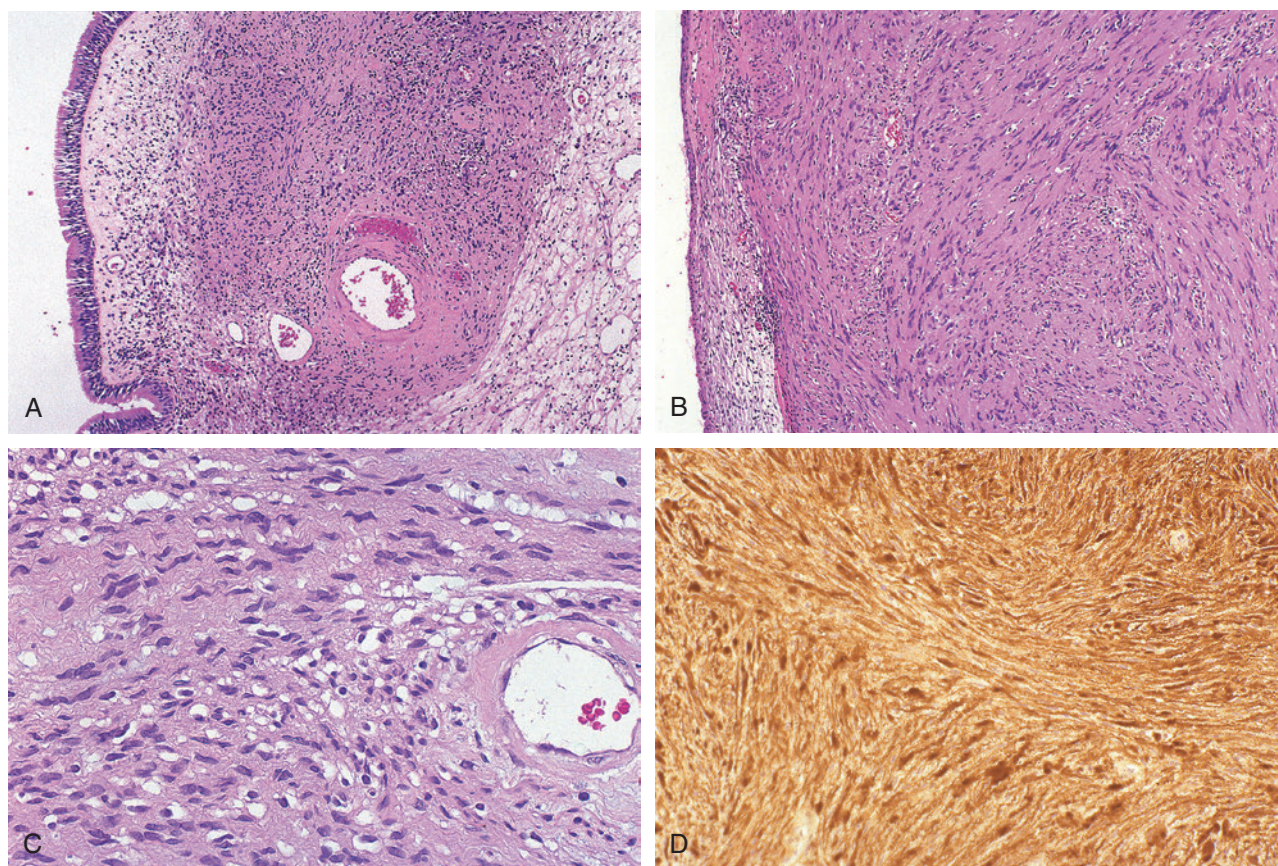


Fig. 3-19. Sinonasal benign peripheral nerve sheath tumor (benign schwannoma).

A, The tumor is submucosal, unencapsulated, and composed of a bland spindle-shaped cellular proliferation with associated blood vessels with perivascular hyalinization. **B,** Storiform growth of cells with spindle-shaped nuclei showing characteristic wavy or buckled appearance. **C,** At higher magnification the wavy nuclei can be seen as well as associated inflammatory cells and a blood vessel with perivascular hyalinization. **D,** Diffuse S100 protein immunoreactivity is present.

Benign Schwannoma

- Unlike their soft tissue counterparts, benign schwannomas of the upper aerodigestive tract are unencapsulated although circumscribed.
- Aside from the lack of encapsulation, the histologic features are similar to those described for benign peripheral nerve sheath tumors at other sites.
- These tumors are submucosal, show variable cellularity, including increased cellularity, but significant pleomorphism is not seen.
- Scattered mitotic figures may be present, but the mitotic rate is low and atypical mitoses are not present.
- Immunohistochemistry:
 - Diffuse and intense S100 protein and SOX10 immunoreactivity (cytoplasmic and nuclear pattern) are present.
 - Cytokeratins, actins, desmin, CD34, and epithelial membrane antigen staining are absent.
 - Low proliferation rate less than 5% is seen by Ki67 (MIB1) staining.

- Surgical resection is the preferred treatment and is curative.

Neurofibroma

- Submucosal, circumscribed tumors composed of spindle-shaped cells with “wavy” or buckled, hyperchromatic nuclei, and indistinct cytoplasm
- An associated collagenized and/or myxoid stromal component is present.
- Neoplastic cells are S100 protein (and SOX10) positive but extent of staining is less than that seen in schwannomas.
- Surgical resection is curative.

BENIGN FIBROUS HISTIOCYTOMA (Fig. 3-20)

Definition: Benign neoplasm composed of an admixture of fibroblasts and histiocytic cells.

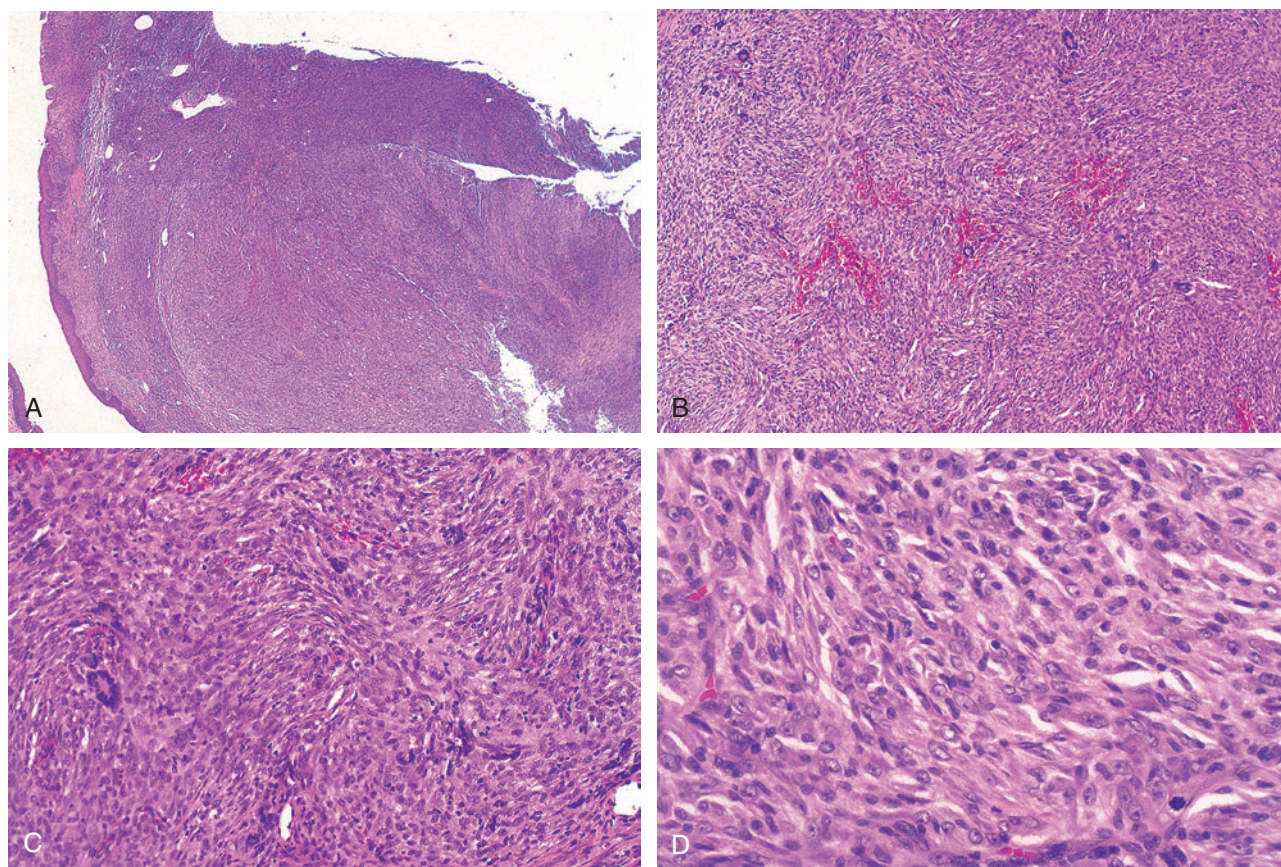


Fig. 3-20. Sinonasal benign fibrous histiocytoma.

A, A submucosal densely cellular proliferation is present. **B** and **C**, The tumor has a fascicular to storiform growth pattern composed of an admixture of spindle-shaped cells (fibroblasts) and epithelioid cells (histiocytes), as well as scattered multinucleated giant cells and scattered chronic inflammatory cells. **D**, Benign fibrous histiocytomas may be cellular with mild cellular pleomorphism and scattered mitotic figures (*upper left*), but in the absence of other features (e.g., anaplasia, atypical mitoses, necrosis), these features are not indicative of malignancy.

Synonyms: Sclerosing hemangioma; cutaneous-derived are called dermatofibroma

Clinical

- Relatively uncommon neoplasm in the head and neck accounting for less than 5% of all fibrous histiocytomas
- More common in men than in women; occurs over a wide age range with a median age in the fifth decade of life
- Excluding cutaneous sites, the most common location in the head and neck is the nasal cavity and paranasal sinuses; other more common sites of occurrence include neck, larynx, and trachea.
- Symptoms vary according to site and include painless mass, nasal obstruction, epistaxis, pain, facial asymmetry, proptosis, loosening of teeth, hemoptysis, dyspnea, and stridor.

Pathology

Gross

- Polypoid or nodular, tan-white to yellow lesions varying in size

Histology

- Submucosal lesion composed of an admixture of spindle-shaped cells (fibroblasts) and epithelioid cells (histiocytes) in a fascicular or storiform growth pattern
- Multinucleated giant cells, an inflammatory cell infiltrate (lymphocytes, plasma cells, and eosinophils), and foam cells are seen scattered throughout the tumor.
- Stroma varies and may consist of collagen production, myxoid change, and hyalinization.
- Vascularity varies from relatively inconspicuous vessels to prominent vascular pattern with striking hyalinization.
- Pleomorphism and mitoses may be seen, but these features in excess or the presence of abnormal mitotic figures suggest malignancy.
- Histologic variants include:
 - Cellular fibrous histiocytoma:
 - Characterized by increased cellularity and more fascicular and less storiform growth pattern
 - Increased mitotic activity (mean 3 mitoses per 10 high-power fields) may be present.
 - Atypical fibrous histiocytoma:
 - Significantly greater nuclear atypia and mitotic activity in a lesion with background of classic fibrous histiocytoma
- Immunohistochemical staining reflects presence of multiple cell types including reactivity for:
 - CD68 (macrophages)
 - S100 protein (Langerhan cells)

- Vimentin
- Desmin may occasionally be reactive.
- No immunoreactivity for CD31, CD34, epithelial markers, endothelial cell markers
- Cellular fibrous histiocytomas commonly express smooth muscle actin.

Differential Diagnosis

- Nodular fasciitis
- Fibromatosis (see Section 4, Neck, for more complete discussion)
- Benign peripheral nerve sheath tumors (benign schwannoma, neurofibroma)
- Leiomyoma
- Solitary fibrous tumor
- Dermatofibrosarcoma protuberans (DFSP):
 - See Section 7, Ear and Temporal Bone, for a more complete discussion.
 - Most frequent on the trunk and extremities
 - Histologically, DFSP infiltrates the dermis and subcutis and in its central aspect is composed of plump fibroblasts arranged in a distinct storiform pattern; cellular pleomorphism is mild and variable mitotic activity is seen.
 - CD34 immunoreactive
 - Wide local excision is the preferred treatment.
- Undifferentiated pleomorphic sarcoma (formerly malignant fibrous histiocytoma)

Treatment and Prognosis

- Complete surgical excision is generally curative.

LEIOMYOMA

(Figs. 3-21 and 3-22)

Definition: Benign tumor of smooth muscle.

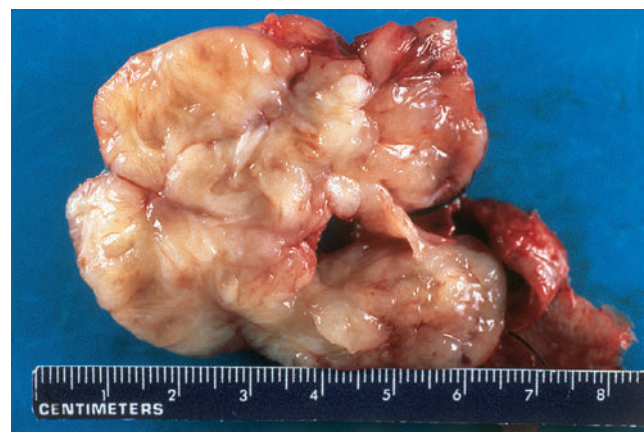


Fig. 3-21. Sinonasal leiomyoma characterized by a tan-white and whorled appearance.

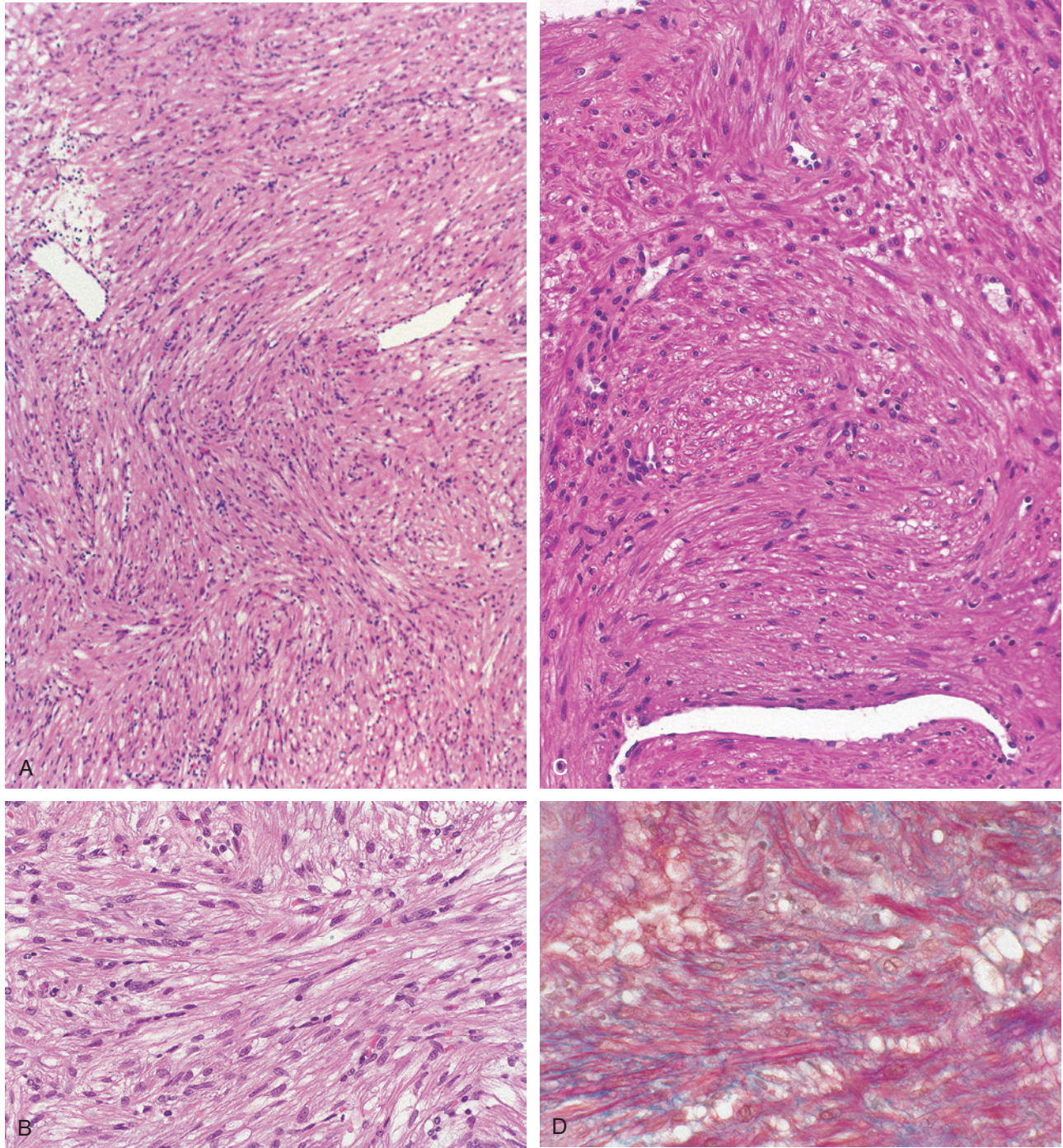


Fig. 3-22. Sinonasal leiomyoma.

A, This spindle cell lesion was submucosal and shows a fascicular growth composed of interlacing cellular bundles and associated vascular spaces. **B**, The cellular component consists of cells with blunt-ended or "cigar-shaped" nuclei, abundant eosinophilic cytoplasm, and perinuclear vacuolization; no significant pleomorphism is present and there is absence of mitotic activity. **C**, Sinonasal (and other mucosal-based) leiomyomas may originate from smooth muscle cells of vascular walls as is seen in this illustration, with the neoplastic cells in direct continuity with the endothelial-lined blood vessel at the bottom; these tumors have been referred to as vascular leiomyomas. **D**, Masson trichrome stain highlights the cytoplasmic myofibrils.

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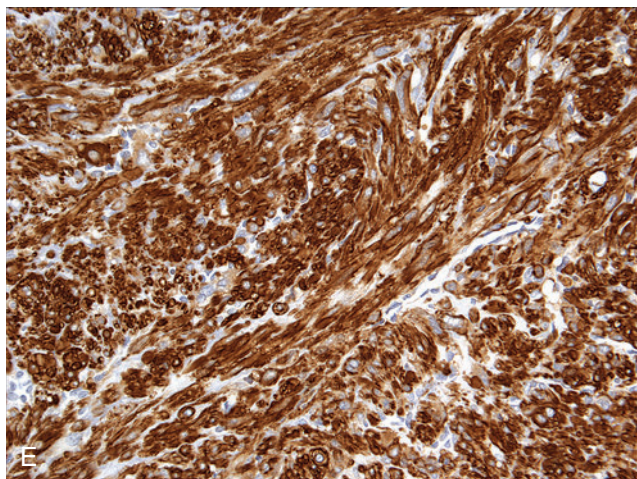


Fig. 3-22, cont'd

E, Neoplastic cells are diffusely and intensely immunoreactive for smooth muscle actin.

Clinical

- In general, one of the least common mesenchymal tumors in the head and neck area owing to the relative absence of smooth muscle in this region:
 - Smooth muscle found in association with blood vessels or cutaneous appendages represents origin for many head and neck leiomyomas
 - Leiomyoma arising from blood vessels termed vascular leiomyoma
- More common in men than in women; may occur in all ages but generally is a tumor of adult life with a peak incidence in the sixth decade of life
- Most common sites of occurrence in the head and neck are:
 - Skin and oral cavity (lips, tongue, and palate)
 - Other sites that may be affected include the sinonasal tract and larynx.
- Within the sinonasal tract leiomyomas most often involve the turbinates.
- Usually presents as a painless mass and nasal obstruction; other symptoms include dysphagia, voice changes, and pain.

Pathology

Gross

- Solitary, well-demarcated, sessile, tan-white submucosal lesion usually measuring less than 3 cm in diameter but may attain larger sizes
- On cut section the tumor is homogeneous with a whorled appearance.

Histology

- Localized to the submucosa, appearing delineated, and characterized by the presence of interlacing

bundles or fascicles of cells composed of blunt-ended or “cigar-shaped” nuclei with abundant eosinophilic cytoplasm

- Nuclear palisading and perinuclear vacuolization may be seen, but there is no significant pleomorphism or mitotic activity; the nuclei may appear epithelioid.
- Neoplastic cells are seen in intimate association with vascular spaces (vascular leiomyoma).
- Degenerative type changes, including stromal fibrosis and mucinous or myxoid alterations, may be present.
- Hypercellular tumors, referred to as cellular leiomyoma, characterized by an absolute increase in cells, but lacking significant pleomorphism, mitotic activity, necrosis, or invasive growth may be identified.

Smooth Muscle Tumors of Uncertain Malignant Potential (SMTUMP)

- SMTUMP is histologically characterized by increased cellularity, moderate nuclear pleomorphism, and the presence of no more than four mitoses per 10 high-power fields.
- Locally, infiltrative growth (i.e., into bone) may occur in association with SMTUMP.
- Histochemistry:
 - Cytoplasmic myofibrils can be demonstrated by special stains appearing red with Masson trichrome and blue with phosphotungstic acid-hematoxylin (PTAH).
- Immunohistochemistry (for leiomyoma and SMTUMP):
 - Actin (smooth muscle and muscle-specific), vimentin, and desmin positive
 - S100 protein, CD34, CD31 negative
 - Proliferation rate for leiomyoma and SMTUMP as seen by Ki67 (MIB1) staining is low (less than or equal to 5%).
- Electron microscopy:
 - Myofilaments, pinocytotic vesicles, investing basal laminae

Differential Diagnosis

- Peripheral nerve sheath tumor (neurofibroma, schwannoma)
- Solitary fibrous tumor

Treatment and Prognosis

- Complete surgical excision is curative.
- Rarely recurs

RHABDOMYOMA

- Adult or fetal types of rhabdomyoma rarely occur in the sinonasal tract or nasopharynx.

- See Section 5, Larynx, for a more complete discussion.
- The cellular features of fetal rhabdomyomas show rhabdomyoblasts in different stages of differentiation, including spindle-shaped and strap cells; these findings may be worrisome for a diagnosis of rhabdomyosarcoma; however, in contrast to rhabdomyosarcoma, fetal rhabdomyomas tend to be circumscribed and lack nuclear atypia or mitotic activity.

OSSEOUS, FIBRO-OSSEOUS, AND CARTILAGINOUS TUMORS/LESIONS

Osteoma (Figs. 3-23 and 3-24)

Definition: Benign bone-forming tumors that are almost exclusively identified in the craniofacial skeleton.

- Controversy exists as to whether the osteoma represents a true neoplasm or possibly represents the end-stage of fibro-osseous lesion.

Clinical

- Sinonasal osteomas are more common in men and occur over a wide age range but are most often encountered in the second to fourth decades of life.
- These tumors are usually asymptomatic and are found only by radiographic studies.
- Symptoms associated with paranasal sinus osteomas include headaches, facial swelling or deformity, and ocular disturbances; meningitis secondary to cranial cavity extension and sinus or aural obstruction may occur.
- Most common sites of involvement are the paranasal sinuses with the frontal and ethmoid sinuses most often involved (frontal > ethmoid > maxillary > sphenoid); other sites of involvement include:
 - Temporal bone (osseous external auditory canal), skull, mandible, maxilla
- Radiology:
 - Sharply delineated radiopaque lesion confined to bone or protruding into a sinus
- Cause linked to trauma, infection (sinusitis), and development
- Sinonasal osteomas usually occur as a single lesion but may be associated with Gardner syndrome:
 - Autosomal dominant inheritance
 - Sentinel lesion for adenomatous polyposis coli (APC)
 - Characterized by intestinal (colorectal) polyposis, soft tissue lesions (fibromatosis, cutaneous epidermoid cysts, lipomas, leiomyomas), and multiple craniofacial osteomas

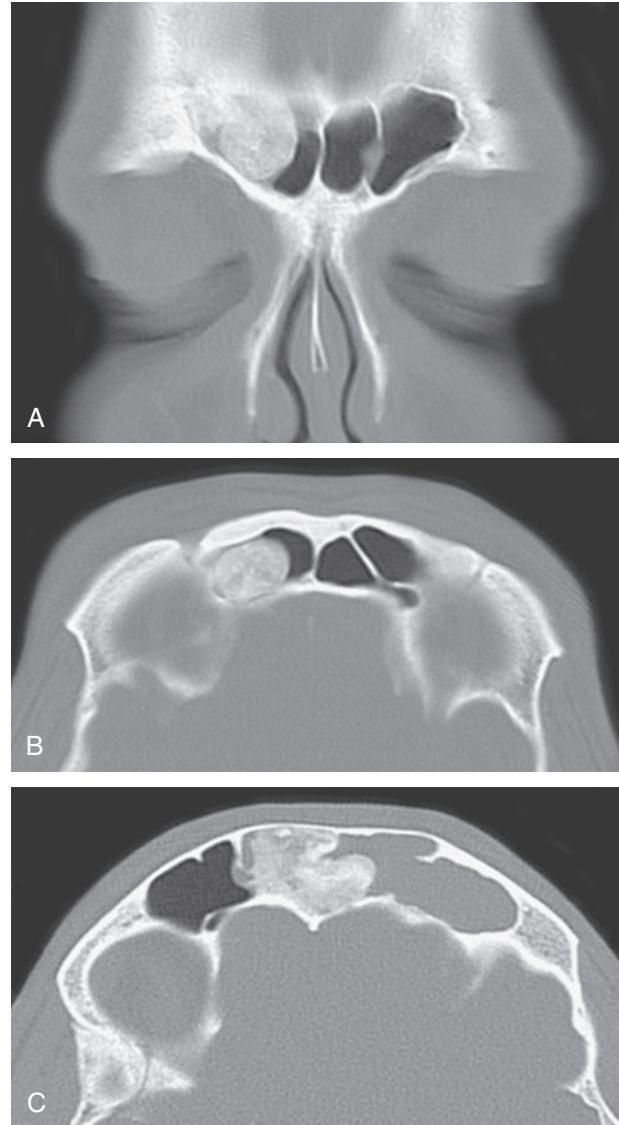


Fig. 3-23. Sinonasal osteoma.

Coronal (**A**) and axial (**B**) CT scans show an osteoma in the right frontal sinus. This osteoma arises from the roof of the sinus. Axial CT scan (**C**) on another patient shows a large left frontal sinus osteoma that obstructs the sinus. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia 2011, Elsevier, p 334, Fig. 4-164.)

Pathology

Histology

- Osteomas are well circumscribed and are composed of dense, mature, predominantly lamellar bone sometimes rimmed by osteoblasts.
- Interosseous spaces may be composed of fibrous, fibrovascular, or fatty tissue, and hematopoietic elements may be present.

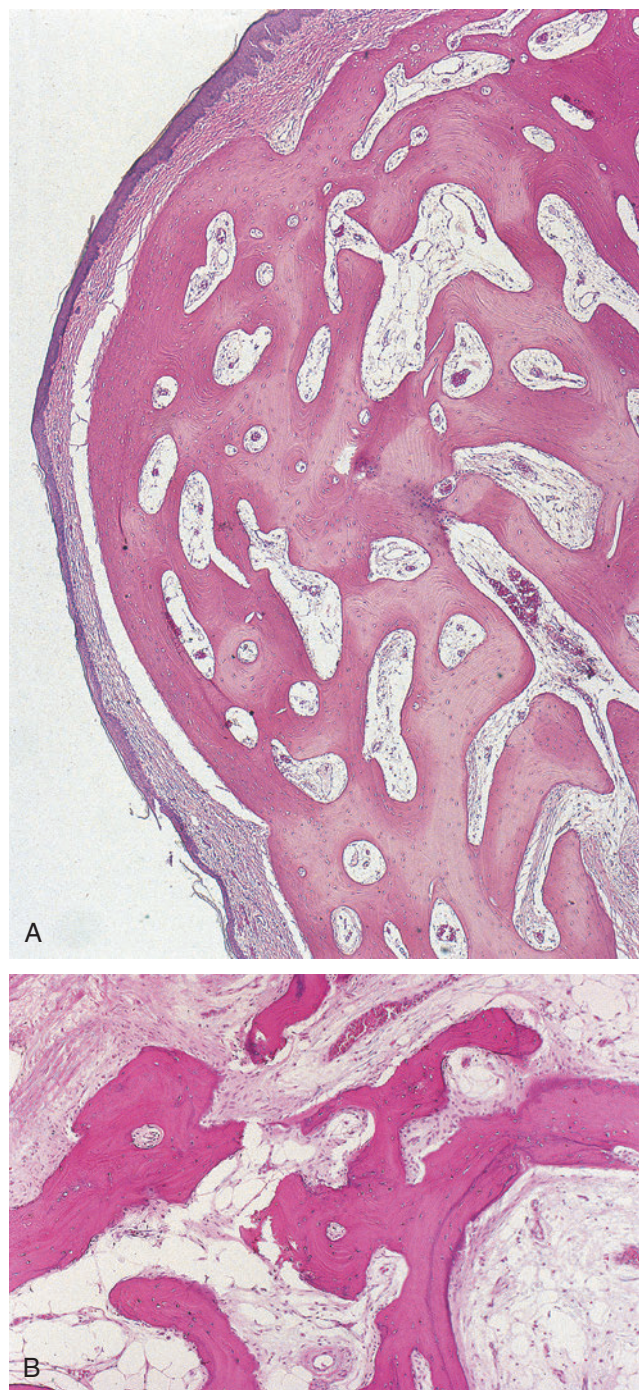


Fig. 3-24. Sinonasal osteoma.

A, Submucosal proliferation composed of dense, mature predominantly lamellar bone associated with interosseous spaces composed of a loose fibrovascular stroma.

B, Portion of the osteoma composed of mature bony spicules associated with an interosseous fatty tissue component.

Differential Diagnosis

- Exostosis

Treatment and Prognosis

- Unless symptomatic, osteomas require no treatment.
- Symptomatic osteomas require complete surgical excision, which is curative.
- No known link to the development of osteosarcoma

Benign Fibro-osseous Lesions of Craniofacial Bones

- Category of histologically similar-appearing benign fibro-osseous lesions that include ossifying fibroma and fibrous dysplasia
- In the head and neck, occur most often in relation to gnathic (maxillary and mandibular) bones
- For a more complete discussion on ossifying fibroma and fibrous dysplasia see Section 2, Oral Cavity.
- Given its localization to the sinonasal tract, the psammomatoid ossifying fibroma is discussed here.
- See [Table 3-4](#) for a comparison of ossifying fibroma, psammomatoid ossifying fibroma, and fibrous dysplasia.

Psammomatoid (Active) Ossifying Fibroma (Figs. 3-25 and 3-26)

Definition: Variant of ossifying fibroma that typically occurs in the sinonasal tract and potentially may behave aggressively with locally invasive and destructive capabilities.

Synonyms: Cementifying or cemento-ossifying fibroma; juvenile active ossifying fibroma

Clinical

- No gender predilection; generally occurs in younger age groups (first and second decades) but can occur over a wide age range, including older individuals.
- Presenting symptoms include facial swelling, nasal obstruction, pain, sinusitis, headache, and proptosis.
- These lesions may occur in any area of the sinonasal tract but are most frequent in the ethmoid sinus and supraorbital frontal region (ethmoid > nasal cavity > maxillary sinus > frontal sinus); the orbit may also be involved.
- There may be involvement of a single site or multiple sinuses.
- Radiology:
 - Lytic or mixed lytic/radiopaque osseous and/or soft tissue mass varying from well-demarcated to invasive with bone erosion

TABLE 3-4 Benign Fibro-osseous Lesions: Clinicopathologic Comparison

	POF	OF	FD
Gender/age	F = M; younger age groups (first and second decades), but may occur in older individuals	F > M; third-fourth decades	F = M; first two decades of life
Location	Ethmoid sinus; supraorbital frontal region	No specific site of involvement	No specific site of involvement
Focality	Single site or involvement of multiple (contiguous) sites/sinuses	Single site	Monostotic (75%-80%); polyostotic (20%-25%)
Radiology	Lytic or mixed lytic/radiopaque osseous and/or soft tissue mass varying from well-demarcated to invasive with bone erosion	Well-circumscribed or sharply demarcated lesion with smooth contours	Poorly defined expansile osseous lesion with a thin intact cortex; predominantly fibrous lesions are radiolucent; predominantly osseous lesions are radiodense; lesions with an equal admixture of fibrous and osseous components have a ground-glass appearance
Histology	Bony spicules and distinctive mineralized or calcified "psammomatoid" bodies or ossicles admixed with a fibrous stroma; psammomatoid bodies vary from a few in number to a dense population of innumerable spheric bodies; osteoclasts are present within the ossicles, and osteoblasts can be seen along their peripheral aspects; the bony trabeculae vary in appearance and include odd shapes with a curvilinear pattern. The trabeculae are composed of lamellar bone with associated osteoclasts and osteoblastic rimming	Randomly distributed mature (lamellar) bone spicules rimmed by osteoblasts admixed with a fibrous stroma; central portions may be woven bone with lamellar bone at the periphery	Fibrous tissue component is nondescript and of variable cellularity; osseous component includes irregularly shaped trabeculae of osteoid and immature (woven) bone that is poorly oriented with misshapen bony trabeculae with odd geometric patterns including "C"-shaped or "S"-shaped configurations; the trabeculae typically lack osteoblastic rimming
Syndromes	No known association	No known association	Albright syndrome (1%-3%)
Treatment	Surgical resection	Surgical resection	Disease may stabilize at puberty and, in children, therapy should be delayed if possible until after puberty; surgical resection indicated in cases with compromise of function, progression of deformity, associated pathologic fracture(s), or the development of a malignancy
Prognosis	Good following complete excision; recurrence(s) often occur due to incomplete excision; may behave in an aggressive manner with local destruction and potential invasion into vital structures	Excellent	Good prognosis; recurrence rates are low and death due to extension into vital structures rarely occurs
Malignant transformation	Not known to occur	Not known to not occur	Malignant transformation (osteosarcoma) occurs in less than 1%

FD, Fibrous dysplasia; OF, ossifying fibroma; POF, psammomatoid ossifying fibroma.

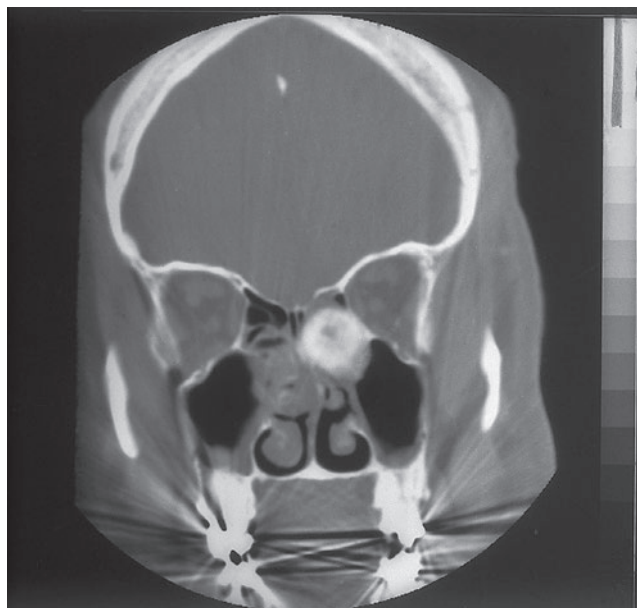


Fig. 3-25.

Axial CT of psammomatoid active ossifying fibroma (PAOF) demonstrating an inhomogeneous, radiodense mass in the left ethmoid and maxillary sinuses causing bowing outward of the medial wall of the left orbit and displacement but not destruction of the nasal septum.

- Presenting symptoms include facial swelling, nasal obstruction, pain, sinusitis, headache, and proptosis.

Pathology

Histology

- The histology is that of a benign fibro-osseous proliferation composed of bony spicules and spherules admixed with a fibrous stroma.
- Most distinctive component is the presence of mineralized or calcified “psammomatoid” bodies or ossicles:
 - These ossicles vary from a few in number to a dense population of innumerable spheric bodies.
 - Ossicles are demarcated with a central blue to black appearance surrounded by a pink-appearing rim and with concentric laminations.
 - Ossicles vary from small with a round to oval shape to being larger and irregularly shaped and are present within the bony trabeculae as well as within the adjacent cellular stroma.
 - Osteoclasts are present within the ossicles, and osteoblasts can be seen along their peripheral aspects.
- Bony trabeculae vary in appearance and include odd shapes with a curvilinear pattern:
 - Trabeculae are composed of lamellar bone with associated osteoclasts and osteoblastic rimming.

- Transition zones between the spherical ossicles and bony trabeculae can be seen.
- Nonosseous component includes a cellular stroma with a fascicular to storiform growth composed of round to polyhedral to spindle-shaped cells with prominent basophilic nuclei and inapparent cytoplasmic borders:
 - Mitotic figures can be seen, but mitotic activity is not prominent and atypical mitoses are not present.
 - Cellular pleomorphism may be present, but anaplasia and necrosis are not identified.
- Giant cells can be seen among the psammomatoid ossicles or scattered throughout the nonosseous stromal component.
- Osteoid formation may be focally present.
- Trabecular (juvenile) ossifying fibroma:
 - Considered to be clinicopathologically distinct from psammomatoid ossifying fibroma
 - Less common than psammomatoid ossifying fibroma
 - Reported to occur in more narrow age range (2 to 12 years) and younger mean age (8.5 to 12 years) than psammomatoid ossifying fibroma (3 months to 72 years and 16 to 33 years)
 - Predominantly affects the jaws
 - Histologically composed of trabeculae of fibrillary osteoid and woven bone
 - Aggressive growth occurs in some—but not all—cases of both types.

Differential Diagnosis

- Fibrous dysplasia (see [Table 3-4](#))
- Ossifying fibroma (see [Table 3-4](#))
- Osteoblastoma
- Osteosarcoma
- Psammomatoid meningioma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
- Prognosis is good following complete excision but, if margins are involved, recurrences often occur, and the tumors may behave in an aggressive manner with local destruction and potential invasion into vital structures.

Chondroma ([Fig. 3-27](#))

Definition: Benign neoplasm of cartilage.

Clinical

- Chondromas of the sinonasal tract and nasopharynx are rare.
- The most frequent sites of occurrence include the nasal septum and the nasopharynx.

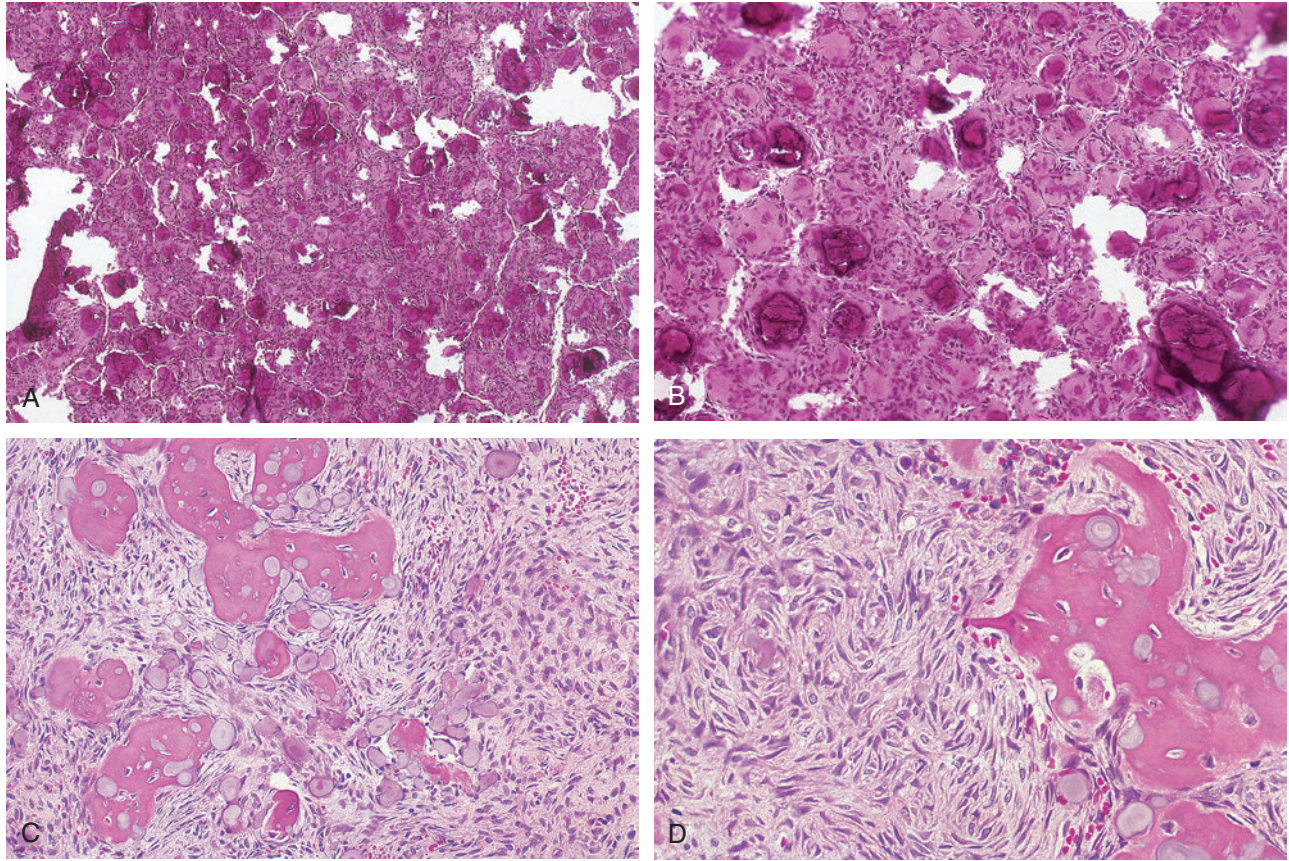


Fig. 3-26. Psammomatoid active ossifying fibroma.

A and **B**, The lesions are characterized by the presence of numerous, small ovoid, calcified, or mineralized bony spicules with a psammomatoid appearance admixed and surrounded by a cellular (active) spindle cell component with hyperchromatic nuclei and indistinct cytoplasmic borders. **C** and **D**, Irregularly shaped bony spicules associated with spindle-shaped cells and myxomatous stroma; lighter-staining psammomatoid spherules that are present in association with the bony spicules and in the cellular stromal component may be seen focally, resulting in the production of cystic spaces.

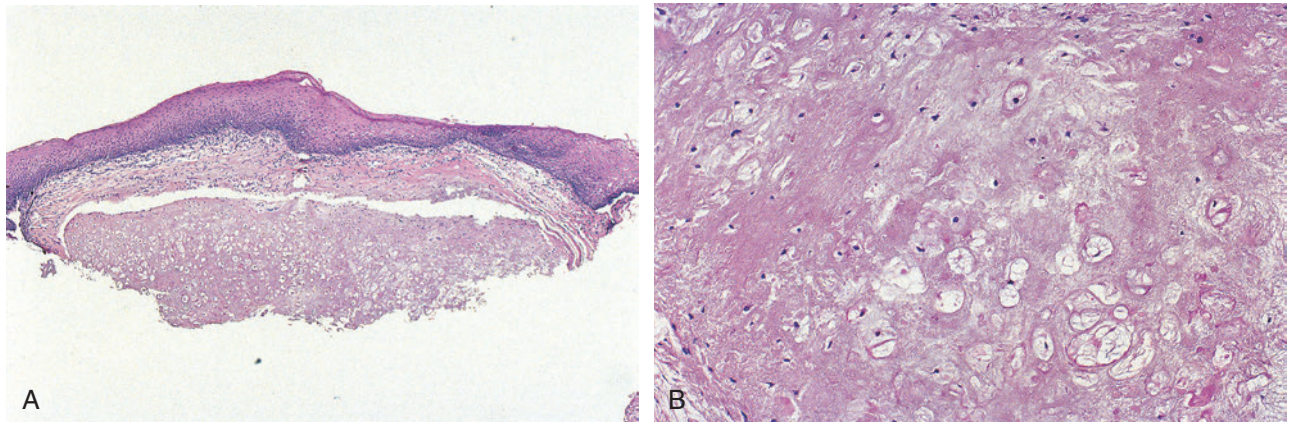


Fig. 3-27. Nasal septal chondroma.

A, The cartilaginous tumor is situated below an intact squamous epithelium and clinically produced a polypoid, smooth-surfaced nodule. **B**, The chondrocytes are bland and lack features worrisome for a low-grade chondrosarcoma.

- Radiology:
 - Sinus opacification or a circumscribed radiolucent lesion can be seen by radiographic studies.
- Sinonasal chondromas appear as a polypoid, firm, smooth-surfaced nodule measuring usually from 0.5 to 2.0 cm and rarely greater than 3.0 cm.
- Histologically, these are lobulated tumors composed of chondrocytes recapitulating the normal histology of cartilage.
- Cellular pleomorphism, binucleate chondrocytes, or increased mitotic activity is not present.
- Conservative but complete surgical excision is the preferred treatment.
- Recurrences are uncommon.

SINONASAL MYXOMA AND FIBROMYXOMA

(Figs. 3-28 through 3-32)

Definition: Myxomas and fibromyxomas are benign neoplasms of uncertain histogenesis with a

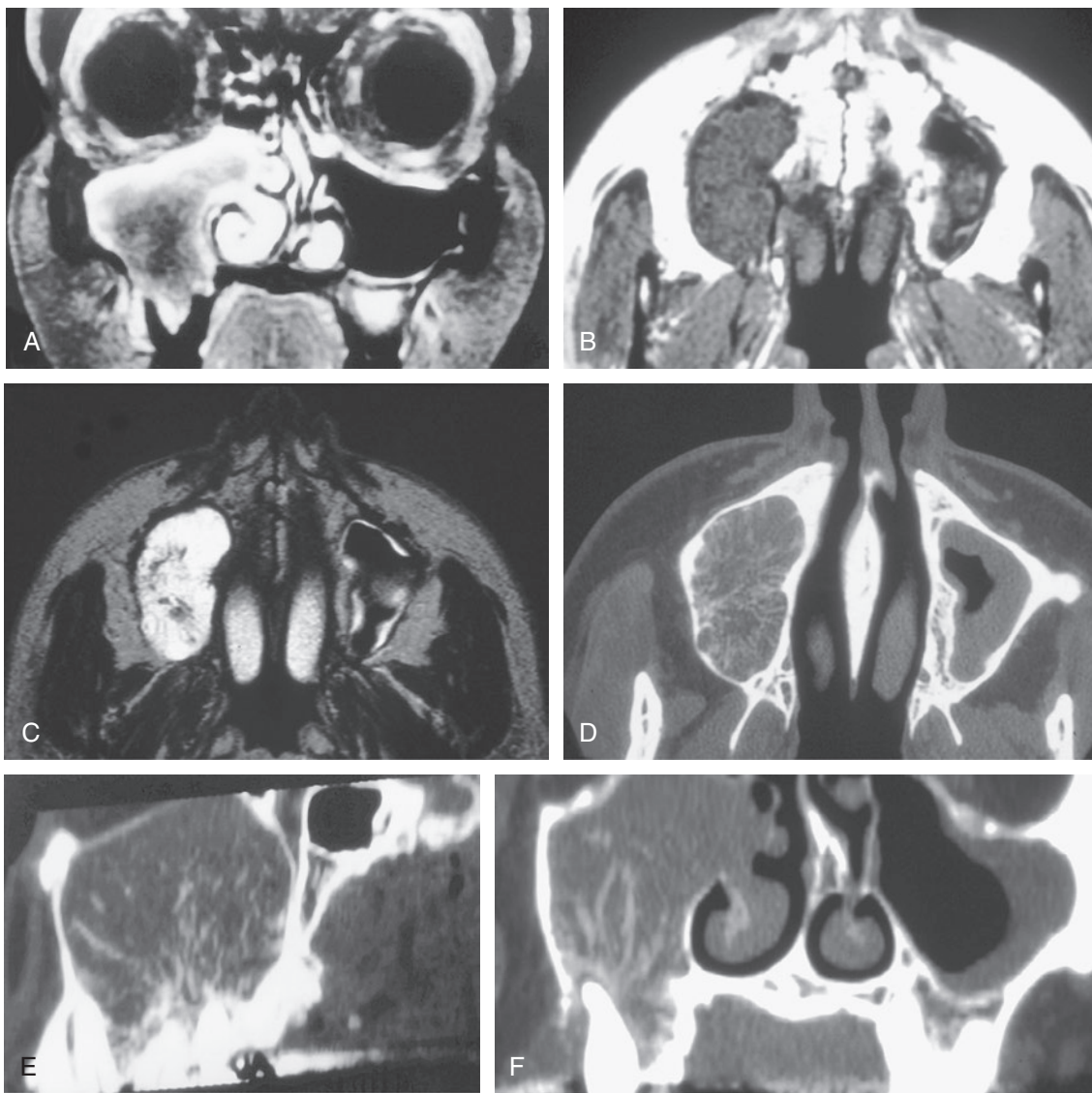


Fig. 3-28. Sinonasal fibromyxoma.

Coronal T1-weighted (A), axial T1-weighted (B), and T2-weighted (C) MR images, axial CT scan (D), and reformatted sagittal (E) and coronal (F) CT scans show an expansile low signal intensity mass filling the right maxillary sinus. Minimal nonhomogeneity is seen in B. Very fine lace-like signal voids are seen in C. Entrapped high signal intensity secretions are present around the lesion. The CT scans show that within the lower portion of the mass there are thin, lace-like calcifications. This patient had a fibromyxoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, 2011, p 331, Fig. 4-160.)



Fig. 3-29. Sinonasal fibromyxoma.

The lesion is large, multinodular with a glistening tan-yellow appearance.

characteristic histologic appearance often behaving in an aggressive (infiltrating) manner. When a relatively greater amount of collagen is present, the term fibromyxoma (or myxofibroma) is used.

Clinical

- In the head and neck two forms of myxomas/fibromyxomas are identified:
 - Facial skeletal-derived
 - Soft tissue-derived

Facial Skeletal-Derived Myxoma

- No gender predilection; occurs over a wide age range but most frequently seen in the second and third decades of life
- In general, this is a tumor of the jaw bones and is uncommon in extragnathic locations:
 - The mandible (posterior and condylar regions) is affected more often than the maxilla (zygomatic process and alveolar bone).
 - Extragnathic tumors are uncommon and primarily involve the sinonasal tract; specifically, the maxillary sinus (antrum) is most often involved with secondary extension into the nasal cavity; extension to orbit and cranial cavity may occur.
- Presentation usually is as a painless swelling of the affected area.
- Radiology:
 - Unilocular or multilocular radiolucency with a “honeycomb” or “soap-bubble” appearance
 - May vary from being delineated or circumscribed to expansile and infiltrative

- Localization to the jaw bones has led to the belief that these tumors take origin from the primordial odontogenic mesenchyme or from an osteogenic embryonic connective tissue; in the sinonasal tract, these tumors appear to be of osseous derivation.

Myxoma of Soft Tissues

- Primarily a tumor involving the extremities
- No gender predilection; seen over a wide age range and is not specific to any decade of life
- In the head and neck, common sites include the paraoral soft tissues, pharynx, larynx, parotid gland, tonsil, and ear:
 - Myxomas of the ear are associated with Carney complex.
 - See Section 7, Ear and Temporal Bone, for a more detailed discussion.
- Presentation is that of an asymptomatic mass.
- Association between myxomas and fibrous dysplasia has been noted:
 - Referred to as Mazabraud syndrome
 - Multiple myxomas are present and tend to be intramuscular in localization.
 - Majority of patients have polyostotic type of fibrous dysplasia.
 - Patients also may suffer from McCune-Albright syndrome.
- Carney complex:
 - Syndrome of myxomas, spotty pigmentation, and endocrine overactivity
 - Autosomal dominant inheritance
 - Include cardiac myxomas, as well as myxomas of other sites (e.g., intraoral, ear)
 - Death due to cardiac myxoma may occur in up to 25% of patients with this complex.
 - Pigmented nodular adrenocortical hyperplasia, Cushing syndrome, and acromegaly also occur in this complex.

Pathology

Gross

- Delineated but unencapsulated multinodular, rubbery to firm, tan-yellow to gray-white lesion with a gelatinous appearance

Histology

- Histology is the same irrespective of the setting in which it occurs.
- These tumors show a scant, loosely cellular proliferation consisting of spindle-shaped or stellate-appearing cells embedded in an abundant mucinous stroma.
- Nuclei are small and hyperchromatic; cellular pleomorphism, mitotic figures, and necrosis are absent.
- The amount of collagenous fibrillary material varies between cases and, depending on the

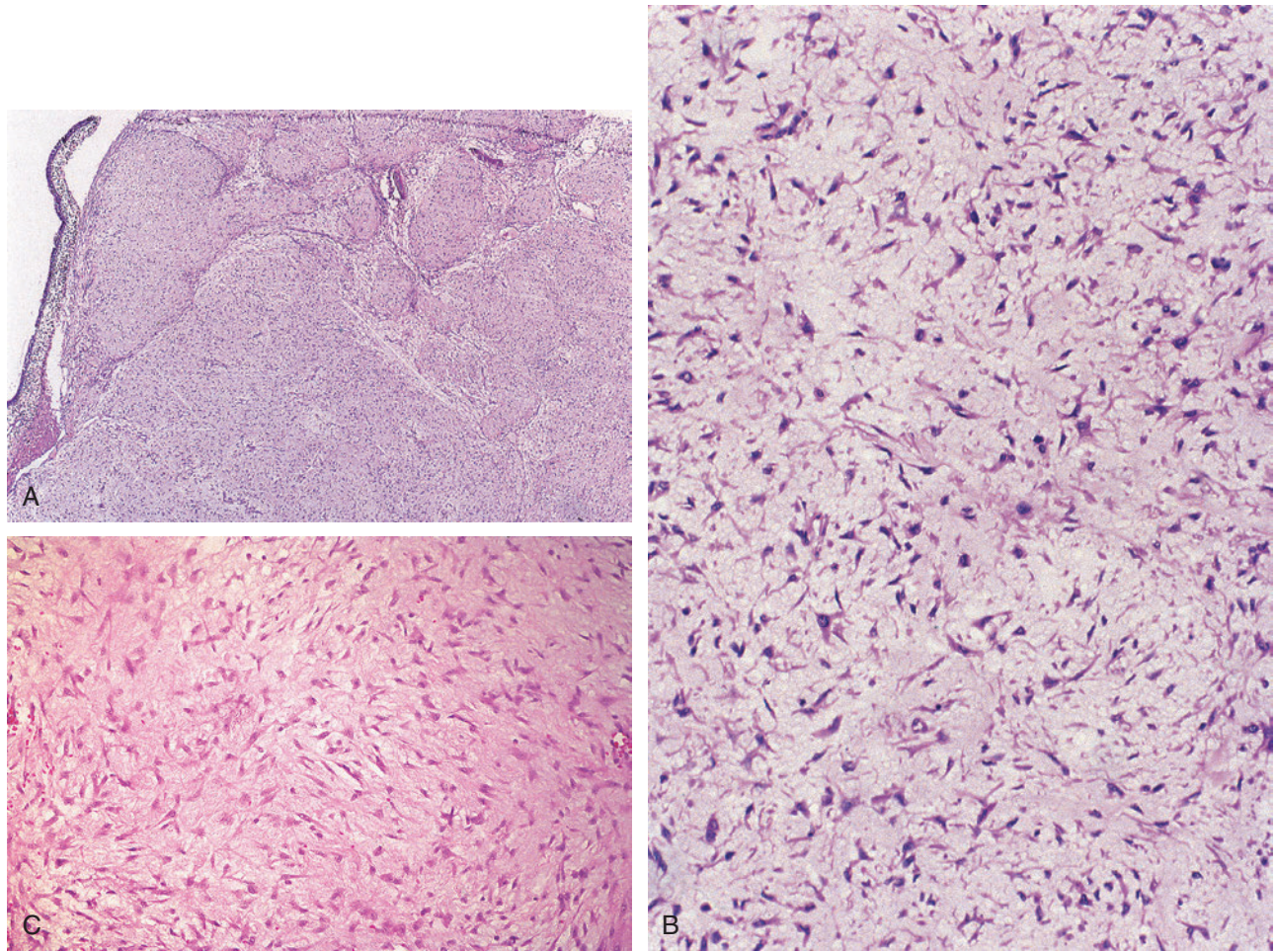


Fig. 3-30. Sinonasal fibromyxoma.

A, The lesion is characterized by a lobular growth composed of spindle-shaped cellular proliferation associated with a mucinous stroma; compressed, slit-like vascular component can be identified. **B** and **C**, Loosely cellular proliferation consisting of spindle-shaped or stellate-appearing cells embedded in a fibrous or fibromyxomatous stroma.

extent, its presence may confer designation “fibromyxoma.”

- Periphery of the tumor appears circumscribed, but local infiltration with replacement of bone can be seen.
- A vascular component is present but is limited in extent:
 - Absence of the delicate plexiform capillary vascular network, a finding that can be seen in various sarcomas
- In intraoral location, odontogenic epithelium may or may not be seen.
- Mucinous stroma stains positively for acid mucopolysaccharides.
- Immunohistochemistry:
 - Vimentin positive
 - Negative for MUC4, β -catenin, CD34

Differential Diagnosis

- Sinonasal inflammatory polyps
- Dental papillae (for intraoral lesions)
- Vocal cord polyps (for laryngeal lesions)
- Peripheral nerve sheath tumors
- Low-grade fibromyxoid sarcoma
- Sarcomas with myxoid component (e.g., myxofibrosarcoma, liposarcoma, rhabdomyosarcoma, others)
- Cartilaginous tumors:
 - A separate and distinct benign tumor of cartilaginous origin that may involve the craniofacial and paranasal sinus bones is the chondromyxoid fibroma ([Fig. 3-33](#)):
 - More common in men than in women; most common in the second to third decades of life
 - Mandible is the most common site (symphysis or molar-retromolar area).

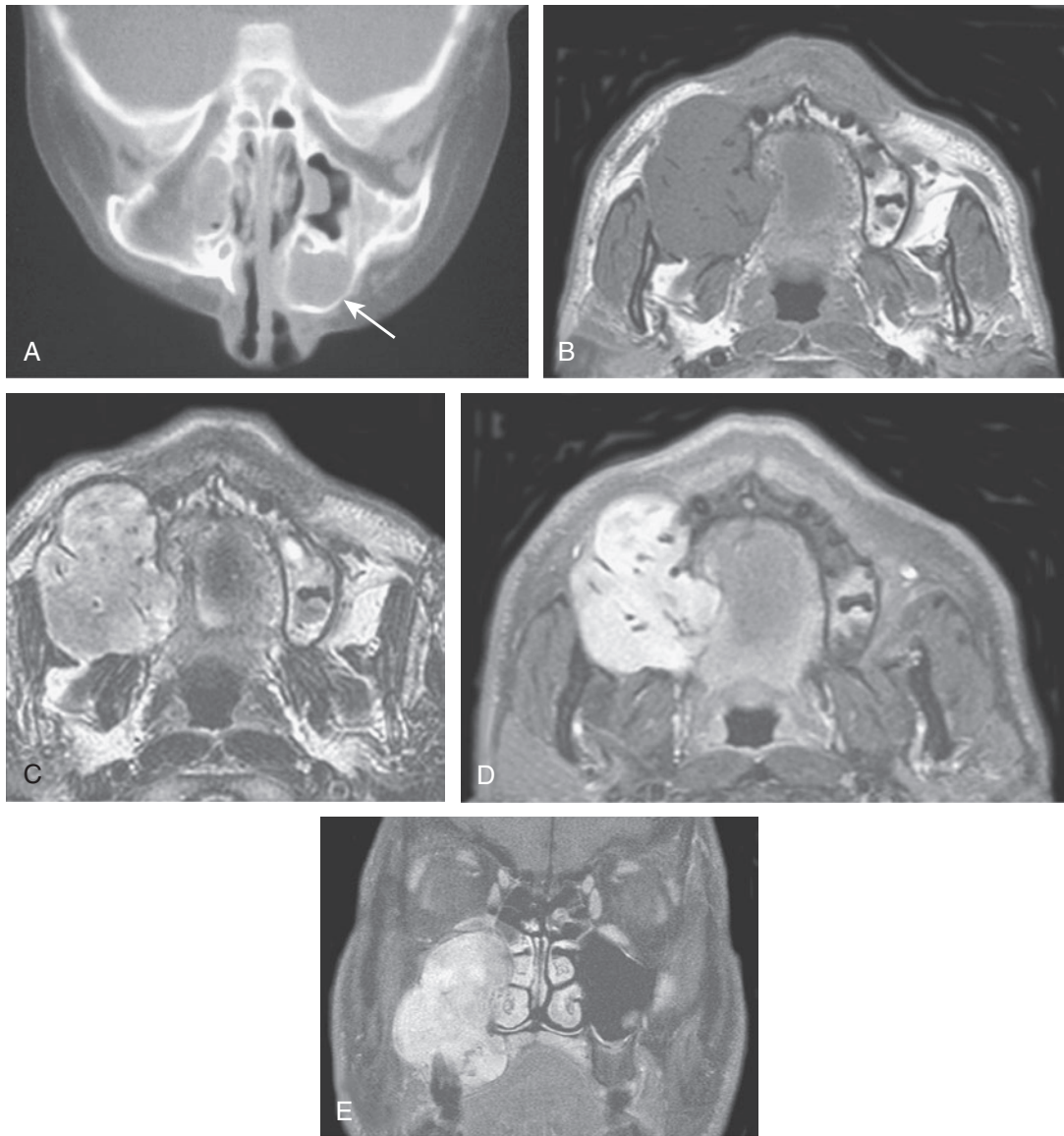


Fig. 3-31. Sinonasal myxoma.

Coronal CT scan (**A**) shows an expansile mass in the left anterior maxilla (*arrow*). The surrounding bone is intact. This patient had a myxoma. Axial T1-weighted (**B**), axial T2-weighted (**C**), and axial (**D**) and coronal (**E**) T1-weighted contrast-enhanced MR scans on a different patient show a large mass destroying part of the right maxillary alveolus and expanding and filling the left maxillary sinus, elevating and thinning the orbital floor. There is no infiltration of the orbit. The teeth roots are exposed by the tumor, and the tumor is fairly homogeneous in signal intensity. This patient had a myxoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 332, Fig. 4-162.)

- Symptoms include pain, loosening of the teeth, difficulties in opening the jaws, and headaches.
- Radiographic appearance varies, depending on the involved bone, from round or oval; well-demarcated, radiolucent lesion usually measuring less than 5 cm in long bones to large, irregularly outlined lesions in flat bones.
- Histology is characterized by a lobular appearance with lobules separated by vascularized connective tissue and a zonal arrangement of the cellular component: center of the lobules are predominantly myxoid with scattered stellate-appearing cells; periphery of the lobules are more cellular, composed of cells with round to oval to spindle-shaped nuclei, an

eosinophilic to amphophilic cytoplasm often with multipolar, stellate extensions

- FGF-23 expression reported in some cases of chondromyxoid fibroma (as well as aneurysmal bone cyst)
- With time, the myxoid areas may become fibrotic; presence of cartilage varies but never exceeds 75% of the total tumor volume;

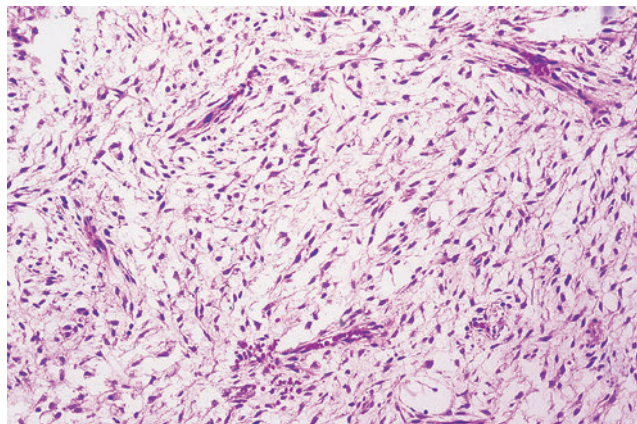


Fig. 3-32.

Sinonasal myxoma with predominant myxoid stroma and a relatively hypocellular spindle-shaped cellular proliferation. A nondescript (compressed) identifiable vascular component is present, lacking the delicate plexiform capillary network often seen in association with various (myxoid) sarcomas.

osteoclastic giant cells and calcifications may be seen.

- Surgery (en bloc resection) is the preferred treatment; local recurrences may occur if incompletely excised (curettage); malignant transformation in the absence of prior irradiation rarely occurs.

Treatment and Prognosis

- Conservative but wide local excision is the preferred treatment.
- These tumors tend to be slow-growing and usually follow a benign course but may have the potential for local destruction following inadequate excision.
- Recurrence or metastasis does not occur:
 - Metastasis from a presumptive sinonasal myxoma or fibromyxoma should seriously place that diagnosis in doubt and probably represents a myxoid variant of a sarcoma (liposarcoma, myxofibrosarcoma, or rhabdomyosarcoma).

OSSIFYING (AND NONOSSIFYING) FIBROMYXOID TUMOR (OFMT) (Fig. 3-34)

Definition: Benign soft tissue tumor of uncertain differentiation.

NOTE: Although evidence suggests that this tumor is of peripheral nerve sheath origin (i.e., Schwannian differentiation), its definitive origin remains uncertain.

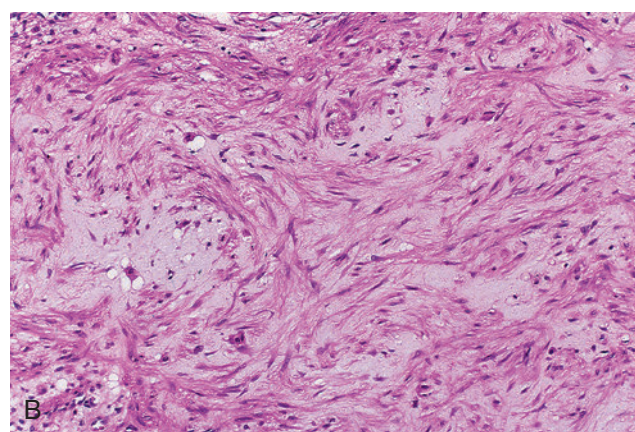
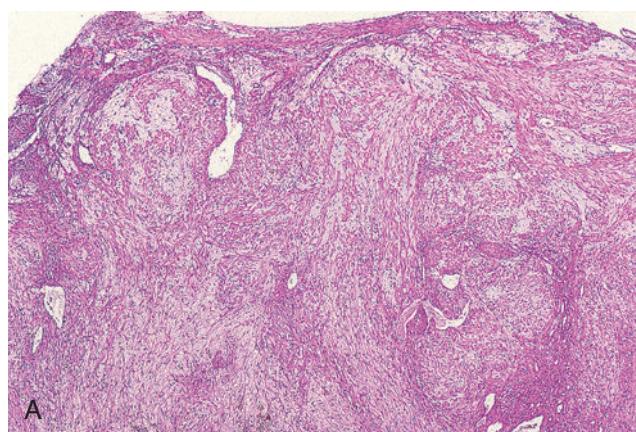


Fig. 3-33.

Chondromyxoid fibroma is characterized by **(A)** lobular appearance with lobules separated by vascularized connective tissue; the lobules demonstrate a zonal arrangement of the cellular component, with the center of the lobules being predominantly composed of a chondromyxoid matrix with scattered stellate-appearing cells and the periphery of the lobules being more cellular. **B,** Cellular components of the chondromyxoid fibroma include cells with round to oval spindle-shaped nuclei, an eosinophilic to amphophilic cytoplasm often with multipolar, stellate extensions set in a chondroid to mucinous-appearing matrix.

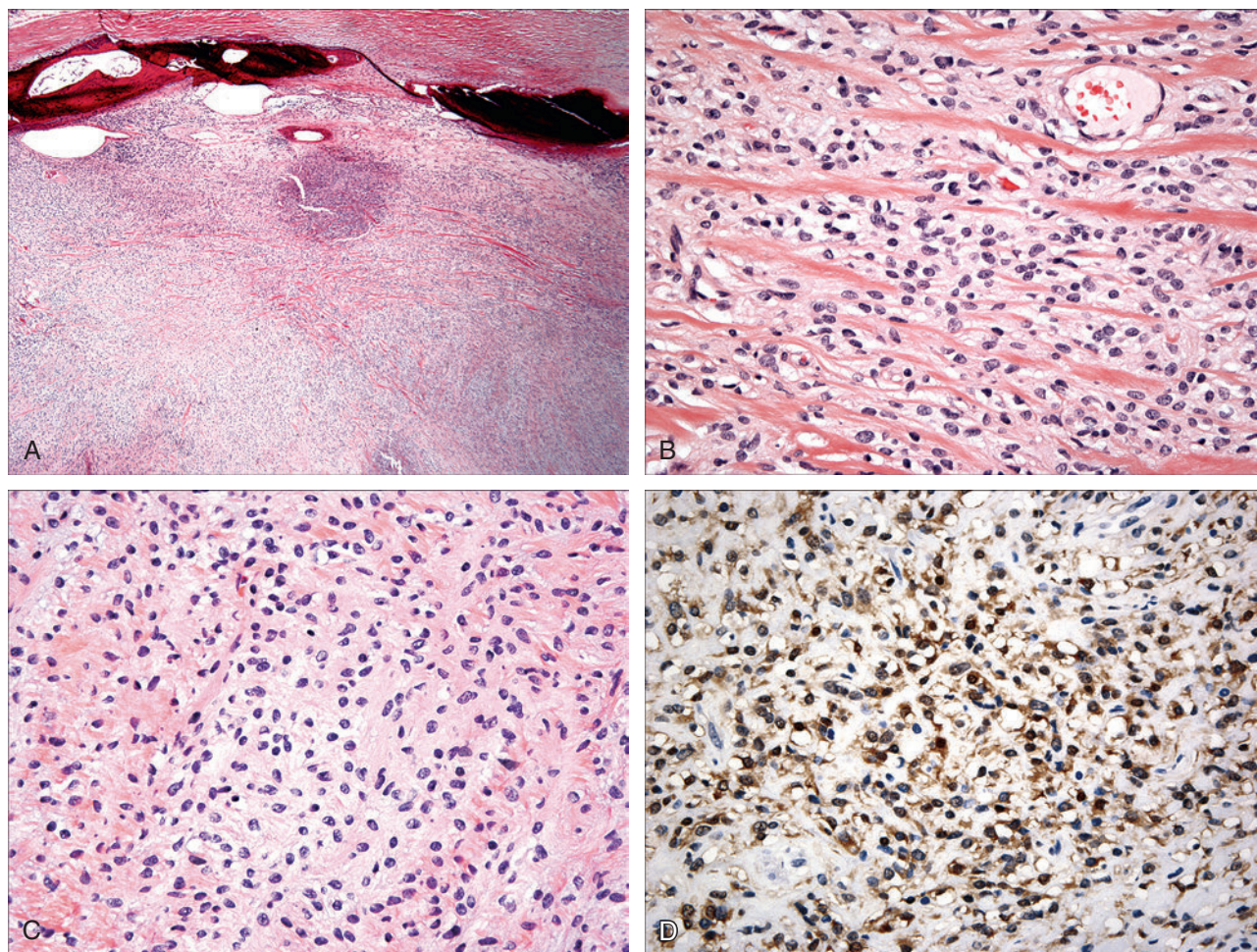


Fig. 3-34. Sinonasal ossifying fibromyxoid tumor.

A, This submucosal variably cellular proliferation was rimmed along its periphery by an incomplete shell of lamellar bone (top). **B** and **C**, Diffuse growth of neoplastic cells composed of uniform round to ovoid to spindle-shaped cells with small round to oval vesicular-appearing nuclei with indistinct eosinophilic cytoplasm set in collagenized or fibromyxoid stroma. **D**, S100 protein immunoreactivity is present but is less intense as compared with S100 protein staining of benign peripheral nerve sheath tumors.

Clinical

- In general an uncommon tumor, including in head and neck sites
- More common in men than in women; occurs over a wide age range but most often occurs in the fifth and sixth decades of life
- Most commonly is a soft tissue tumor of the upper and lower extremities:
 - Deep subcutis with attachment to underlying fascia and connective tissues (skeletal muscle, tendon)
 - Up to one third originate in muscle
 - May occur in the head and neck, including skin, sinonasal tract, oral cavity, pharynx, and neck

- In the sinonasal tract, symptoms may include nasal obstruction or a painless mass.
- Radiology:
 - Well-circumscribed mass with a peripherally situated incomplete ring of calcification
 - Intralesional calcifications may be present.
- No known cause but a number of cases reported following trauma/surgery to a given site

Pathology

Gross

- Well-circumscribed, lobulated, or multinodular lesions with a rubbery to firm consistency and a tan-white appearance; range in size from 1 to 7 cm in greatest dimension

Histology

- Well-circumscribed, lobular, or multinodular proliferation often with an incomplete peripheral shell of lamellar bone in or below a fibrous capsule:
 - The majority of cases (approximately 80%) show an incomplete peripheral shell of lamellar bone representing the ossifying variant.
 - Up to 20% may lack a bony shell, representing the nonossifying variant.
- Tumor lobules composed of uniform round, ovoid, or spindle-shaped cells with eccentrically located small round to oval vesicular-appearing nuclei with inconspicuous to small nucleoli and scant eosinophilic cytoplasm:
 - Cellularity is limited as is nuclear pleomorphism.
 - Scattered mitotic figures may be seen (one to two mitoses per 10 high-power fields).
- Growth patterns include diffuse or sheetlike, cords, nests, or randomly distributed.
- Stromal component may be myxoid, mucoid, hyalinized/collagenized or fibromyxoid; well-vascularized component that may include the presence of perivascular hyalinization:
 - Calcification and/or mature cartilage may rarely be seen.
 - Osteoid may infrequently be present.
- Atypical OFT has been applied for those tumors with increased cellularity, nuclear pleomorphism, and more than two mitoses per 10 high-power fields but without metastatic disease.
 - In the presence of metastasis the tumor is malignant (see below).
- Immunohistochemistry:
 - S100 protein, vimentin, and neurofibrillary protein (NFP) positive in the majority of cases:
 - S100 protein immunoreactivity tends to be less intense as compared with benign peripheral nerve sheath tumors.
- Desmin positive in approximately 40% of cases
- Variable reactive for GFAP, CD56, CD57, NSE, GFAP
- Occasionally may express cytokeratin, EMA, MUC5, smooth muscle actin
- Identification of collagen II production (suggests limited cartilaginous differentiation)
- Loss of SMARCB1/INI-1 (putative tumor suppressor gene located on chromosome 22q11.2 that encodes a protein that is expressed essentially in all nucleated cells) in majority of cases:
 - Loss of INI-1 or other genes on 22q is likely important in pathogenesis of these tumors.
- Expression of neuron-related markers, in addition to Schwann cell- and cartilage-associated markers, suggests a “scrambled” phenotype in OFMTs.

- Electron microscopy:
 - Abundant intracytoplasmic intermediate filaments with perinuclear whorl
 - External lamina, interdigitating cell processes, and ribosome-lamellar complexes may be identified.
- Cytogenetics and molecular genetics:
 - Recurrent rearrangements of the *PHF1* gene reported in OFMT, including typical, atypical, and malignant variants:
 - Supports importance of *PHF1* rearrangements in the pathogenesis of these lesions
 - Confirm relationship between typical and malignant OFMT
 - Suggests a role for *PHF1* fluorescent in situ hybridization (FISH) in the diagnosis of morphologically challenging cases

Differential Diagnosis

- Benign peripheral nerve sheath tumors:
 - “Conventional” and epithelioid variants
- Malignant peripheral nerve sheath tumors:
 - “Conventional” and epithelioid variants
- Solitary fibrous tumor
- Myxoid chondrosarcoma
- Epithelioid smooth muscle tumors

Treatment and Prognosis

- Complete surgical resection is the preferred treatment.
- Local recurrence may be seen in up to one third of cases and is likely due to incomplete surgical excision.
- Malignant OFMT:
 - Diagnosis predicated on the presence of metastatic disease
 - As compared with benign OFMTs, malignant OFMTs show increased cellularity, nuclear pleomorphism, increased mitotic activity (greater than two mitoses per 10 high-power fields), and increased osteoid.
 - However, cytologically bland tumors have rarely been reported to metastasize.
 - May show osteosarcomatous areas
 - Metastatic disease occurs primarily to lungs.

SINONASAL AMELOBLASTOMA (Figs. 3-35 and 3-36)

Definition: Ameloblastomas are locally aggressive (jaw) tumors with a high propensity for recurrence that are thought to arise from remnants of odontogenic epithelium, lining of odontogenic cysts, and the basal layer of the overlying oral mucosa.

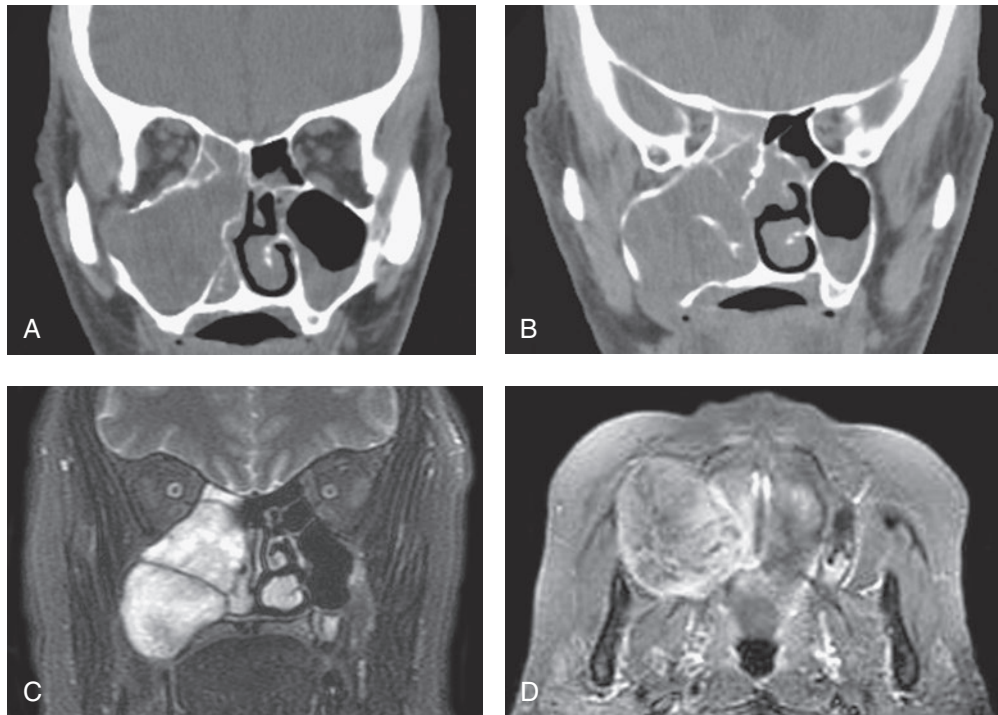


Fig. 3-35. Sinonasal ameloblastoma.

Coronal CT scans (**A** and **B**) and coronal T2-weighted (**C**) and axial T1-weighted, fat-suppressed, contrast-enhanced (**D**) MR images show an expansile mass in the right maxillary sinus that has destroyed portions of the lower and lateral sinus walls. A bony fragment is seen within the mass that represents the elevated sinus floor. The right ethmoid sinuses are obstructed by the mass. This tumor has a high T2-weighted signal intensity and has enhanced nonhomogeneously. This patient had an ameloblastoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 385, Fig. 4-258.)

- See Section 2, Oral Cavity, for a more complete discussion of the more common gnathic ameloblastomas.
- Ameloblastomas of the sinonasal tract are uncommon but do occur and in particular involve the maxillary sinus:
 - Usually occurs by secondary extension from the maxilla
 - True primary sinonasal ameloblastomas without connection to gnathic sites uncommonly occur.
- Radiology:
 - In contrast to the characteristic multilocular and radiolucent presentation of ameloblastomas within the jaws, sinonasal ameloblastomas are described radiographically as solid masses or opacifications.
 - Bone destruction, erosion, and remodeling (remnant of bony shell delimiting the lesion as it grew) may be present.
- Suggested sources for the odontogenic epithelium include cell rests of the dental lamina, a developing enamel organ, the lining of an odontogenic cyst, basal cells of oral mucosa, or heterotopic embryonic organ epithelium.

Primary Sinonasal Ameloblastoma

- Decided male predilection; mean age at presentation of 59.7 years (approximately 15 to 25 years later than in patients with ameloblastoma occurring within the jaws)
- Patients usually present with a mass lesion and nasal obstruction; symptoms range from 1 month to several years in duration.
- Sites of involvement included the nasal cavity only, the paranasal sinuses only, or the nasal cavity and the paranasal sinuses.

Pathology Histology

- Similar in appearance to their gnathic counterparts and include unencapsulated proliferating nests, islands, or sheets of odontogenic epithelium resembling the enamel organ
- Epithelium is composed of:
 - Central area of loosely arranged cells similar to the stellate reticulum of the enamel organ

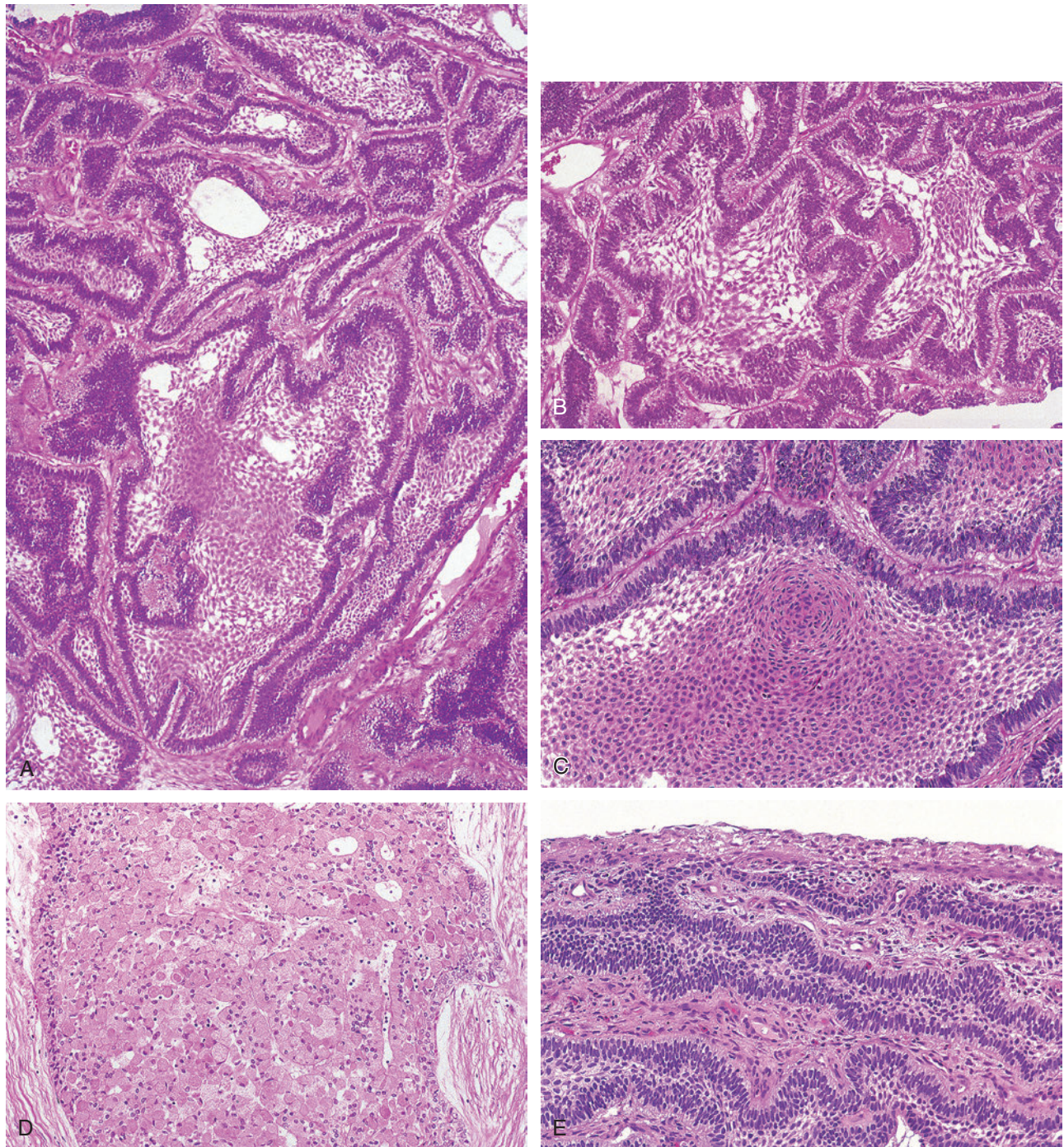


Fig. 3-36. Sinonasal ameloblastoma.

A, The tumor is composed of unencapsulated proliferating nests or islands of odontogenic epithelium. **B**, Ameloblastic epithelium includes a central area of loosely arranged cells similar to the stellate reticulum of the enamel organ and a peripheral area of palisading columnar or cuboidal cells with hyperchromatic small nuclei oriented away from the basement membrane (reverse polarity). **C**, Acanthomatous ameloblastoma. **D**, Granular cell ameloblastoma. **E**, Ameloblastomatous proliferation is arising in direct continuity with the intact sinonasal surface mucosal epithelium (top). This finding in the face of an isolated sinonasal mass without continuity with gnathic sites supports the histogenesis of these sinonasal tumors from totipotent cells of the sinonasal mucosal epithelium.

- Peripheral area of palisading columnar or cuboidal cells with hyperchromatic small nuclei oriented away from the basement membrane (so-called reverse polarity)
- Areas of hyalinization are often seen surrounding nests or follicles.
- Ameloblastomatous proliferation can be seen arising in direct continuity with the intact sinonasal surface mucosal epithelium, a finding that in conjunction with the absence of continuity with gnathic sites supports the histogenesis of these sinonasal tumors from totipotent cells of the sinonasal mucosal epithelium.
- Histologic subtypes include:
 - Follicular (solid and cystic)
 - Plexiform
 - Acanthomatous
 - Basal cell
 - Granular cell:
 - Histologic subtypes can be found independently or within the same tumor.
 - Have no bearing on treatment or prognosis except for the granular cell variant, which appears to be associated with increased recurrence rate
- Special stains are of limited utility in the diagnosis.

Differential Diagnosis

- Sinonasal nonkeratinizing carcinoma
- Basaloid squamous cell carcinoma
- Adenoid cystic carcinoma
- HPV-related carcinoma with adenoid cystic-like features
- Craniopharyngioma

Treatment and Prognosis

- Surgical excision is the preferred treatment in all cases:
 - Type and extent of surgery varies from conservative procedures such as polypectomy to more aggressive surgical procedures, including the Caldwell–Luc resection, lateral rhinotomy, and partial or radical maxillectomy.
- Recurrence of the tumor may occur within 1 to 2 years of the initial procedure but may occur years after initial surgery.
- Overall treatment success correlates with complete surgical eradication when performed in conjunction with thoroughly detailed radiographic imaging.
- No tumor deaths, metastases, or malignant transformation have been reported.

MALIGNANT NEOPLASMS OF THE NASAL CAVITY AND PARANASAL SINUSES

CARCINOMA OF THE NASAL VESTIBULE

- Carcinoma of the nasal vestibule is uncommon and considered to represent cutaneous carcinomas instead of mucosal carcinomas.
- More common in men than in women; occurs in age ranges from the sixth to ninth decades of life
- Tumors are located either in the nasal vestibule or at the mucocutaneous junction.
- Most common tumor type is squamous cell carcinoma:
 - Majority are keratinizing and well differentiated
- Cutaneous basal cell carcinomas may also occur but are uncommon.
- Cutaneous adnexal tumors may also occur in this location.
- No association with EBV or HPV
- The differential diagnosis for squamous cell carcinoma includes:
 - Cutaneous squamous papilloma
 - Schneiderian-type papillomas
 - Verrucous carcinoma

- Treatment includes local excision and/or radiotherapy.
- Staging follows AJCC system for primary cutaneous carcinomas excluding carcinoma of the eyelid:
 - T1: tumor 2 cm or smaller in greatest dimension with fewer than two high-risk features
 - T2: tumor >2 cm or any size with two or greater high-risk features
 - T3: tumor with invasion of the maxilla, mandible, orbit, or temporal bone
 - T4: tumor with invasion of the skeleton (axial or appendicular) or perineural invasion of skull base

NOTE: High-risk features refer to depth of invasion, perineural invasion, or high-grade histology.

- Wang classification of nasal vestibular carcinomas felt to be superior to AJCC classification regarding prognostic value and more relevant to use, as it is designed specifically for the nasal vestibule:
 - T1: limited to the nasal vestibule, relatively superficial, involving one or more sites
 - T2: extended from the nasal vestibule to adjacent structures, such as the upper nasal septum, upper

- lip, philtrum, skin of the nose, and/or nasolabial fold, but not fixed to the underlying bone
- T3: massive with extension to the hard palate, buccogingival sulcus, large portion of the upper lip, upper nasal septum, turbinate, and/or paranasal sinuses; fixed with deep muscle or bone involvement
- Most patients have an excellent prognosis:
 - 5-year results include:
 - Overall survival 50%
 - Cancer-specific survival 74%
 - Locoregional control 67%
- Cancer-specific survival according to Wang classification reported to be:
 - 83% for T1
 - 63% for T2
 - 39% for T3
 - For T1 tumors, 5-year locoregional control for surgery, surgery + radiotherapy (RT), or RT includes 94%, 87%, or 61%, respectively
 - Invasion of the subjacent nasal septal perichondrium or bone may occur.
 - Metastasis to cervical neck lymph nodes may occur but is uncommon.
- Carcinomas of the sinonasal tract account for approximately 3% of head and neck malignant neoplasms.
- In consideration of the entire sinonasal tract, malignant neoplasms originate (in descending order of occurrence) from:
 - Maxillary sinus (60%)
 - Nasal cavity (20% to 30%)
 - Ethmoid sinus (10% to 15%)
 - Sphenoid and frontal sinuses (1%)
- In consideration of the entire paranasal sinuses alone, malignant neoplasms originate (in descending order of occurrence) from:
 - Maxillary sinus (77%)
 - Ethmoid sinus (22%)
 - Sphenoid and frontal sinuses (1%)
- Causes of sinonasal malignant neoplasms include:
 - Occupational exposure to wood dust is linked to the development of sinonasal adenocarcinomas, intestinal types, and to a lesser extent squamous cell carcinoma.
 - Occupational exposure to nickel refining and chromate pigment manufacture is linked to an increased risk of sinonasal carcinoma.
 - Viruses including HPV and EBV: see below
- Premalignant lesions of the sinonasal tract:
 - Unlike other upper aerodigestive tract sites, in particular the oral cavity and larynx, isolated precursor lesions of the sinonasal tract (i.e., high-grade intraepithelial dysplasia and carcinoma in situ) are rarely seen unless associated with another neoplasm:
 - Often seen in association with an invasive squamous cell carcinoma, including conventional keratinizing type, nonkeratinizing carcinoma, basaloid squamous cell carcinoma
 - May be seen in association with a carcinoma arising in association with a benign neoplasm (e.g., malignant transformation of Schneiderian papilloma)
 - Although an extremely rare occurrence, sinonasal high-grade intraepithelial dysplasia can be seen in association with non-neoplastic sinonasal tract lesions such as inflammatory polyps.
 - Squamous cell carcinoma and variants thereof may develop from inverted and oncocytic types of Schneiderian papillomas:
 - HPV can be found in these types of Schneiderian papillomas, but there is no definitive link between the presence of HPV and the development of sinonasal squamous cell carcinoma.
 - There is no known association between the presence of squamous metaplasia of the sinonasal epithelium and the development of squamous cell carcinoma.

SINONASAL TRACT SQUAMOUS CELL CARCINOMA

General Considerations

- The epithelium lining of the sinonasal tract is capable of differentiating along various cell lines, accounting for the morphologic variety of carcinomas seen to arise from these surfaces, including squamous cell carcinoma, variants of squamous cell carcinoma, and adenocarcinomas.
- Squamous cell carcinomas of the upper aerodigestive tract mucosa are divided according to histologic subtype:
 - Most common type of squamous cell carcinoma of the sinonasal tract is the conventional type, including keratinizing and nonkeratinizing squamous cell carcinomas.
 - A number of “variants” of conventional squamous carcinoma may occur in the sinonasal tract, including papillary squamous cell carcinoma, verrucous carcinoma, spindle cell squamous carcinoma, basaloid squamous cell carcinoma, and adenosquamous carcinoma.
 - These variants of squamous cell carcinoma are sufficiently different in their pathologic features, biologic behavior, and therapeutic approach to merit separate discussion.
- Carcinomas of the sinonasal tract account for less than 1% of all malignant neoplasms.

- Viral-associated sinonasal carcinomas:
 - Human papillomavirus (HPV):
 - High-risk types of HPV now well-established as major etiologic factors in head and neck carcinomas especially of the oropharynx (see Section 3 for more complete discussion)
 - Transcriptionally active high-risk types of HPV are an important oncologic agent of certain carcinomas arising in the sinonasal tract.
 - HPV-associated sinonasal tract carcinomas proven to harbor transcriptionally active high-risk HPV by p16 immunohistochemistry and HPV DNA in situ hybridization (ISH) or polymerase chain reaction (PCR) include:
 - Nonkeratinizing carcinoma, as well as partially keratinizing squamous cell carcinoma
 - Basaloid squamous cell carcinoma
 - Papillary squamous cell carcinoma
 - Adenosquamous carcinoma
 - Adenoid cystic-like carcinoma
 - Rare examples of other sinonasal carcinoma types in which HPV identified by p16 immunohistochemistry and HPV DNA ISH or PCR include:
 - Small cell undifferentiated neuroendocrine carcinoma
 - Sinonasal undifferentiated carcinoma
 - In the oropharynx, HPV-associated carcinomas have distinct clinically epidemiologic and biologic characteristics (see Section 3 Pharynx for more complete discussion).
 - To date, it is yet to be determined if sinonasal carcinomas associated with HPV also have distinct clinically epidemiologic and biologic characteristics although appears HPV-associated nonkeratinizing carcinoma may have a better prognosis.
 - Epstein-Barr virus (EBV):
 - Extranodal NK/T-cell lymphoma, nasal type is associated with EBV (see later in this section).
 - Confirmation can be made by in situ hybridization for Epstein-Barr-encoded DNA (EBER).

SINONASAL SQUAMOUS CELL CARCINOMA

(Figs. 3-37 through 3-42)

Definition: Malignant epithelial neoplasm arising from the surface epithelium with squamous cell differentiation.

Synonyms:

- For keratinizing squamous cell carcinoma: sinonasal carcinoma; epidermoid carcinoma
- For nonkeratinizing squamous cell carcinoma: transitional carcinoma; respiratory epithelial

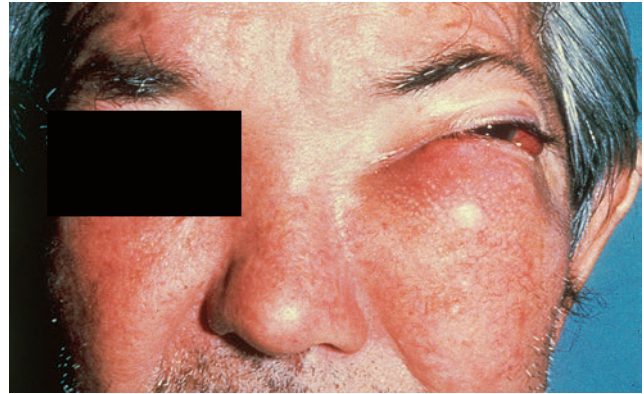


Fig. 3-37.

Sinonasal (maxillary sinus) keratinizing squamous cell carcinoma presenting with marked facial deformity, facial nerve paralysis, and orbital involvement.

carcinoma; Ringertz carcinoma; cylindrical cell carcinoma:

- Similar nonkeratinizing carcinomas of the oropharynx represent HPV-associated carcinomas, and such terminology (i.e., HPV-associated carcinoma) may in the future also be applicable for sinonasal nonkeratinizing carcinoma (for more complete discussion see Section 3, Pharynx).

Clinical

- Represents approximately 3% of head and neck malignant neoplasms and less than 1% of all malignant neoplasms
- Represents the most common type of malignant epithelial neoplasm of the sinonasal tract
- More common in men than in women; most frequently seen in the sixth and seventh decades of life, with 95% of cases arising in patients older than 40 years
- In decreasing order of frequency, the sites of occurrence include:
 - Antrum of the maxillary sinus > nasal cavity > ethmoid sinus > sphenoid and frontal sinuses
 - Although the frontal and sphenoid sinuses may be the sites of a primary carcinoma, most of the neoplasms involving these sinuses arise from the ethmoid sinus or from the nasopharynx.
 - Carcinoma of the nasal septum is extremely rare.
- Clinical presentations include facial asymmetry, unilateral nasal obstruction, epistaxis, a tumor mass palpable or visible in the nasal or oral cavity, pain, persistent purulent rhinorrhea, nonhealing sore or ulcer, and exophthalmos.
- Diagnosis of paranasal sinus carcinoma is often delayed as the clinical signs and symptoms in the earlier stages of disease are similar to those of chronic sinusitis, whereas the diagnosis of carcinoma of the

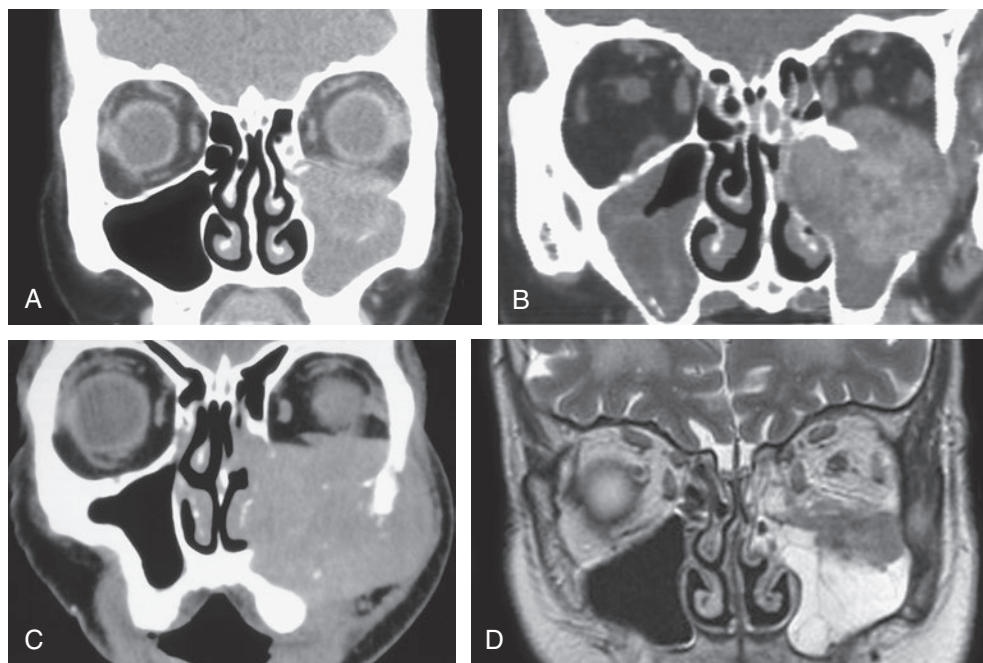


Fig. 3-38. Sinonasal squamous cell carcinoma.

Coronal CT scans (**A** to **C**) on three different patients show in **A**, an antral tumor that has destroyed the orbital floor and obstructed the antrum. The tumor has extended through the periorbita, which is noted by the infiltration of the extraconal fat planes in the lower orbit. In **B**, the antral tumor has destroyed more of the antral walls, obstructed the antrum, and more grossly infiltrated the orbit and the inferior musculature. In **C**, the tumor has caused even more bone destruction and infiltrated more of the orbit, causing clinical elevation of the left eye. In **D**, a coronal T2-weighted MR image shows a low signal intensity antral tumor that has destroyed the orbital floor and invaded the left ethmoid cells. The orbital invasion is extensive with infiltration of the inferior and medial muscles. All of these patients had maxillary squamous cell carcinomas. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 268, Fig. 4-23.)

nasal cavity is usually recognized relatively early as symptoms prompt earlier clinical detection.

- Radiology:
 - Nonexpansile mass causing sinus opacification with erosion and/or destruction of the sinus bony confines and extension to adjacent soft tissue structures
- Risk factors that have been associated with sinonasal tract squamous carcinoma include:
 - For keratinizing squamous cell carcinoma:
 - Cigarette smoking
 - Not associated with HPV
 - Occupational exposure, as well as exposure to textile dust and nickel, prior Thorotrast use, and development from Schneiderian papilloma
 - For nonkeratinizing or partially keratinizing:
 - Associated with high-risk HPV:
 - p16 positive (nuclear and cytoplasmic in >75% of tumor cells)
 - Transcriptionally active high-risk HPV identified by molecular analyses (ISH, PCR)

- In carcinomas arising in association with a Schneiderian papilloma, low-risk HPV may be found, but a direct cause and effect has not been definitively found.

- Patients with nasal cavity squamous carcinomas are at greater risk for a second primary malignancy either at another mucosal site in the upper aerodigestive tract or involving the nonhead and neck sites including lung, gastrointestinal tract, or breast.

Pathology

Gross

- Polypoid, papillary, fungating, or inverted growth patterns that may be well circumscribed, with an expansile growth and limited invasion, or necrotic and friable with a hemorrhagic appearance and destructive growth

Histology

- Sinonasal squamous cell carcinomas are histologically divided into keratinizing and nonkeratinizing subtypes.

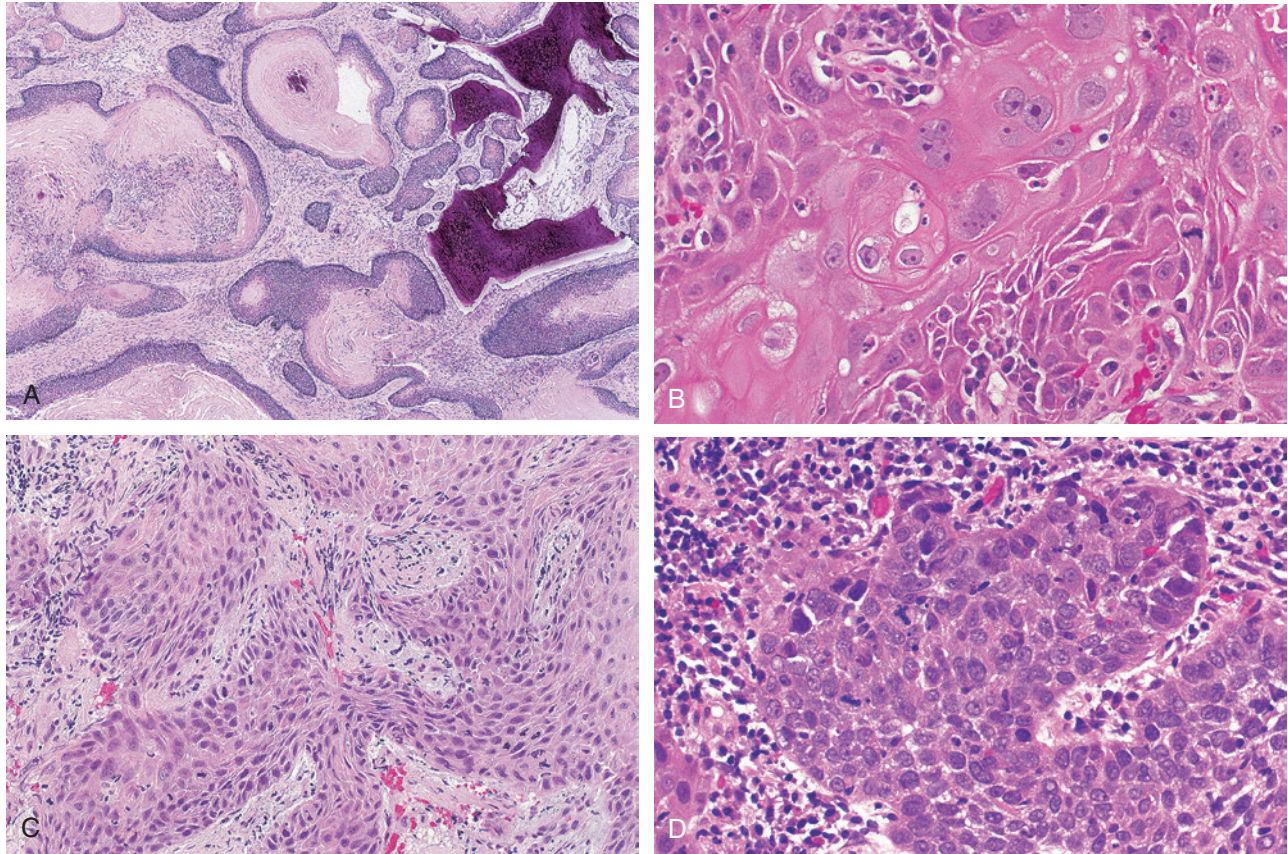


Fig. 3-39. Sinonasal (maxillary sinus) keratinizing squamous cell carcinoma.

A, The carcinoma is invasive including into soft tissue structures; the histology of the invasive carcinomas may range from **(B)** well differentiated with cohesive tumor nests showing keratinization, intercellular bridges, and limited cytomorphic atypia. **C**, Moderately differentiated with cohesive tumor nests retaining their squamous cell appearance with individual cell keratinization and intercellular bridges but with greater nuclear pleomorphism with increased nuclear-to-cytoplasmic ratio and increased mitotic activity. **D**, Poorly differentiated with cohesive tumor nests with limited squamous cell features and marked nuclear pleomorphism and mitotic activity including atypical mitoses.



Fig. 3-40. Nonkeratinizing squamous cell carcinoma of the right maxillary sinus.

The patient presented with facial deformity with deviation of the nose to the left of midline and slight closure of the right eye.

Keratinizing Squamous Cell Carcinoma (SCC)

- Keratinizing SCC is the most common sinonasal carcinoma, representing 80% to 85% of all cases.
- Histologic grading includes well-differentiated, moderately differentiated, and poorly differentiated carcinoma.
- Well-differentiated squamous cell carcinomas are characterized by:
 - Readily apparent keratinization with keratin pearl formation or individual cell keratinization
 - Dyskeratosis (abnormal keratinization), which may be prominent
 - Intercellular bridges are identifiable.
 - Neoplastic cells showing mild to moderate nuclear atypia with enlarged, hyperchromatic nuclei and low mitotic activity
- Dysplasia of the adjacent or overlying surface epithelium may be seen; if present, the dysplasia may

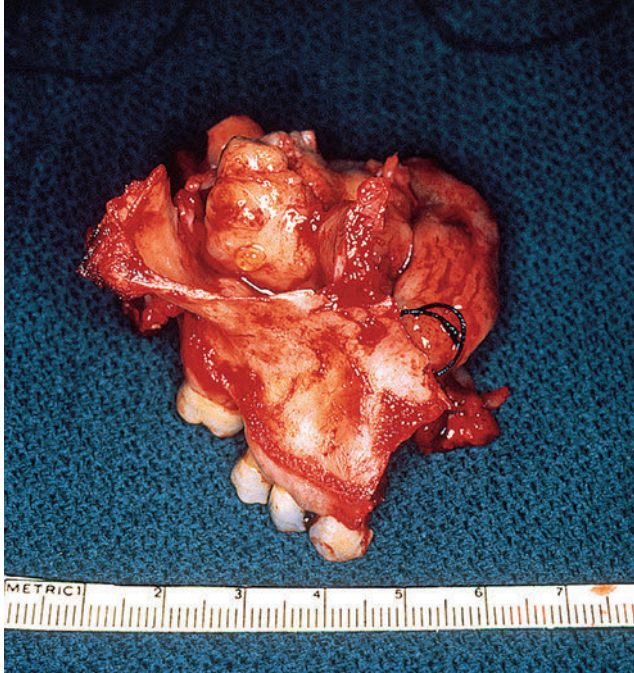


Fig. 3-41. Nonkeratinizing squamous cell carcinoma.

Portion of resected specimen showing a bulging, tan-white mass in the maxillary sinus.

vary from low-grade (mild dysplasia) to high-grade dysplasia (i.e., moderate to severe); severe dysplasia is synonymous with carcinoma in situ.

- As a squamous cell carcinoma becomes less differentiated (higher histologic grade), the tumor shows less evidence of squamous differentiation including absence of keratinization and identifiable intercellular bridges and greater degree of anaplasia as well as increased mitotic activity, including atypical forms.
- Even in the poorly differentiated carcinomas, evidence of keratinization is usually focally present.
- Stromal invasion may include cohesive nests or cords of malignant cells or may be represented by isolated invasive malignant cells:
 - Host response to invasive carcinoma (desmoplasia) includes collagen deposition with or without an associated chronic inflammatory cell reaction.
- Immunohistochemistry:
 - Cytokeratins, p63 and p40 positive
 - p16 negative

Nonkeratinizing Squamous Cell Carcinoma

- Represents approximately 15% to 20% of all cases
- May also have a papillary or exophytic growth pattern but often shows a downward (inverted or

endophytic) growth with broad interconnecting bands or nests of neoplastic epithelium

- Tumor nests may have rounded or smooth borders or may be delineated by basement membrane-like material:
 - This pattern of growth is similar to that of bladder cancers, hence the designation of these tumors as transitional-type carcinoma.
 - Given the smooth borders or surrounding basement membrane-like material, these tumors may not be interpreted as invasive and may be underdiagnosed as papillomas with severe dysplasia/carcinoma in situ.
- This tumor type is composed of elongated cells with a cylindric or columnar appearance, oriented perpendicular to the surface and generally lacking evidence of keratinization; keratin may be present focally but does not represent a significant component of the tumor.
- In general, this is a hypercellular neoplasm characterized by nuclear pleomorphism, hyperchromasia, increased nuclear-to-cytoplasmic ratio, loss of cell polarity, and increased mitotic activity, including atypical forms although in any given case degree of nuclear pleomorphism and mitotic activity may not be high.
- Dysplasia of the adjacent or overlying surface epithelium may be seen; the dysplasia may vary from low-grade (mild dysplasia) to high-grade (moderate to severe dysplasia).
- Immunohistochemistry:
 - Cytokeratins, p63 and p40 positive
 - p16 positive (diffuse nuclear and cytoplasmic) – Reported in approximately 40% of cases
 - Neuroendocrine markers typically negative but patchy staining (e.g., synaptophysin, others) may be present
 - *SMARCB1* (INI-1) positive.

Differential Diagnosis

- Schneiderian papilloma, inverted type:
 - Growth characteristics seen in nonkeratinizing carcinoma, in particular presence of broad interconnecting or ramifying cords of tumor, are not the pattern seen in association with Schneiderian papilloma, inverted type; presence of such growth characteristics even in face of tumor with limited nuclear pleomorphism and increased mitotic activity should raise serious concern for diagnosis of nonkeratinizing carcinoma.
- ***SMARCB1* (INI-1)-deficient carcinoma of sinonasal tract:** (Figures 3.43)
 - *SMARCB1* (INI-1) tumor-suppressor gene located on chromosome 22q11.2
 - Gene product ubiquitously expressed in nuclei of normal tissues

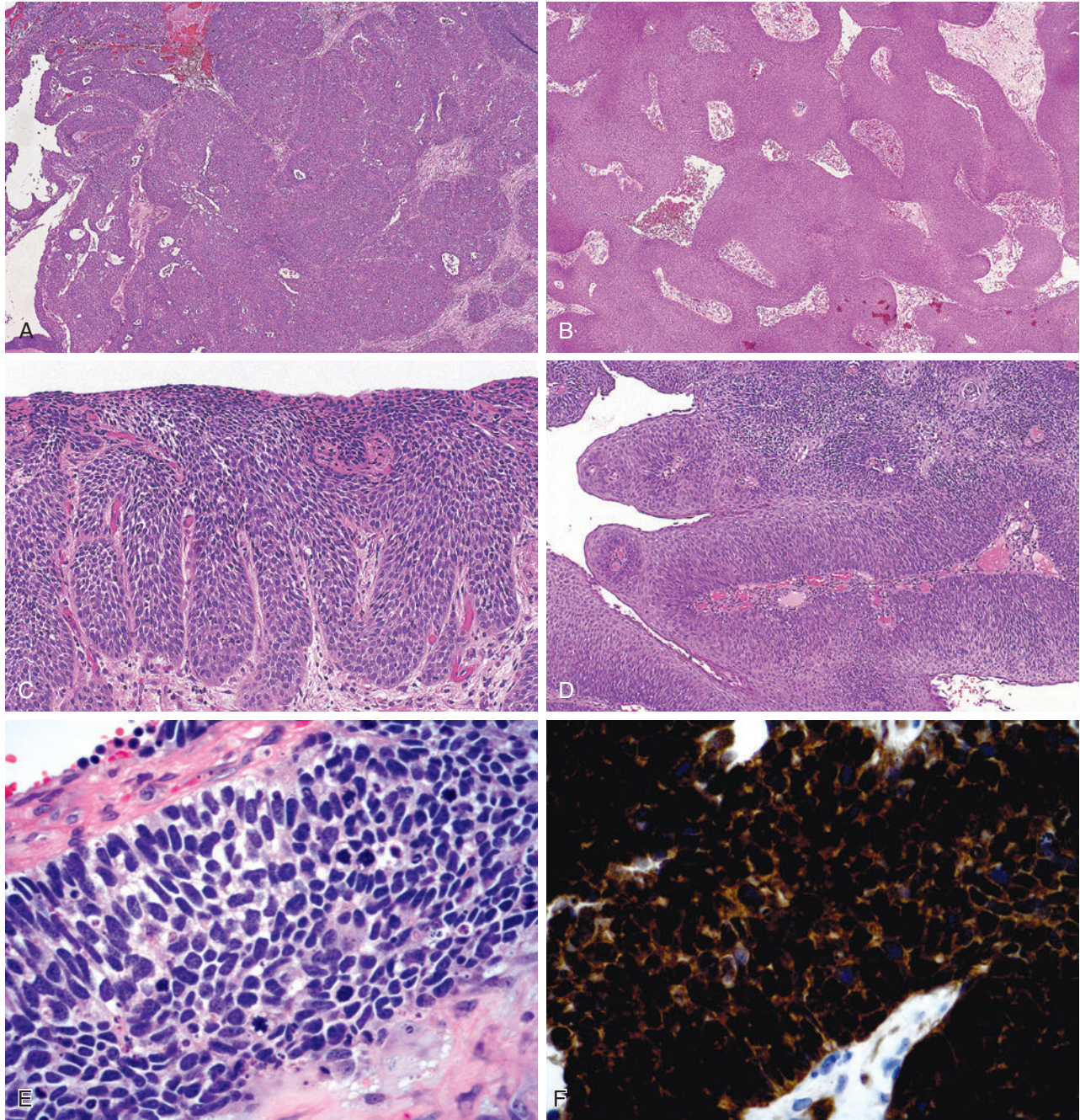


Fig. 3-42. Nonkeratinizing squamous cell carcinoma.

A and **B**, The tumor originates from the surface epithelium and invades into the submucosa as broad interconnecting bands of the neoplastic epithelium growing down ("inverted") into the stroma. **C**, Focally, carcinoma in situ may be present. **D**, The neoplastic epithelium is nonkeratinizing; cells are elongated with a cylindric or columnar appearance, oriented perpendicularly to the surface. **E**, Marked cellular pleomorphism with loss of polarity, increased nuclear-to-cytoplasmic ratio, and increased mitotic activity. Similar to oropharyngeal nonkeratinizing carcinoma, this type of sinonasal carcinoma has been associated with human papillomavirus (HPV) and in the future may be referred to as a sinonasal HPV-associated (nonkeratinizing) carcinoma. **F**, Lesional cells show diffuse (nuclear and cytoplasmic) p16 immunoreactivity with subsequent confirmation by molecular analysis for the presence of transcriptionally active HPV.

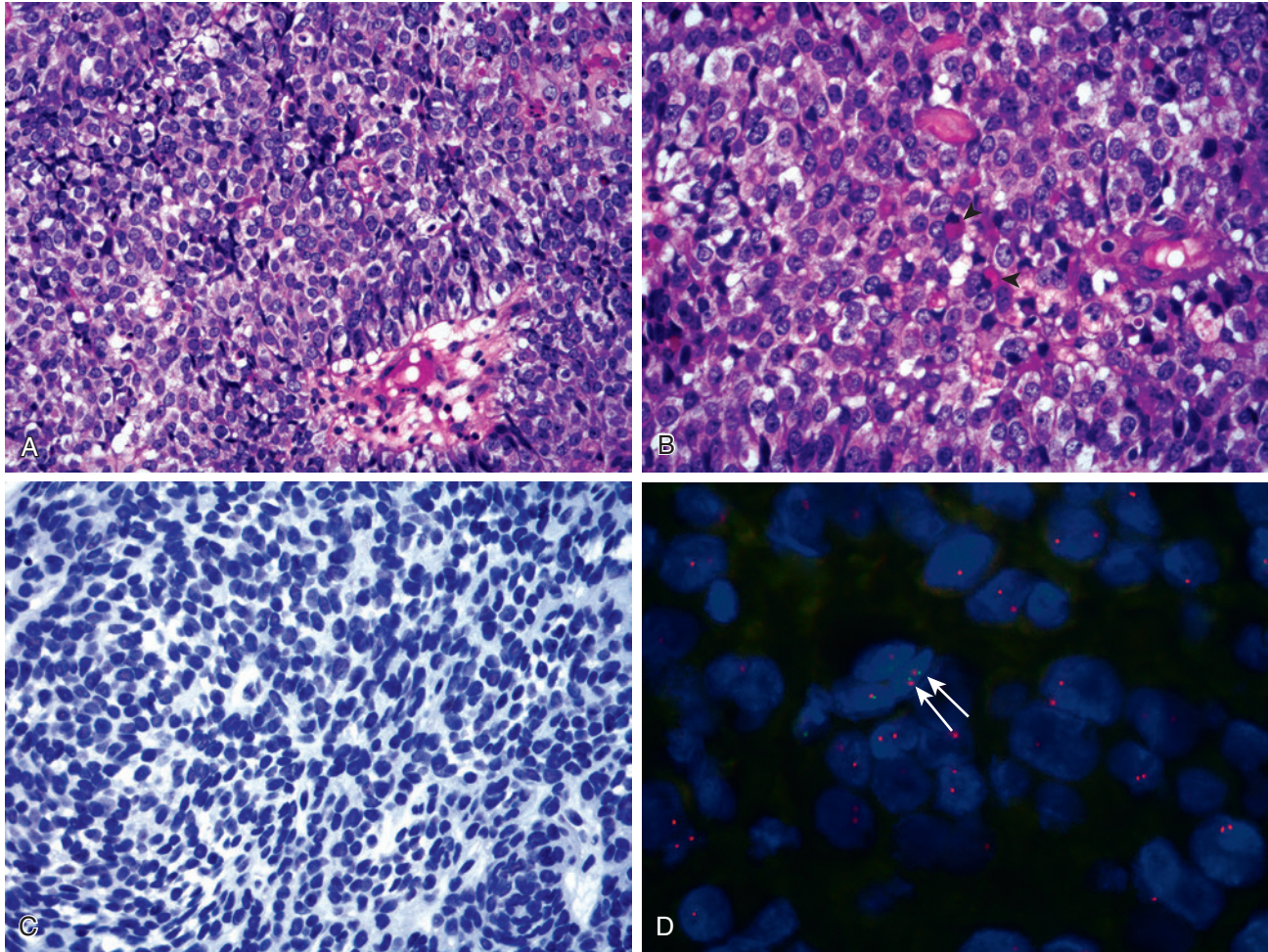


Fig. 3-43. *SMARCB1* (INI-1)-deficient carcinoma of the sinonasal tract.

A and B, Tumor predominantly comprised of basaloid cells with enlarged round nuclei with inconspicuous to enlarged nucleoli and variable amount of cytoplasm; note the absence of significant nuclear pleomorphism although increased mitotic activity and necrosis commonly present (not shown); in **(B)** intermixed among the basaloid cells are cells with abundant, eccentric eosinophilic cytoplasm (*arrowheads*) imparting rhabdoid features. Immunohistochemical staining showed the lesional cells to be reactive for cytokeratins (not shown) with absence of **(C)** INI1 (nuclear) reactivity. Molecular analysis confirmed the loss of *SMARCB1* expression characterized by *SMARCB1* deletions by FISH. **D,** Two orange signals (CEN22) but no green signals (*SMARCB1*) in a majority of tumor cells indicating biallelic (homozygous) deletion of *SMARCB1* locus. One normal stromal spindle cell (likely fibroblast, *arrows*) showed intact two signals of both colors. (Slides for photography and image for part D provided by A. Agaimy, MD).

- Considered integral component of chromatin remodeling complex *SWI/SNF*
- Loss of nuclear *SMARCB1* expression characterizes heterogeneous family of neoplasms with highly varying histologic appearance and biological behavior including:
 - Pediatric atypical teratoid/rhabdoid tumors, malignant rhabdoid tumors of kidney and extrarenal tissues, renal medullary carcinoma, both types of epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumors, and some myoepithelial soft tissue neoplasms
 - In addition to these predominantly pediatric aggressive neoplasms defined by primary loss of *SMARCB1* expression as a consequence of deletions or mutations involving *SMARCB1* locus, secondary *SMARCB1* loss reported in carcinomas arising in different organs including gastrointestinal tract, pancreas, uterus and nervous system
- Common to most of these entities:
 - Loss of *SMARCB1* (INI-1) reactivity
 - Presence of rhabdoid cell component that varies from subtle (few scattered cells) to extensive comprising (almost entire neoplasm)

- Frequent although not uniformly aggressive clinical course with widespread metastasis at time of diagnosis
- *SMARCB1* gene inactivation implicated in pathogenesis of diverse group of malignant neoplasms that tend to share “rhabdoid” cytomorphology
- Recent reports document presence of *SMARCB1*-deficient carcinomas arising in sinonasal tract (9 total cases) characterized by:
 - Slight female predilection; occurrence in adults (mean in sixth decade of life)
 - Presence of nests, sheets, and cords of cells without any histologic evidence of specific cellular differentiation (e.g., squamous, glandular, other).
 - Primarily comprised of basaloid cells with scattered intermixed rhabdoid cells:
 - Basaloid cell nests and lobules with intervening desmoplastic stroma
 - Basaloid cells comprised of enlarged round nuclei with inconspicuous to enlarged nucleoli and scant cytoplasm
 - Rhabdoid cells characterized by abundant, eccentric eosinophilic cytoplasm:
 - Such cells may suggest plasmacytoid appearance and a possible diagnosis of a myoepithelial neoplasm
 - Generally absence of significant nuclear pleomorphism but increased mitotic activity (3 to 30 mitoses per 10 high power fields) and necrosis commonly seen
 - Additional features may include:
 - papilloma-like exophytic component
 - peripheral palisading, perivascular pseudorosettes
 - intraepithelial dysplasia (i.e., carcinoma in situ) may or may not be identified
 - extensive pagetoid surface growth with prominent denuding features
 - replacement of underlying mucous glands mimicking inverted papilloma
 - Immunohistochemical staining includes:
 - INI-1 negative staining in all cases:
 - Absence of INI1 reported in both invasive and in situ components
 - Consistent reactivity for cytokeratins (AE1/AE3, CK5) with diffuse or punctate paranuclear staining, latter reported relative to rhabdoid cells
 - Variable p63 and p40 reactivity with diffuse or focal nuclear staining
 - Vimentin reactivity varying from diffuse to scattered positive cells; rhabdoid cells with paranuclear dot-like pattern
 - Focal synaptophysin reactivity in majority of cases
- Variable expression for p16 but no evidence of transcriptionally active HPV by molecular analyses
- E-cadherin strong membranous reactivity
- Absence of S100 protein except for 1 reported case with focal staining
- No reactivity for chromogranin, smooth muscle actin and NUT protein marker
- Molecular biology:
 - Loss of *SMARCB1* expression characterized by *SMARCB1* deletions by FISH
 - Absence of EBV by in situ hybridization
- Differential diagnosis includes:
 - Nonkeratinizing squamous cell carcinoma
 - Sinonasal undifferentiated carcinoma
 - Schneiderian papilloma
 - NUT midline carcinoma
 - Myoepithelial carcinoma
- Treatment includes surgery and adjuvant chemoradiation
- Prognosis:
 - Majority of patients present with advanced clinical (and pathologic) stage disease (T4/pT4)
 - Local recurrences and/or distant metastases are common, including:
 - locoregional lymph nodes
 - distant visceral sites (liver, lung, pleural, pericardium)
 - Of patients reported to date, 8 with follow-up including:
 - 63% (5/8) dead of disease from 15 months to as long as 102 months
 - 4 alive without disease up to 84 months from diagnosis
 - 1 alive with disease at 70 months from diagnosis
- Inactivation of *SMARCB1* tumor-suppressor gene appears to be involved in pathogenesis of a subset of sinonasal carcinomas further expanding family of *SMARCB1*-deficient neoplasms

Treatment and Prognosis

- Treatment for sinonasal squamous cell carcinoma is complete surgical resection and adjuvant radiotherapy with or without chemotherapy:
 - Surgical advances now permit complex tumor removal and reconstruction surrounding these structures, resulting in functional and cosmetic improvements.
- Induction chemotherapy may be used in patients with advanced stage disease:
 - Favorable response to induction chemotherapy associated with better survival and reasonable chance of organ preservation.

- Local recurrences frequently occur, but metastatic disease is uncommon if the tumor is confined to the involved sinus:
 - Local failure remains the dominant cause of poor outcome.
 - Death due to disease usually the result of uncontrollable local recurrent disease
- Regional lymph node metastatic rate of approximately 15%:
 - Given central location, metastatic disease may occur to ipsilateral or contralateral lymph nodes.
 - Primary lymph node drainage is to submental and submandibular lymph nodes.
 - Secondary drainage to facial, superficial parotid, and deep cervical lymph nodes
- Owing to low rate of nodal metastases, regional lymph node dissection and/or radiation of regional lymph nodes not advocated as part of initial management protocol
- Tumor extension beyond the sinus wall results in a higher incidence of regional lymph node metastasis.
- In general, the prognosis is poor:
 - 5-year survival rates include:
 - 65% for carcinomas confined to nasal cavity
 - 45% for carcinoma of the maxillary antrum
 - Clinical stage is of more importance to prognosis than histologic type.
 - Factors portending a poorer prognosis include:
 - Higher clinical stage disease with involvement of more than one anatomic area
 - Extension beyond the nasal cavity or paranasal sinuses
 - Regional lymph node metastasis
- Presence of HPV associated with better disease-free survival and overall survival than non-HPV cancers
- Pattern of invasion may also affect prognosis:
 - Tumors with “diffuse spread” or single cell invasive growth pattern have a decreased survival of 30% to 40% as compared with 80% to 90% survival in patients with a more cohesive or “pushing” pattern of invasion.
 - Invasive cancers with single cell or small aggregates of tumor cells invading into the host stroma are much more capable of lymph-vascular invasion as compared with large cohesive tumor nests.
- TNM staging of sinonasal tract mucosal carcinomas applies only to the maxillary sinus (see [Table 3-2](#)).

VARIANTS OF SQUAMOUS CELL CARCINOMA

- Variants of conventional squamous cell carcinoma include:
 - Verrucous carcinoma
 - Papillary squamous cell carcinoma
 - Spindle cell squamous carcinoma

- Basaloid squamous cell carcinoma
- Adenosquamous carcinoma
- All of these variants may occur in the sinonasal tract but are more common in other mucosal sites of the head and neck.
- For a detailed discussion of these histologic variants, see appropriate sections including Section 2, Oral Cavity; Section 3, Pharynx; and Section 5, Larynx.

SINONASAL UNDIFFERENTIATED CARCINOMA (SNUC)

(Figs. 3-44 through 3-46)

Definition: Highly aggressive and clinicopathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease and is composed of pleomorphic tumor cells with frequent necrosis without evidence of squamous or glandular differentiation; neuroendocrine differentiation may or may not be present.

Synonym: Anaplastic carcinoma

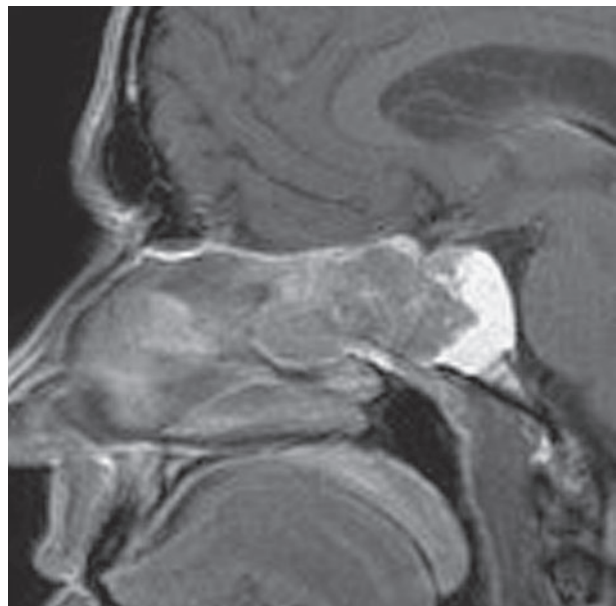


Fig. 3-44. Sinonasal undifferentiated carcinoma (SNUC).

SNUCs typically are rapidly growing, usually presenting over weeks to months, and at the time of presentation frequently are widely invasive with destructive growth. Sagittal T1-weighted, fat-suppressed, contrast-enhanced MR image shows a large mass in the ethmoid and sphenoid sinuses. The remaining sphenoid sinus is obstructed. Some dural enhancement is also present. This patient had an SNUC. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 291, Fig. 4-78.)

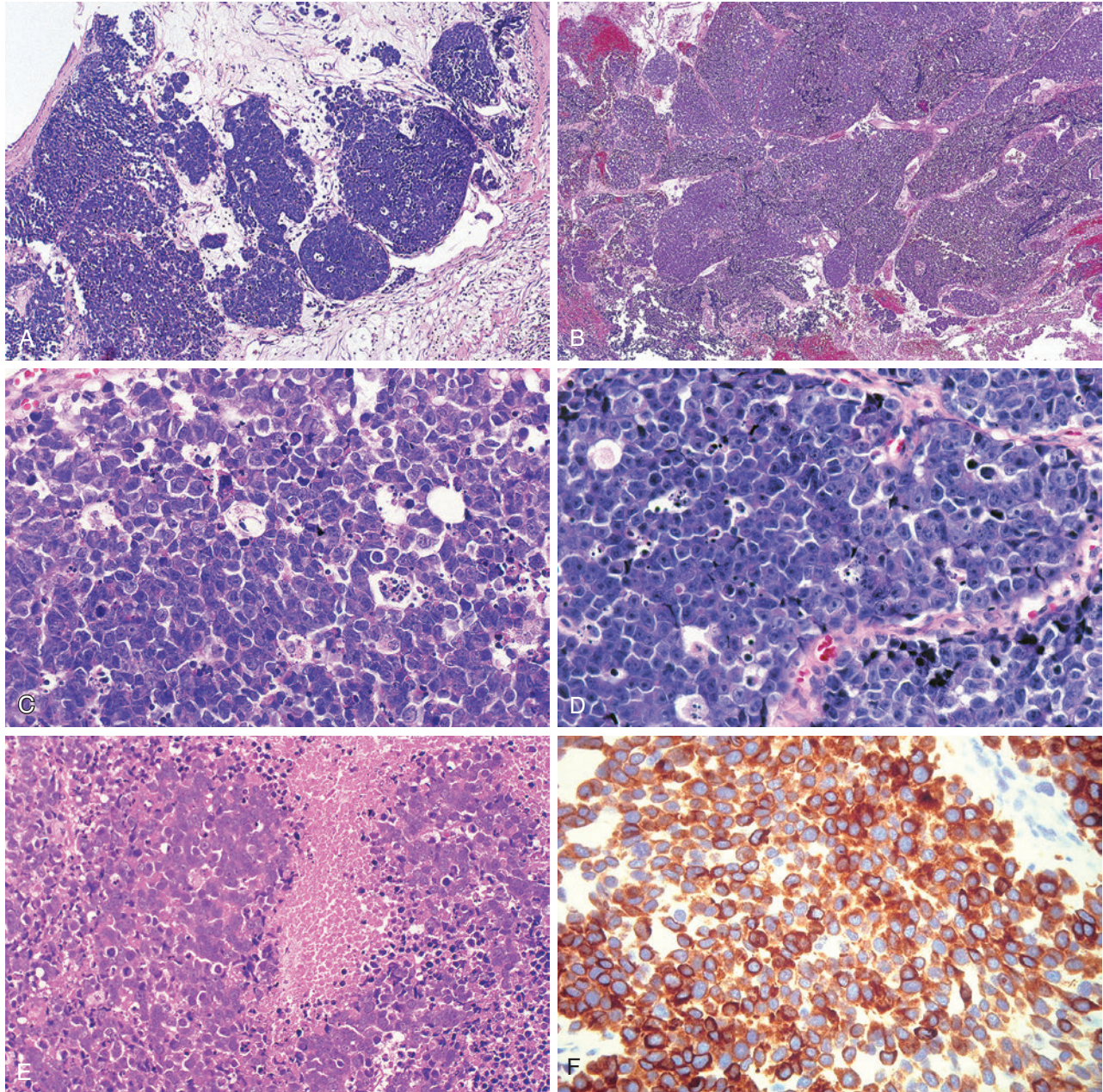


Fig. 3-45. Sinonasal undifferentiated carcinoma.

A, Invasive tumor showing a lobular growth, a frequent feature of this tumor; the surface epithelium is attenuated (*upper left*), and it is uncommon to find evidence of carcinoma in situ and/or continuity of tumor to the surface epithelium. **B**, In addition to a lobular pattern, trabecular (as well as diffuse—not shown) growth may be identified. **C** and **D**, These tumors are markedly cellular and characterized by the presence of polygonal to oval-appearing cells composed of medium to large, round to oval, hyperchromatic to vesicular nuclei, inconspicuous to prominent nucleoli, and a varying amount of eosinophilic-appearing cytoplasm with poorly defined cell membranes; increased mitotic activity is present, including atypical mitoses and individual cell necrosis. **E**, Usually, prominent confluent foci of tumor necrosis is present. **F**, Diffuse cytokeratin immunoreactivity is present.

Clinical

- Considered an uncommon neoplasm but being recognized with greater frequency
- More common in men than in women; occur over a wide age range, including third to ninth decades of life, with a median at presentation in the sixth decade
- Typically, patients present with multiple symptoms that include nasal obstruction, epistaxis, proptosis, visual disturbances (e.g., diplopia), facial pain, and symptoms of cranial nerve involvement.

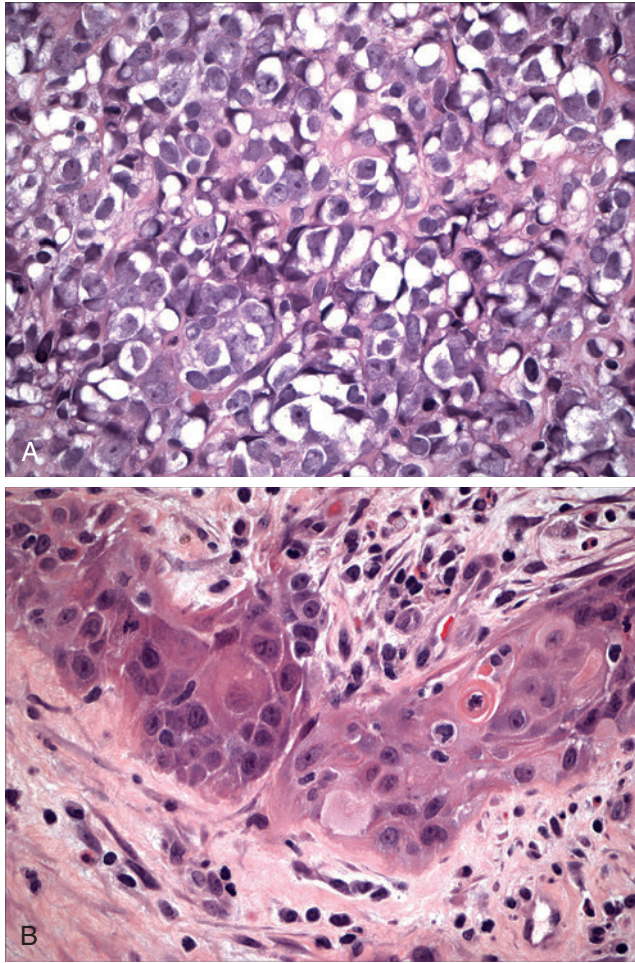


Fig. 3-46. SNUC.

Additional cytologic features that can be seen in sinonasal undifferentiated carcinomas include **(A)** the presence of cells with clear cytoplasm and **(B)** focal squamous cell differentiation. The latter if present must represent an extremely limited component of a tumor that otherwise shows unequivocal cytomorphic features and associated clinical parameters of sinonasal undifferentiated carcinoma. However, alternative diagnostic consideration in the face of an undifferentiated carcinoma with squamous differentiation would include NUT midline carcinoma.

- A characteristic clinical phenomenon is that patients with SNUC develop symptoms usually of a relatively short duration (weeks to months).
- Extensively infiltrative at presentation involving multiple sites, including the nasal cavity, one or more paranasal sinuses, orbit, skull base, and the brain
- Most patients have unilateral disease, but bilateral disease may occur.
- Radiology:
 - CT scan, MRI often demonstrate a large (sinonasal) mass typically with local invasive growth

extending beyond its bony confines with involvement of orbital and/or cranial bones.

- Intracranial extension may occur.
- SNUC is a tumor of uncertain histogenesis:
 - It seems reasonable that SNUC arises from the Schneiderian epithelium and therefore is of ectodermal derivation.
 - Although speculative, given overlapping clinical, light microscopic, immunohistochemical, and ultrastructural features with olfactory neuroblastoma and neuroendocrine carcinoma, the cell of origin may be related to the Schneiderian membrane and olfactory epithelia.
 - On the basis of finding neuroendocrine features by immunohistochemistry and electron microscopy, SNUC may be a neuroendocrine carcinoma with classification essentially equivalent to the pulmonary large cell (neuroendocrine) carcinoma; however, most authorities do not consider SNUC to be a variant of neuroendocrine carcinoma.
- There are no known etiologic agents:
 - SNUCs are typically negative for Epstein-Barr virus (EBV) even though there are reports of EBV RNA identified in Asian and Italian patients with SNUC but not in other Western patients with SNUC:
 - Such EBV-positive sinonasal carcinomas more likely are lymphoepithelial-like carcinomas (see later in this chapter).
 - HPV (by p16 immunohistochemistry and molecular analysis) identified in a limited number of SNUCs; uncertain relationship between HPV and SNUCs
 - Some cases have been reported to develop following radiation therapy for nasopharyngeal carcinoma.
 - Although no specific cause is linked to the development of SNUC, cigarette smoking and nickel exposure have been identified in patients with SNUC.
 - Deletion of the retinoblastoma gene has been implicated in the development of SNUC.

Pathology

Cytology

- Hypercellular smears with:
 - A single-cell-predominant pattern
 - Intermediate-sized cells with irregular nuclear contours and small nucleoli
 - Nuclear pleomorphism and mitotic figures present
 - Background of naked nuclei and karyorrhectic debris
 - Vacuoles or extracellular lumina may be identified.

Gross

- Usually large tumors typically measuring more than 4 cm in greatest dimension and tend to be fungating with poorly defined margins, and with invasion into adjacent structures and/or anatomic compartments, including bone destruction

Histology

- Characterized by submucosal cellular proliferation with varied growth, including trabecular, sheet-like, ribbons, solid, lobular, and organoid patterns.
 - Surface involvement may be seen in the form of severe dysplasia/carcinoma in situ, but often there is ulceration, which precludes evidence of surface epithelial derivation.
 - Cellular infiltrate consists of polygonal cells composed of medium to large-sized, round to oval, hyperchromatic to vesicular nuclei, inconspicuous to prominent nucleoli, and a varying amount of eosinophilic-appearing cytoplasm with poorly defined cell membranes, although distinct cell borders may be present; occasionally, cells with clear cytoplasm can be identified:
 - The nuclear-to-cytoplasmic ratio is high.
 - Increased mitotic activity is present, including atypical mitoses.
 - Often prominent tumor necrosis (confluent areas and individual cells) and apoptosis
 - Cell types may include:
 - Cells with round to oval hyperchromatic nuclei, inconspicuous to small nucleoli, and limited pink to amphophilic cytoplasm
 - Cells similar to those seen in nasopharyngeal undifferentiated carcinoma:
 - Cells with large vesicular nuclei and prominent nucleoli and associated lymphocytes
 - Reported to be seen predominantly in Asian patients but not exclusive to Asian patients
 - Large cell type with features similar to large cell carcinoma of the lung:
 - Large cells with pleomorphic nuclei, prominent eosinophilic nucleoli
 - Reported to be seen predominantly in Asian patients but is not exclusive to Asian patients
- NOTE:** Cell types described are not mutually exclusive but can be seen to a variable extent in a single tumor. Further, the increased mitotic activity and necrosis is present in all cell types.
- Lymph-vascular invasion and neurotropism are often present.
 - By definition, squamous or glandular differentiation is not present; however:
 - Squamous cell differentiation may be present without excluding the diagnosis of SNUC.

- The diagnosis of SNUC can still be retained in the presence of squamous differentiation if:
 - The squamous foci (keratinization and intercellular bridges) are limited in extent (e.g., less than 5%) and occur in a neoplasm where the dominant histologic features are those of SNUC
 - The clinical parameters are those associated with SNUC, including:
 - Rapid onset and tumor growth (weeks)
 - Presence of multiple symptoms that may include visual disturbances and symptoms of cranial nerve involvement
 - Extensively infiltrative at presentation involving multiple sinonasal tract (and adjacent) sites
 - Sinonasal squamous cell carcinoma and variants thereof usually do not present with the above clinical parameters, especially rapid onset and tumor growth over a few weeks.
- Neurofibrillary material and true neural rosettes are not identified.
- Histochemistry:
 - Noncontributory to diagnosis
 - Stains for epithelial mucin are negative.
- Immunohistochemistry:
 - SNUCs are consistently immunoreactive with epithelial markers, including pankeratins and simple keratins (i.e., CK7, CK8, and CK19); reactivity for pankeratins is often intense and diffuse.
 - CK4, CK5/CK6, and CK14 reported to be negative
 - Variable reactivity can be identified for p63:
 - Some cases scattered focal positive staining
 - Some cases negative
 - Less common is the presence of diffuse positivity.
 - p40 may be positive.
 - Less than half of the cases have been reported to be positive for epithelial membrane antigen, neuron specific enolase (NSE), or p53.
 - S100 protein rarely observed and never in the peripheral sustentacular cell pattern characteristically observed in olfactory neuroblastoma
 - Focal reactivity for synaptophysin, chromogranin, CD56, CD57 (Leu-7) may be seen.
 - Vimentin, calretinin, muscle markers (desmin, myoglobin, myf-4, actins) hematolymphoid markers (leukocyte common antigen, B- and T-cell), melanocytic cell markers (HMB-45, melana, tyrosinase), and CD99 (Ewing marker) are usually absent.
 - Absence of Epstein-Barr virus by immunohistochemical staining (LMP-1) and/or in situ hybridization for Epstein-Barr encoded RNA (EBER)

- Electron microscopy:
 - Rare membrane-bound, dense core neurosecretory granules have been noted, and poorly formed desmosomes may occasionally be found.
- Cytogenetics and molecular genetics:
 - Sex-determining region Y-Box 2 (SOX2) amplification detected in SNUCs as well as squamous cell carcinoma and carcinomas arising in inverted papillomas, suggesting that SNUCs are molecularly closely related to these other cancers
 - No other specific molecular profiling identified and SNUC remains a poorly characterized malignancy at the clinical and molecular level.

Differential Diagnosis

- Squamous cell carcinoma, keratinizing and nonkeratinizing types (Table 3-5)
- Olfactory neuroblastoma (high grade) (see Table 3-5)
- Small cell undifferentiated neuroendocrine carcinoma (see Table 3-5)
- Nasopharyngeal-type, nonkeratinizing undifferentiated carcinoma (see Table 3-5)
- Sinonasal-based lymphoepithelial carcinoma
- NUT midline carcinoma
- Mucosal malignant melanoma
- Nasal-type NK/T-cell lymphoma
- Rhabdomyosarcoma
- Ewing sarcoma family of tumors

NOTE: Although differences can be identified by light microscopic evaluation, often the differentiation of all these tumor types rests on the immunohistochemical staining profile for a given tumor (Table 3-6).

Treatment and Prognosis

- Multimodality therapy considered best treatment approach to provide best chance for survival and includes radical surgery and postoperative chemoradiotherapy
- Prognosis for patients treated with definitive radiotherapy ± chemotherapy considered less promising than for those receiving surgery and postoperative radiotherapy ± chemotherapy.
- HPV-positive SNUCs may benefit from improved survival, but this finding requires further substantiation.
- Generally considered a highly aggressive neoplasm with poor survival:
 - 5-year overall and disease-free survival rates of 45.2% and 50.7%, respectively, reported in one series (n = 19) with no significant difference between treatment types
 - Another series (n = 23) prognosis included:
 - Actuarial 5-year survival outcomes (n = 23) include:

- Progression-free survival, 42%
 - Cause-specific survival, 43%
 - Overall survival, 32%
- Actuarial 5-year disease control rates include:
 - Local control (in field or marginal), 74%
 - Local-regional control (excluding leptomeningeal spread), 58%
 - Regional control, 78%
 - Freedom from leptomeningeal recurrence, 72%
 - Distant metastasis-free survival, 73%
- Another series (n = 18):
 - 2-, 3-, and 4-year local control (LC), disease-free survival (DFS), and overall survival (OS) were:
 - 78%, 72%, and 56%
 - 75%, 65%, and 52%
 - 75%, 50%, and 48%
 - Trimodality treatment approach provided 83% local control and 92% distant metastasis-free survival
 - Other modalities provided 50% local control and 33% distant metastasis-free survival.
- Local recurrence is common and is the major cause of morbidity and mortality.
- Metastatic spread occurs to bone, brain, liver, and cervical lymph nodes.
- Causes of death primarily related to distant metastases and local invasion

NUT MIDLINE CARCINOMA (NMC) (Figs. 3-47 and 3-48)

Definition: Carcinoma characterized by squamous differentiation or expression of epithelial markers originating from midline epithelial structures with chromosomal rearrangements of the gene encoding nuclear protein in testis (NUT) at 15q14:

- Unique chromosomal translocation, which is the sole identifier of this disease
- t(15;19) results in a novel fusion oncogene, bromodomain-containing protein 4 (BRD4)-NUT
- Some patients harbor NUT with BRD4 gene break point (BRD4-NUT fusion).
- Some patients harbor NUT without BRD4 gene break point (NUT variant).

Synonym: Midline carcinoma with NUT rearrangement

Clinical

- Rare neoplasm with less than 30 cases reported in the literature

TABLE 3-5 Comparison of Sinonasal Undifferentiated Carcinoma (SNUC), Olfactory Neuroblastoma, High-Grade (ONB, HG), SNT Keratinizing Squamous Cell Carcinoma (SCC), SNT Nonkeratinizing Squamous Cell Carcinoma (NKSCC), Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type (NPC), and Small Cell Undifferentiated Neuroendocrine Carcinoma (SCUNC)

	SNUC	ONB, HG	SCC	NKSCC	NPC	SCUNC
Site(s)	SNT usually more than one site	Roof of nasal cavity	Maxillary > nasal > other sinuses	Maxillary > nasal > other sinuses	Nasopharynx	Superior or posterior nasal cavity often with extension into adjacent paranasal sinuses (e.g., maxillary and ethmoid sinuses)
Onset	Rapid (weeks to months)	Not rapid	Not rapid	Not rapid	Not rapid; may present as an occult metastasis to cervical lymph nodes	Not rapid
Intraepithelial premalignant lesion	Typically absent but may be present	Absent	Present	Present	Typically absent but may be present	Typically absent but may be present
Squamous differentiation	Absent	Absent	Present	May be present	Absent	May be present
Pseudorosettes	Absent	Present in histologic grades 1, 2	Absent	Absent	Absent	Absent
True neural rosettes	Absent	Present in histologic grades 3, 4	Absent	Absent	Absent	May be present
CK (AE1/AE3, CAM5.2, CK5/6, OSCAR)	Positive, diffuse and strong although CK5/6 reported as negative in a limited number of cases reported	Negative; scattered lesional cells may be very focally positive	Positive, diffuse and strong	Positive, diffuse and strong	Positive, diffuse and strong	Positive often with punctuate (paranuclear) staining
p63	Variable ranging from negative to focally positive to rare cases extensively positive	Negative	Positive	Positive	Positive	Variably positive
Synaptophysin	Negative	Positive	Negative	Negative	Negative	Positive
S100 protein	Negative although scattered cells may be positive	Characteristic staining along periphery of neoplastic lobules; lesional cells may also be positive	Negative	Negative	Negative	Often positive
NSE	Positive in 50% of cases but typically focal	Consistently positive, diffuse and strong	Negative	Negative	Negative	Positive
p16	Negative but rarely reported as positive	Negative	Negative	Positive; transcriptionally active virus confirmed by ISH or PCR	Negative	May be positive
EBER	Negative	Negative	Negative	Negative	Positive	Negative

EBER, In situ hybridization for Epstein-Barr encoded RNA; SNT, sinonasal tract.

Pseudorosettes, also known as Homer Wright Rosette; True Neural Rosettes, also known as Flexner-Wintersteiner rosettes.

TABLE 3-6 Selective Immunohistochemical Reactivity of Various Sinonasal Tract Malignancies

	CK	p63	SYN	p16	EBER	S100	NSE	CALR	MSM	LCA	CD99	VIM	DES	myf-4
SCC	+	+	–	+	–	–	–	–	–	–	–	–	–	–
SNUC	+	v	–	–	–	–	v	–	–	–	–	–	–	–
ONB	–*	–	v	–	–	+	+	+	–	–	–	–	–	–
SCUNC	+	+	+	+	–	+	+	–	–	–	–	–	–	–
MMM	–	–	–	–	–	+	–	–	+	–	–	+	–	–
NK/T ML	–	+	–	–	+	–	–	–	–	v	–	v	–	–
RMS	–	–	–	–	–	–	–	–	–	–	–	+	+	+
EFT	R+	–	v	–	–	v	v	–	–	–	+	+	–	–

CALR, Calretinin; *CK*, cytokeratins (broad spectrum and simple); *DES*, desmin; *EBER*, in situ hybridization for Epstein-Barr encoded RNA; *EFT*, Ewing sarcoma family of tumors; *LCA*, leucocyte common antigen; *MMM*, mucosal malignant melanoma; *MSM*, melanoma specific markers (HMB45, MelanA, MITF1; tyrosinase); *myf-4*, myogenin (nuclear); *NK/T ML*, nasal-type NK/T cell malignant lymphoma; *NSE*, neuron specific enolase; *ONB*, olfactory neuroblastoma; *R+*, rarely positive; *RMS*, rhabdomyosarcoma; *S100*, S100 protein; *SCC*, squamous cell carcinoma; *SCUNC*, small cell undifferentiated neuroendocrine carcinoma; *SNUC*, sinonasal undifferentiated carcinoma; *SYN*, synaptophysin; *T/NL ML*, nasal type T/NK cell lymphoma; v, variably positive; *VIM*, vimentin.

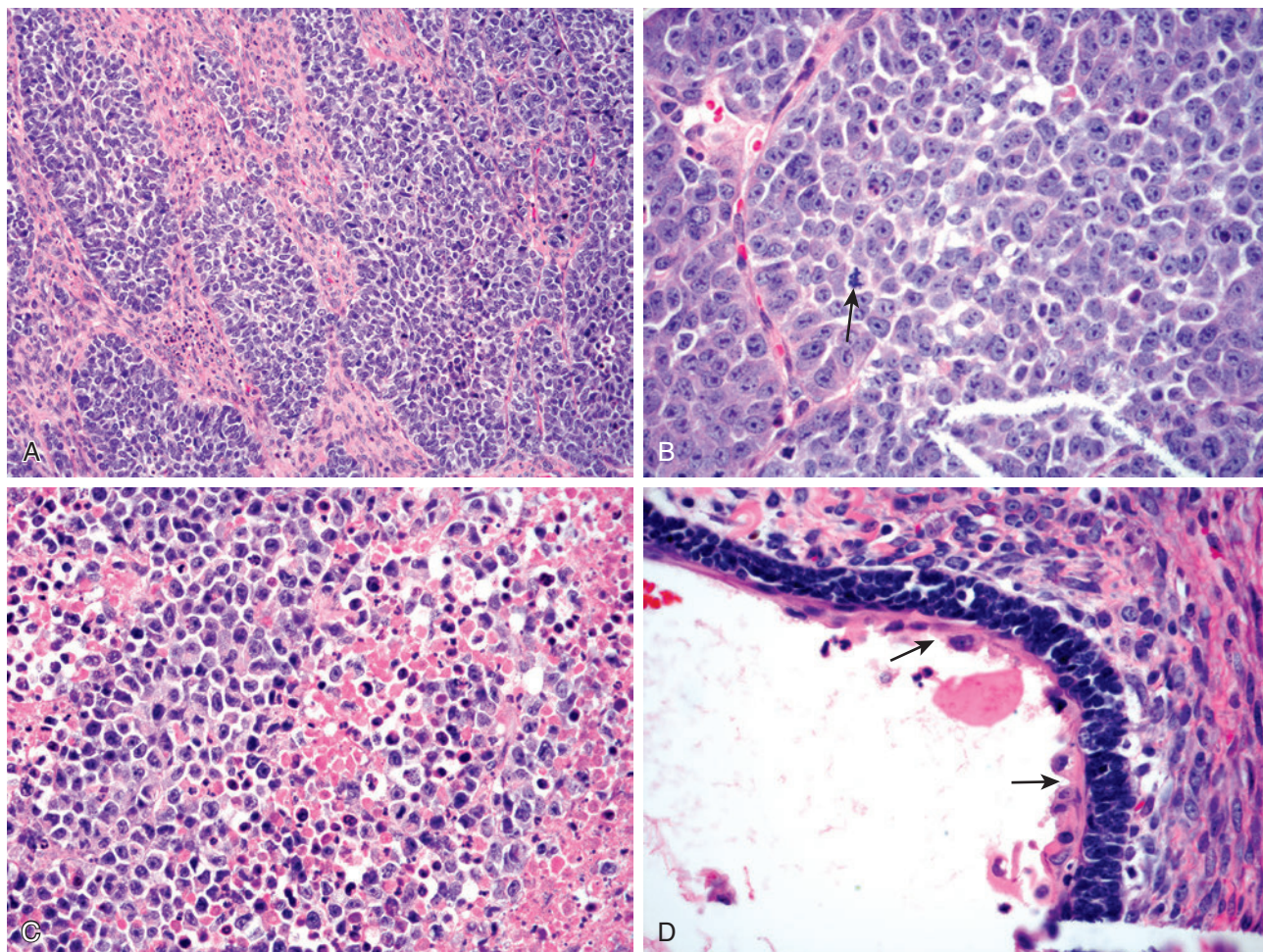
+, positive; –, negative.

*Cytokeratin staining may be focally positive.

†Paranuclear punctate staining pattern often present.

‡Positive in nonkeratinizing carcinoma or partly keratinizing carcinoma; transcriptionally active virus confirmed by molecular analysis.

§Positive in the peripherally situated sustentacular cells.

**Fig. 3-47.** NUT midline carcinoma.

A, Sheets of undifferentiated cells separated by desmoplastic (fibrotic) stroma. **B**, Rather monotonous appearing neoplastic cells with limited nuclear pleomorphism comprised of round to oval nuclei, vesicular chromatin, prominent nucleoli and a minimal amount of amphophilic to eosinophilic appearing cytoplasm; mitotic figures are present (arrow). **C**, Tumor necrosis, including individual cell and/or large confluent foci. **D**, Cystic change with subtle (abrupt) squamous differentiation (arrows) lying adjacent to immature neoplastic cells. (Courtesy C. French, MD.)

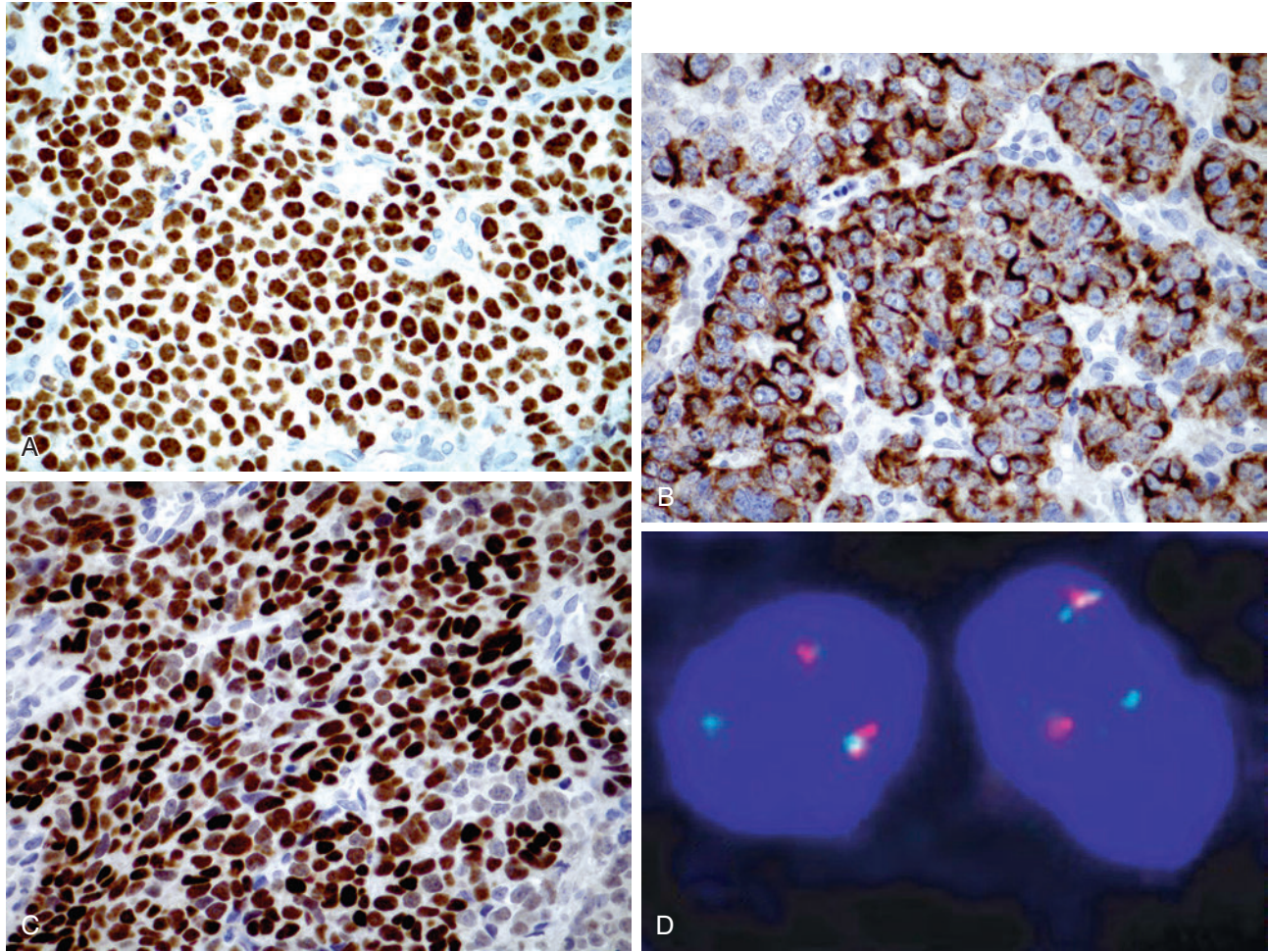


Fig. 3-48. NUT midline carcinoma.

Immunohistochemistry findings include (A) diffuse reactivity (nuclear staining) for antibodies to NUT protein, (B) cytokeratin (AE1/AE3) positivity, and (C) p63 positive (nuclear staining). D, Fluorescent in situ hybridization (FISH) break-apart probe for the NUT gene is diagnostic. (A-C, Courtesy C. French, MD. D, From Orkin S et al: *Oncology of infancy and childhood*, Philadelphia, 2009, Saunders, Fig. 5-15.)

- Slightly more common in women than in men; predominantly affects children and young adults ranging in age from 3 to 35 (median 17.6 years)
- Predominantly but not exclusively occurs in sites above the diaphragm; sites of involvement include:
 - Head and neck:
 - Most common in sinonasal tract
 - Less common sites of occurrence include nasopharynx, larynx (supraglottic larynx and epiglottis), orbit, parotid gland, and tonsils
 - Thorax (mediastinum/thymus > lung and trachea)
 - Urinary bladder
- Symptoms generally related to a mass including obstruction
- There are no known etiologic agents.

Pathology

Gross

- Usually received piecemeal so there are no specific macroscopic findings:
 - Friable tissue fragments with or without necrosis

Histology

- Sheets, ribbons, and/or nests of undifferentiated cells separated by desmoplastic (fibrotic) stroma
- Lesional cells include round to oval nuclei with irregular contours, vesicular chromatin, prominent nucleoli, and a minimal amount of amphophilic-to eosinophilic-appearing cytoplasm:

- Minimal nuclear pleomorphism may be present including cells with monotonous appearance; however, marked nuclear pleomorphism may be present.
- Increased mitotic activity is present and necrosis, including individual cell and/or large confluent foci, may be identified.
- Foci of squamous differentiation frequently present:
 - May be distinct or subtle
 - Mature (well-differentiated) nests of squamous cells and extracellular keratin
 - Foci of squamous differentiation may appear abruptly, lying adjacent to sheets of immature cells.
 - Cystic change of squamous areas may occur.
 - Squamous differentiation is not predictive of the partner gene.
- Immunohistochemistry:
 - Diffuse reactivity (nuclear staining) for antibodies to NUT protein
 - Cytokeratins are positive, including AE1/AE3, CAM 5.2, PanK, CK7, and CK20:
 - Staining may be focal.
 - EMA consistently positive
 - p63 positive
 - p40 may be positive.
 - CD34 may be positive:
 - Initially considered a characteristic feature but no longer felt to be unique or specific
 - Unusual finding for an epithelial neoplasm
 - May be synaptophysin positive but generally negative for neuroendocrine markers (chromogranin, CD56, CD57) and NSE
 - No reactivity for hematolymphoid markers, myogenic markers (desmin, myoglobin, myf-4), actins, S100 protein, HMB45, calretinin, placental alkaline phosphatase (PLAP), alpha fetoprotein, and CD99
 - No known association with HPV or EBV
- Electron microscopy:
 - Composed of cells with large, irregularly shaped nuclei, prominent compact nucleoli, and abundant cytoplasm containing prominent bundles of tonofilaments, occasional clusters of pleomorphic granules, small numbers of lipid inclusions, and rare glycogen deposits
 - Cells exhibit stubby microvillous projections, intermittently enveloped by basal lamina, and interjoined by numerous well-formed desmosomal-type junctions and occasional junctional complexes.
- Cytogenetics and molecular genetics:
 - Translocation involving the NUT gene is (15;19)(q13;p13.1):

- Translocation fuses the NUT gene on chromosome 15 to the *BRD4* gene.
- In approximately one third of cases the NUT gene fuses to a different gene referred to as NUT-variant midline carcinoma.
- Function of the NUT protein is not known.
- Fluorescent in situ hybridization (FISH) using break-apart probe for the NUT gene is diagnostic.

Differential Diagnosis

- Olfactory neuroblastoma (high grade)
- Small cell undifferentiated neuroendocrine carcinoma
- Nasopharyngeal-type undifferentiated carcinoma
- Sinonasal undifferentiated carcinoma
- Mucosal malignant melanoma
- Nasal-type NK/T-cell lymphoma
- Rhabdomyosarcoma
- Ewing sarcoma family of tumors

Treatment and Prognosis

- No established treatment protocols
- Combination multidrug chemotherapy and radiation is most frequent treatment modality.
- Highly lethal despite intensive therapies:
 - Average survival of less than 1 year
- Novel treatment with bromodomain inhibitors and histone deacetylase inhibitors, both of which induce differentiation and growth arrest of NMC cells in vitro and in vivo, being tested in clinical trials for treating patients with NMC.
- Distant metastases may include to bone, lung, pleura, kidney, adrenal, lymph nodes, and skin.
- NUT variant carcinomas may have a less fulminant clinical course.

SINONASAL LYMPHOEPITHELIAL-LIKE CARCINOMA (Fig. 3-49)

Definition: Rare sinonasal tract carcinoma that is morphologically similar to its better known histologic counterpart in the nasopharynx.

Clinical

- Primarily affects men in the fifth to seventh decades of life
- More common in the nasal cavity than the paranasal sinuses
- Clinical presentation includes nasal obstruction, epistaxis, and, in the presence of invasive growth, proptosis and cranial nerve palsies.

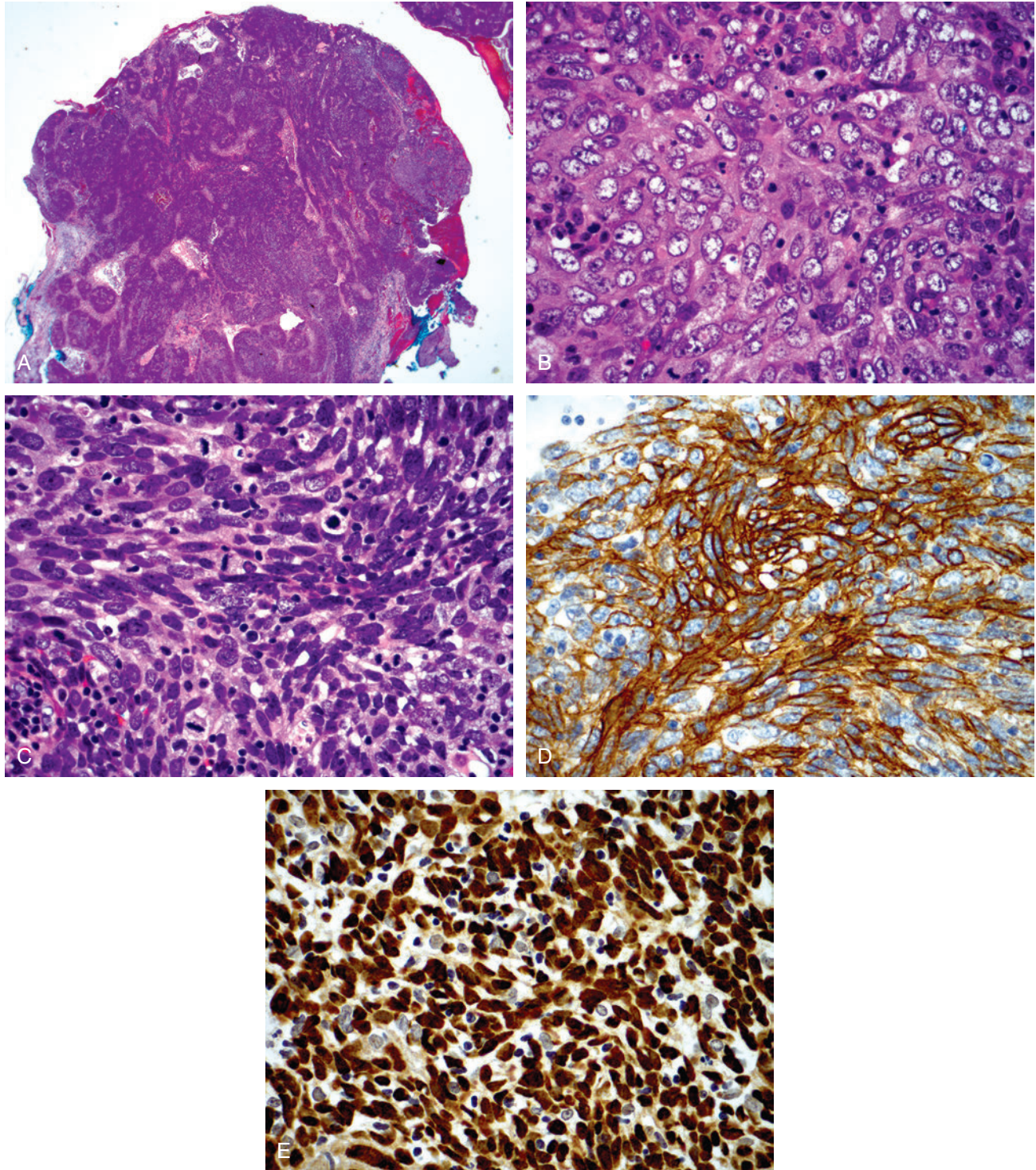


Fig. 3-49. Sinonasal lymphoepithelial-like carcinoma.

A, Polypoid lesion with invasive growth with broad interconnecting cords of tumor similar to the growth pattern seen in sinonasal nonkeratinizing carcinoma. The lesional cells include **(B)** epithelioid-appearing cells and **(C)** spindle-shaped cells. Both cell types comprise enlarged vesicular nuclei and prominent eosinophilic nucleoli. Increased mitotic activity is present. **D**, Lesional cells are immunoreactive for cytokeratin (AE1/AE3). **E**, In situ hybridization for Epstein Barr-encoded RNA (EBER) show diffuse nuclear reactivity.

- Similar to its nasopharyngeal counterpart, there is a strong association with Epstein-Barr virus (EBV).

Pathology

Histology

- Histologic findings are similar to those of nasopharyngeal carcinoma, nonkeratinizing, undifferentiated type (see Section 3, Pharynx).
- Immunohistochemical reactivity:
 - Cytokeratins are positive.
 - Strong expression of EBV-encoded RNA (EBER) in most cases

Differential Diagnosis

- Sinonasal undifferentiated carcinoma:
 - Presence of EBV excludes a diagnosis of SNUC.
- Nasopharyngeal carcinoma, nonkeratinizing, undifferentiated type:
 - It is imperative to exclude sinonasal involvement from a nasopharyngeal primary tumor, and to this end, detailed clinical evaluation of the nasopharynx is indicated.
- Mucosal malignant melanoma
- Non-Hodgkin lymphoma

Treatment and Prognosis

- Prognosis is favorable owing to a good response to local radiotherapy.
- Regional cervical lymph node metastasis may be present at presentation.
- Favorable prognosis is not altered even in the presence of nodal metastasis.

HUMAN PAPILLOMAVIRUS (HPV)-RELATED CARCINOMA WITH ADENOID CYSTIC-LIKE FEATURES (Figs. 3-50 and 3-51)

Definition: Recently described and defined type of sinonasal carcinoma with morphologic features suggestive of adenoid cystic carcinoma and immunohistochemical evidence of myoepithelial differentiation but with features distinctly unusual for adenoid cystic carcinoma, including presence of surface intraepithelial dysplasia, absence of MYB gene rearrangement, and association with HPV.

Clinical

- Rare tumor with limited numbers of cases reported in the literature to date
- More common in women than in men; occur over a wide age range including 40 to 73 years (mean 55 years)

- Presenting symptoms include nasal obstruction and epistaxis; less commonly, epiphora may occur.
- Sites of occurrence include nasal cavity and/or paranasal sinuses, including ethmoid > maxillary and/or sphenoid; orbital involvement may occur.

Pathology

Gross

- Range in size from 1 cm to greater than 5.4 cm; mean 3 cm

Histology

- Invasive hypercellular lesion with solid, lobular, and nested growth separated by fibrous stroma
- Cribriform and microcystic growth, as well as true ductal structures present:
 - Microcystic spaces filled with basophilic material
 - Ductal structures represent a minor component.
- Neoplastic infiltrate includes two cell types:
 - Basaloid cells predominate, characterized by hyperchromatic and angulated nuclei, scant cytoplasm, and increased nuclear-to-cytoplasmic ratio with marked increase in mitotic activity; tumor necrosis and perineural invasion may be present, but lymph-vascular invasion not reported
 - True duct cells appear cuboidal with eosinophilic cytoplasm:
 - Often located at center of lobules surrounded by zones of basaloid cells
- Intraepithelial dysplasia of the surface epithelium present in majority of cases
- Invasive component lacks squamous differentiation
- Immunohistochemistry:
 - Cytokeratin (AE1/AE3) positive in all cases:
 - Strong in duct cells
 - Relatively weaker in basaloid cells
 - Basaloid cells express (usually strong and diffuse) one or more myoepithelial-related markers including p63, calponin, S100 protein, and/or actin.
 - CD117 (c-kit) consistently reactive:
 - Usually limited to ductal cells but occasionally may be diffuse
 - Strong and diffuse p16 reactivity (nuclear)
- HPV DNA in situ hybridization present with hybridization signals distributed:
 - Throughout basaloid cells and ductal cells
 - In surface dysplasia and invasive component
- Quantitative PCR confirmatory of high-risk HPV including HPV33 and less often HPV35.

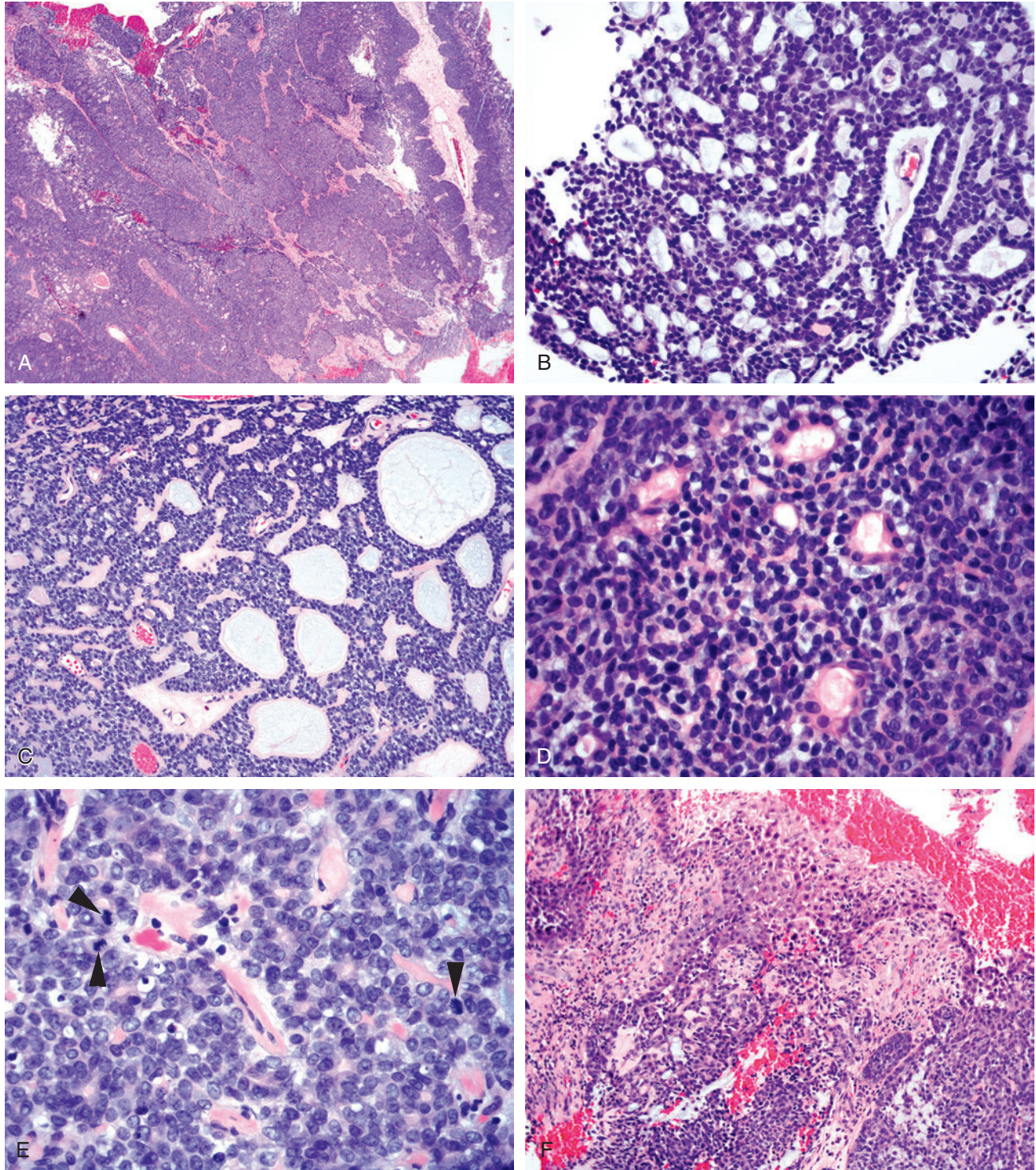


Fig. 3-50. HPV-related carcinoma with adenoid cystic-like features.

A, Invasive hypercellular lesion with solid, lobular, and nested growth separated by fibrous stroma. **B**, Cribriform growth. **C**, Microcystic spaces filled with basophilic material. **D**, The neoplastic cells include a predominant basaloid cell population characterized by hyperchromatic and angulated nuclei, scant cytoplasm, as well as true ducts composed of cuboidal cells with eosinophilic cytoplasm. **E**, Increased mitotic activity (*arrowheads*) is present. **F**, Intraepithelial dysplasia of the surface epithelium.

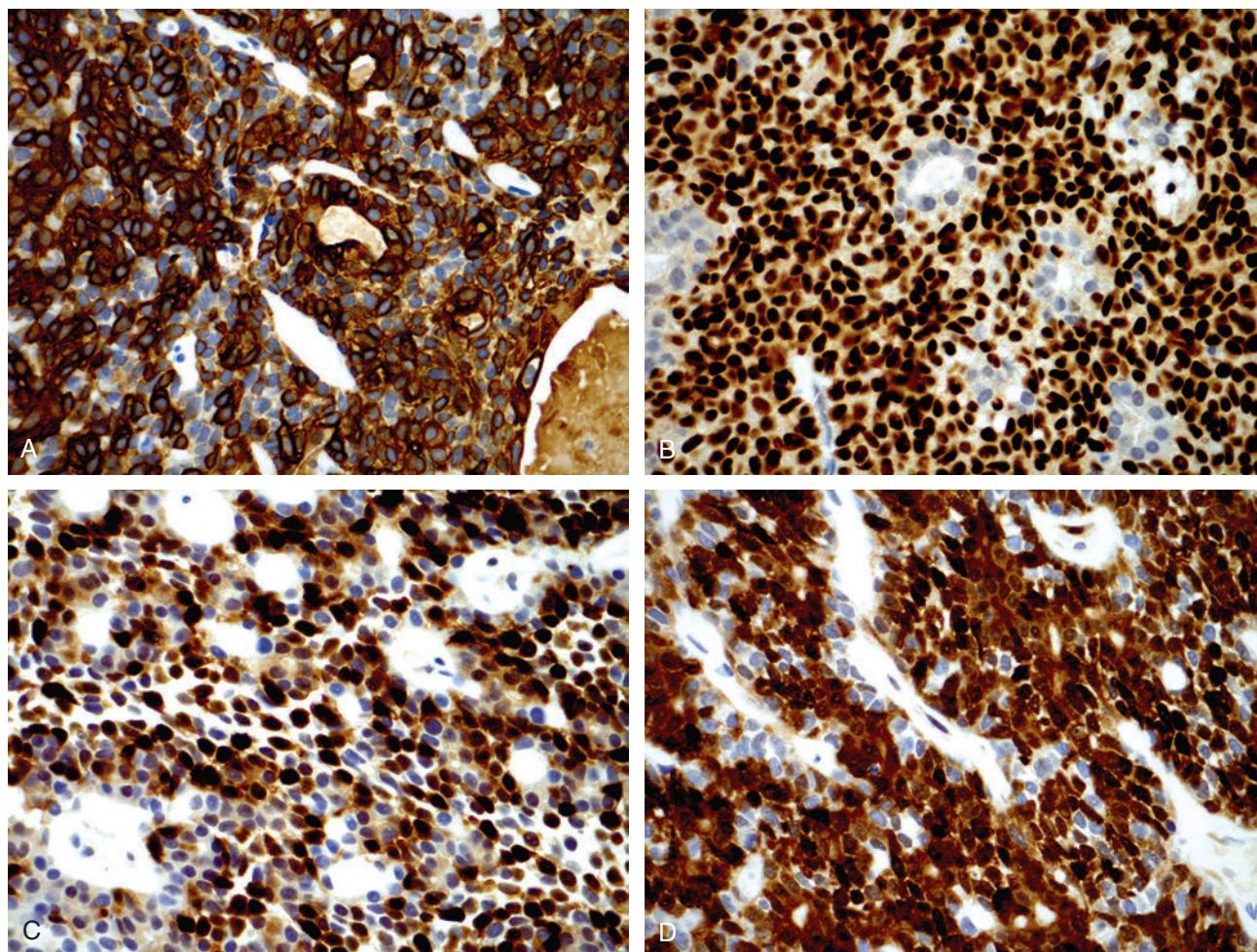


Fig. 3-51. HPV-related carcinoma with adenoid cystic-like features.

Immunohistochemical findings include (A) cytokeratin (AE1/AE3) strong in duct cells and relatively weaker in basaloid cells; (B) basaloid cells show strong and diffuse p63 reactivity but ductal cells are negative; (C) basaloid cells show S100 protein reactivity; (D) strong and diffuse p16 reactivity.

Differential Diagnosis

- Adenoid cystic carcinoma, solid variant
- HPV-associated carcinomas:
 - Nonkeratinizing carcinoma
 - Basaloid squamous cell carcinoma

Treatment and Prognosis

- Treatment options include surgical resection alone, surgery plus postoperative radiotherapy, or combined chemoradiation therapy.
- Given limited long-term follow-up reported in the literature, the true biologic nature of this neoplasm is yet to be determined; cases identified in the literature, albeit with limited follow-up periods (median 15 months), most patients were alive without evidence of disease or with local recurrence.

OLFACTORY NEUROBLASTOMA (ONB) (Figs. 3-52 through 3-60)

Definition: Malignant neuroectodermal neoplasm thought to arise from the olfactory membrane of the sinonasal tract.

Synonyms: Esthesioneuroblastoma; esthesioneurocytoma; esthesioneuroepithelioma; esthesioneuroma; olfactory placode tumor

Clinical

- Uncommon malignant neoplasm representing approximately 2% to 3% of sinonasal tract tumors
- No gender predilection; occurs over a very wide age range from 3 years to the ninth decade, with a bimodal peak in the second and sixth decades of life



Fig. 3-52. Olfactory neuroblastoma.

Patient with a huge olfactory neuroblastoma destroying much of the soft tissue and bony structures between the upper nasal cavity and its appearance along the bridge of the nose resulting in marked facial deformity.

- Main presenting symptoms include unilateral nasal obstruction and epistaxis; less common manifestations include anosmia, headache, pain, excessive lacrimation, proptosis, and ocular disturbances.
- Most common site of occurrence is the upper nasal cavity in the area of the cribriform plate; often there is involvement of the ethmoid sinus:
 - “Ectopic” origin in the lower nasal cavity, within one of the paranasal sinuses (e.g., maxillary sinus) and nasopharynx, may occur.
- May uncommonly be associated with:
 - Syndrome of inappropriate antidiuretic hormone secretion (SIADH):
 - Resolution of SIADH expected following treatment of ONB
 - Absence of resolution of SIADH may be indicative that entire tumor has not been excised.
 - Resolution of SIADH with subsequent recurrence during follow-up suggests recurrence of ONB.
 - Cushing syndrome:
 - Resulting from ectopic ACTH production
 - High ACTH levels and plasma and urine cortisol levels dramatically dropped following multimodality management of ONB
- Radiology:
 - A sinonasal mass causing sinus opacification with or without bone erosion may be seen.
 - May be associated with calcifications, which produce a speckled pattern by radiographic analysis.
 - MRI studies demonstrate the presence of a vascular lesion with enhancement following gadolinium injection as seen on T1-weighted imaging:
 - T1-weighted imaging with gadolinium injection considered optimum method for assessing extent of disease prior to craniofacial resection.

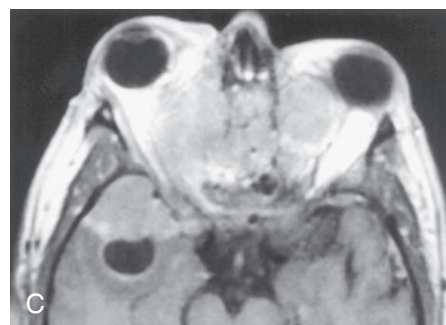
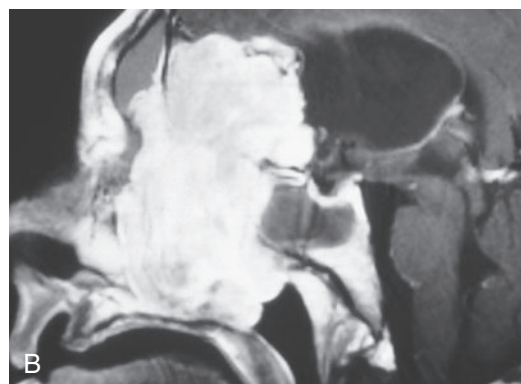
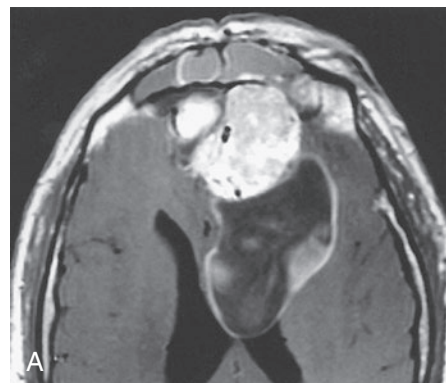


Fig. 3-53. Olfactory neuroblastoma.

Axial (A) and sagittal (B) T1-weighted, fat-suppressed, contrast-enhanced MR images show a large, enhancing sinonasal mass that obstructs the frontal and sphenoid sinuses and extends intracranially. There is a tumoral large cyst at the intracranial margin of the tumor. This patient had an olfactory neuroblastoma. C, Axial T1-weighted, contrast-enhanced MR image on a patient who previously had a craniofacial resection for an olfactory neuroblastoma. There is a large enhancing recurrence extending into the orbits and the anterior cranial fossa. Note the small, broad-based cyst at the intracranial margin of the tumor. Such a cyst is highly suggestive of the diagnosis. This patient had an olfactory neuroblastoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 288, Fig. 4-72.)

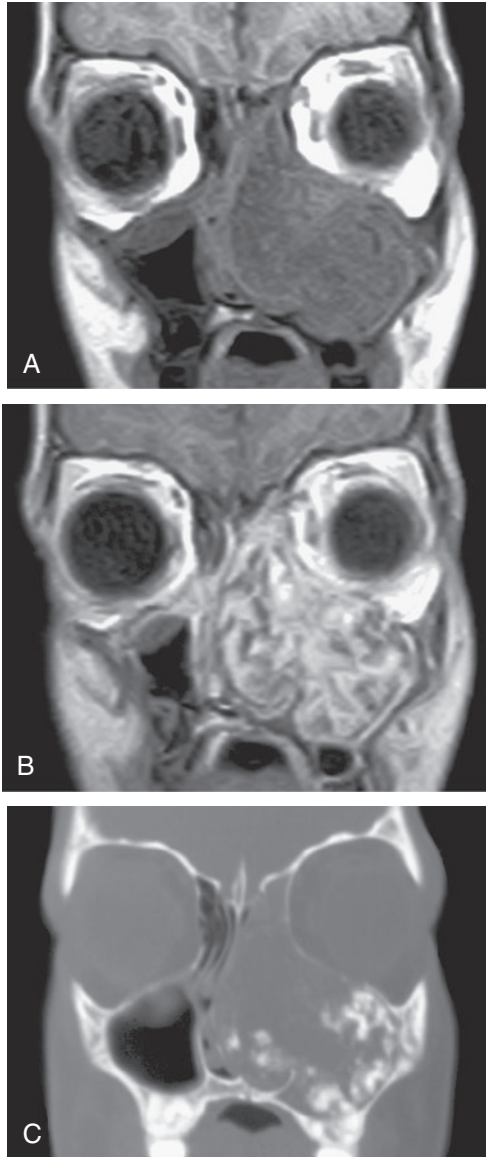


Fig. 3-54. Olfactory neuroblastoma.

Coronal T1-weighted (A), T1-weighted, fat-suppressed, contrast-enhanced (B) MR images and a coronal CT scan (C) show an expansile left antral mass that extends into the left nasal cavity and ethmoid complex. The mass elevated the left orbital floor, but there is no gross invasion of the orbit. There is no intracranial extension. Extensive tumoral calcifications are present within the olfactory neuroblastoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 289, Fig. 4-73.)

- No known etiologic agent(s):
 - Administration of diethylnitrosamine to hamsters and *N*-nitrosopiperidine to rats produces nasal tumors that are histologically identical to ONB.
 - Conflicting data regarding the inclusion of ONB in the category of PNET:

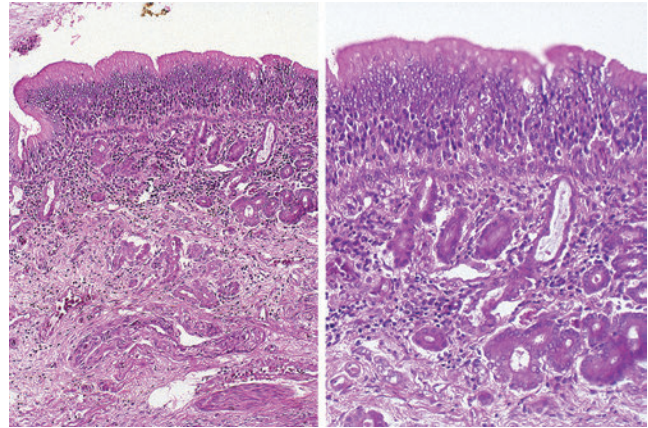


Fig. 3-55.

Normal olfactory mucosa showing a bipolar surface epithelium overlying submucosa that includes seromucous glands referred to as Bowman's glands.

- Classically, PNET shows reactivity with monoclonal antibodies that recognize the Ewing sarcoma cell surface glycoprotein p30/32 and t(11;22) translocation with *EWS/FL1* gene fusion.
- Based on these features of PNET, the t(11;22) translocation reported in ONB and the presence of *EWS/FLI1* gene fusion in ONB would support the inclusion of ONB within the spectrum of PNET related to Ewing sarcoma.
- Other studies using immunohistochemistry, fluorescent in situ hybridization, and reverse transcriptase PCR have failed to identify these “markers” of PNET, thereby failing to confirm this translocation in ONB.
- ONB should be seen as distinct entity from PNET and the Ewing sarcoma family of tumors.
- ONB takes origin from the olfactory neuroepithelium that in the human fetus is found in the upper one third to one half of the nasal septum, the cribriform plate, and the superior-medial surface of the superior turbinate:
 - With aging, the olfactory epithelium degenerates and is replaced by respiratory epithelium.
 - The olfactory neuroepithelium is composed of bipolar sensory neurons, supporting cells, and the reserve (basal) cells.
 - Basal cells are mitotically active and are the presumed progenitor of ONB.

Pathology

Gross

- Glistening, mucosa-covered, soft, polypoid mass varying from a small nodule less than 1 cm to a mass

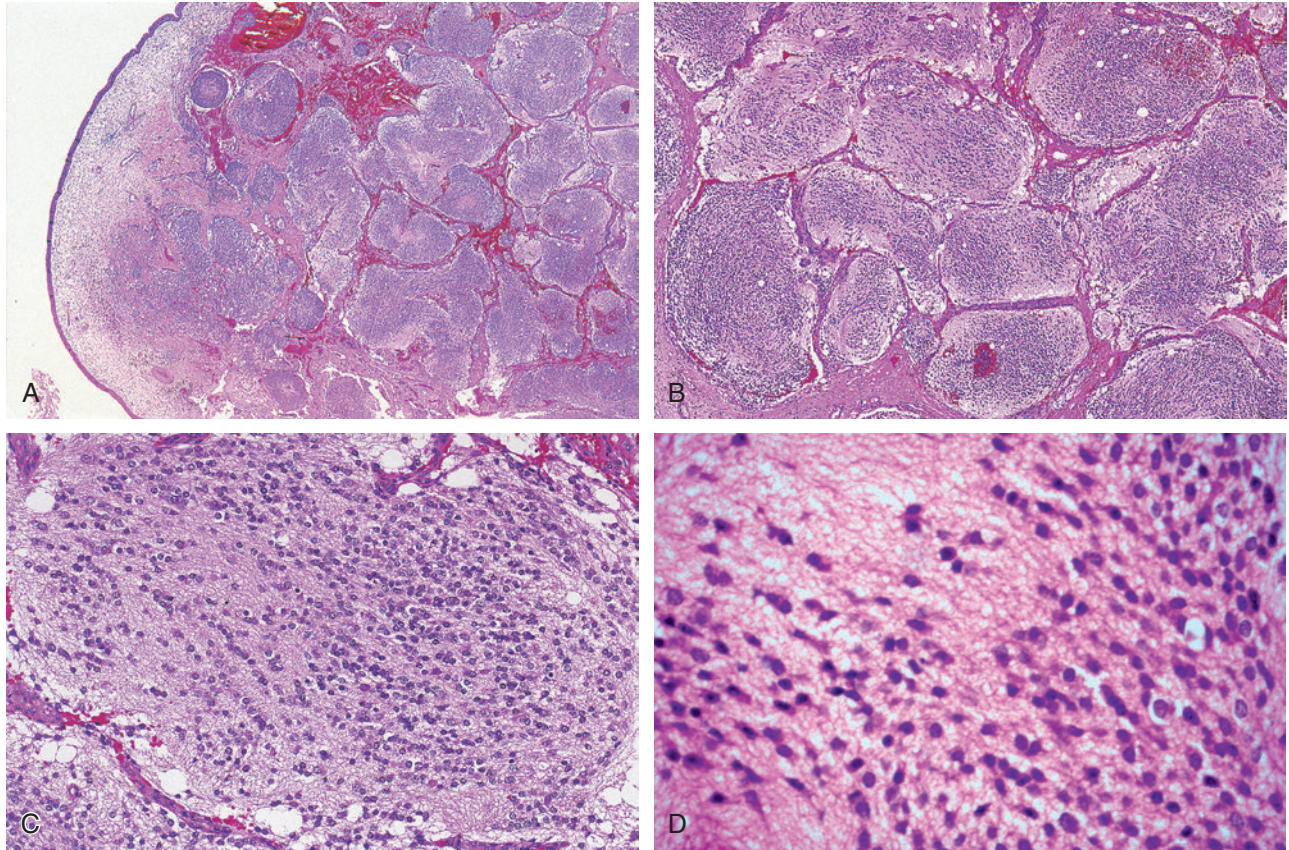


Fig. 3-56. Olfactory neuroblastoma (ONB), grade I.

A, Common to all grades of ONB is a characteristic lobular growth pattern, although in the higher histologic grade neoplasms, the lobular growth but may only be focally present. **B**, Lobular pattern with lobules separated by fibrovascular stroma; tumor nests include small round cells with a pink matrix, the latter representing neurofibrillary matrix seen in these tumors. **C** and **D** The neoplastic cells are well differentiated with uniform round to vesicular nuclei surrounded by abundant neurofibrillary material suggesting cytoplasmic extensions; mitotic figures are rarely seen.

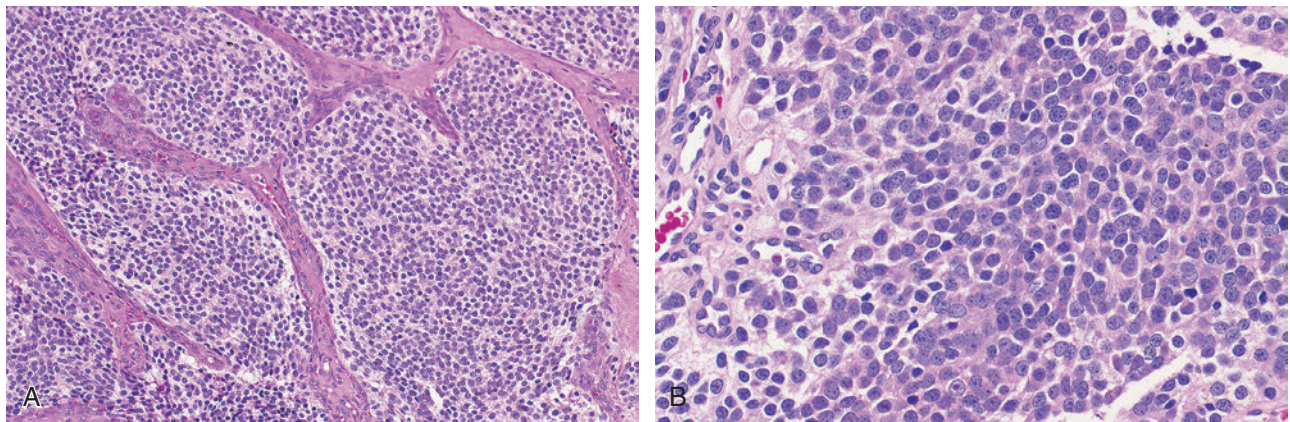


Fig. 3-57. ONB, grade II.

A, Lobule growth is present with neoplastic cells surrounded by a neurofibrillary matrix, which is less well defined as compared with grade I ONB. **B**, The cellular component of grade II demonstrates greater pleomorphism as compared with the features seen in ONB, grade I.

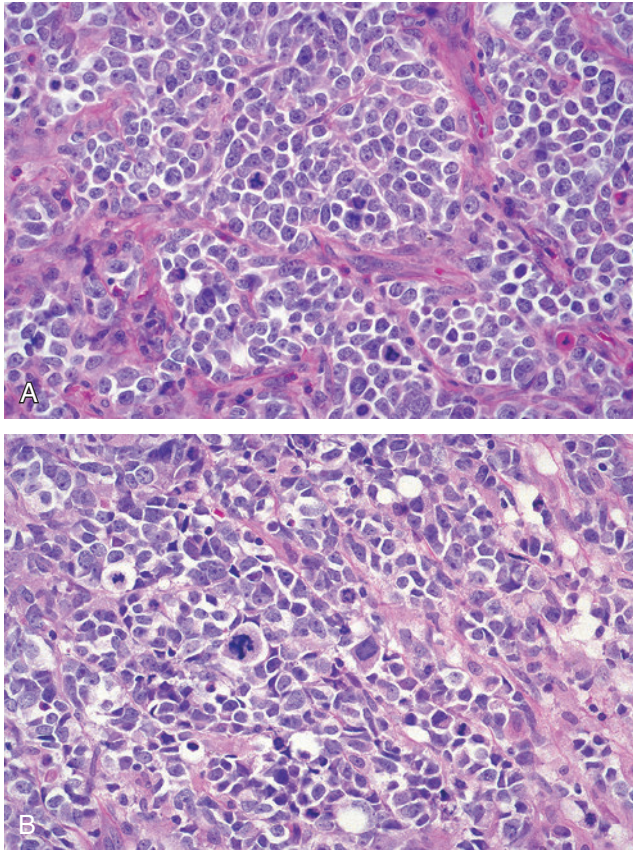


Fig. 3-58. ONB, grades III and IV.

A, In grade III tumors the neoplastic cells demonstrate greater nuclear pleomorphism, less to absent neurofibrillary component as compared with grades I or II ONB. **B**, In grade IV tumors, the cells are the most undifferentiated of all the histologic grades, with anaplasia characterized by hyperchromatic, pleomorphic nuclei, indistinct cytoplasm, increased mitotic activity, including atypical mitoses; neurofibrillary matrix is absent, making identification of this neoplasm as an ONB difficult, with the diagnosis often hinging on location of the tumor and the immunohistochemical antigenic profile.

filling the nasal cavity, with possible extension into adjacent paranasal sinuses and nasopharynx

Histology

- Histologic appearance is divided into four grades as defined by Hyams (Table 3-7):

Grade I

- Most differentiated
- Architecture is lobular with intercommunication between lobules.
- Neoplastic cells are well differentiated with uniform round to vesicular nuclei with or without nucleoli and have indistinct borders.

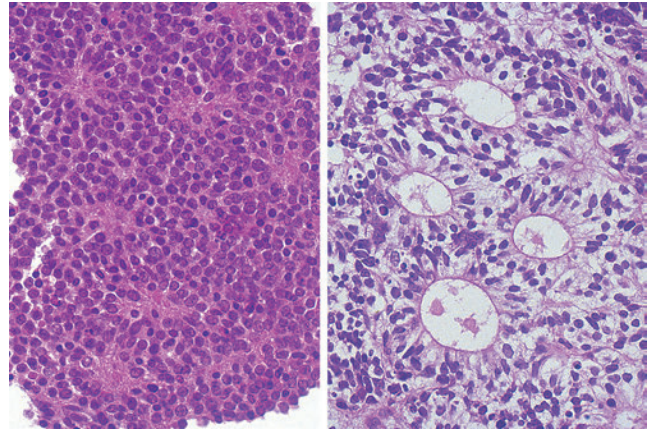


Fig. 3-59. ONBs are associated with the presence of rosettes.

This illustration contrasts (*left*) the Homer Wright pseudorosettes seen in grades I and II ONBs and characterized by grouping of cells in a circumferential fashion around neurofibrillary matrix but without a defining basement membrane with (*right*) Flexner-Wintersteiner true neural rosettes in which cells align in a glandular fashion around spaces lined by distinct cell membranes.

- The nuclei are surrounded by neurofibrillary material:
 - Represents key diagnostic feature for diagnosis
 - Appears as fibrillary intercytoplasmic background
 - Corresponds to neuronal cell processes seen ultrastructurally
- Pseudorosette pattern (Homer Wright rosettes) is frequently seen.
- Varying amounts of calcification may be noted.
- Interlobular fibrous stroma is often extremely vascular.
- Mitotic activity and necrosis are absent.

Grade II

- Share many of the histologic features described for grade I lesions, but the neurofibrillary element is less well defined, and the neoplastic nuclei show increased pleomorphism.
- Scattered mitoses can be seen.

Grade III

- Retain a lobular architecture with an interstitial vascular stroma
- These tumors are characterized by a hypercellular neoplastic cell proliferation, in which the cells are more anaplastic and hyperchromatic and have increased mitotic activity as compared with grade I or II tumors.

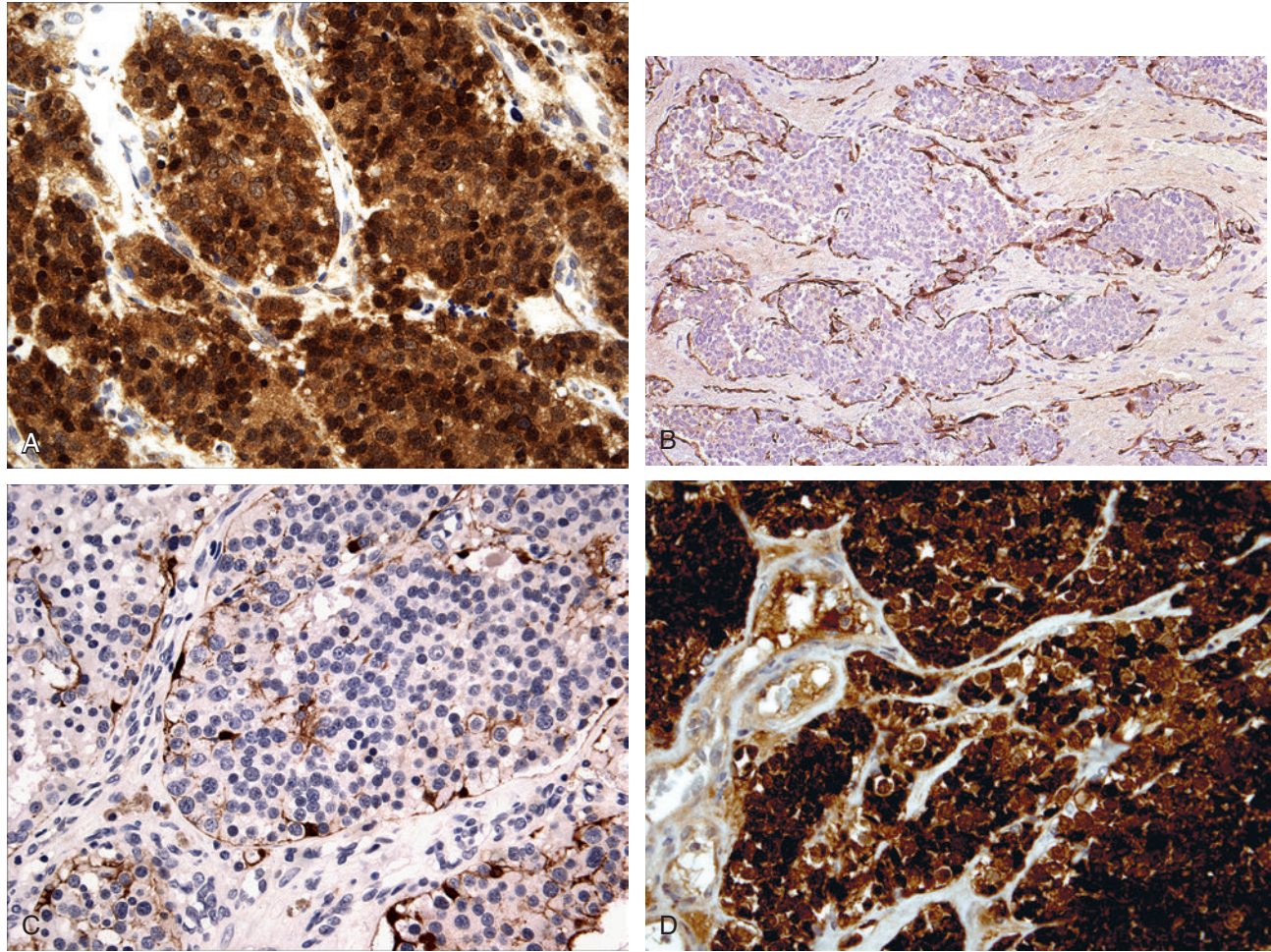


Fig. 3-60. ONB, immunohistochemical findings.

The most consistent immunomarkers include **(A)** neuron specific enolase (NSE) showing diffuse and intense nuclear and cytoplasmic staining and **(B)** S100 protein typically in a peripheral (sustentacular cell-like) staining pattern. **C**, In higher grade ONBs, S100 protein positive staining is markedly decreased with sparse positive cells still mostly distributed along the periphery of the tumor nests. Usually ONBs are cytokeratin negative, and when cytokeratin is present it is often focal; this finding contrasts with sinonasal undifferentiated carcinoma, which has overlapping histologic features with the higher grade ONBs but is consistently cytokeratin positive, and NSE and S100 protein negative; if S100 protein is positive in SNUC it is not in a peripheral cell distribution as occurs in ONB. **D**, Calretinin staining is present in ONBs but is negative in other sinonasal small round cell malignant neoplasms.

TABLE 3-7 Hyams' Histologic Grading System for Olfactory Neuroblastoma

Histologic Features	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	± Lobular	± Lobular
Pleomorphism	Absent to slight	Present	Prominent	Marked
NF matrix	Prominent	Present	May be present	Absent
Rosettes	Present*	Present*	May be present [†]	May be present [†]
Mitoses	Absent	Present	Prominent	Marked
Necrosis	Absent	Absent	Present	Prominent
Glands	May be present	May be present	May be present	May be present
Calcification	Variable	Variable	Absent	Absent

NF, Neurofibrillary.

*Homer Wright rosettes (pseudorosettes).

[†]Flexner-Wintersteiner Rosettes (true neural rosettes).

- Necrosis is present.
- Neurofibrillary component may be focally present but is much less conspicuous as compared with grades I or II tumors.
- True neural rosettes (Flexner–Wintersteiner rosettes) may be seen; however, in general, these structures are uncommonly identified.
- Calcification is absent.

Grade IV

- May also retain the overall lobular architecture, but the neoplastic element is the most undifferentiated and anaplastic of all the histologic grades.
- In these high-grade tumors, the cellular infiltrate is characterized by pleomorphic nuclei, often with prominent eosinophilic nucleoli and indistinct cytoplasm.
- Necrosis is commonly seen and there is increased mitotic activity, including atypical mitoses.
- True neural rosettes may be seen but, as in grade III tumors, are uncommon.
- Neurofibrillary component is generally absent.
- Calcification is absent.
- ONB may coexist with foci of adenocarcinoma, squamous carcinoma, or undifferentiated carcinoma, and in such circumstances may be referred to as mixed ONB and olfactory carcinoma:
 - It has been proposed that the basal cells of the olfactory epithelium may represent progenitor for these mixed neoplasms.
 - Alternatively, these mixed tumors may originate from the seromucous glands (Bowman's glands) lying subjacent to the olfactory epithelium.
- In general, the lower grade ONB are readily recognizable and diagnosable by light microscopy. Adjunct studies, particularly in the higher histologic grade tumors, may assist in the diagnosis.
- Histochemical stains have been replaced by immunohistochemistry in the diagnosis of ONB.
- Immunohistochemistry:
 - Most consistent marker is neuron specific enolase (NSE).
 - S100 protein staining seen in scattered lesional cells but shows characteristic staining of cells situated along the periphery of the neoplastic lobules (sustentacular cell-like pattern of staining), suggesting Schwann cell differentiation:
 - Consistently seen in lower histologic grade tumors
 - May only be focally present in higher histologic grade tumors
 - Peripheral S100 protein staining not usually a feature of other sinonasal malignancies considered in the differential diagnosis of ONB
 - Calretinin shown to be consistently reactive in ONB:
 - Calretinin nonreactive in other sinonasal small round cell malignant neoplasms
 - Reactivity is also present in a majority of cases for synaptophysin, neurofilament protein (NFP), class III beta-tubulin, and microtubule-associated protein.
 - Variable immunoreactivity present for chromogranin, glial fibrillary acidic protein (GFAP), and CD57 (Leu-7)
 - Cytokeratin is usually negative; some cases can show positive cells in a patchy, punctate fashion:
 - Diffuse staining is not typical for ONB, and the presence of diffuse staining should prompt consideration of alternative diagnoses including (but not limited to) sinonasal undifferentiated carcinoma and ectopic pituitary adenoma.
 - With additional findings could represent an olfactory carcinoma (see below)
 - Epithelial markers, including epithelial membrane antigen (EMA), p63, and carcinoembryonic antigen (CEA), are typically absent:
 - Focal p63 staining may be present.
 - Hematolymphoid markers (CD45, B-cell, and T-cell), CD56, melanoma markers (HMB-45, melan A, tyrosinase), myogenic markers (desmin, myoglobin, myf-4), CD99 are absent
 - Absence of HPV or EBV
- Electron microscopy:
 - Useful adjunct in the diagnosis and reveals the presence of dense-core neurosecretory granules measuring from 80 to 250 nm in diameter
 - Neurofilaments and neurotubules, and occasionally Schwann-like cells, can be seen.
- Cytogenetics and molecular genetics:
 - Comparative genomic hybridization (CGH) show high-level genomic instability with many chromosomal deletions and gains.

Differential Diagnosis

- Sinonasal undifferentiated carcinoma
- Small cell undifferentiated neuroendocrine carcinoma
- Nasopharyngeal-type undifferentiated carcinoma
- Sinonasal-based lymphoepithelial-like carcinoma
- Squamous cell carcinoma, keratinizing and nonkeratinizing types
- Mucosal malignant melanoma
- Nasal-type NK/T-cell lymphoma
- Rhabdomyosarcoma
- Ewing sarcoma family of tumors
- NUT midline carcinoma

NOTE: Although differences can be identified by light microscopic evaluation, often the differentiation of

TABLE 3-8 Clinical (Kadish) Staging for Olfactory Neuroblastoma

Stage	Extent of Tumor	5-Year Survival
A	Tumor confined to the nasal cavity	75% to 91%
B	Tumor involves the nasal cavity plus one or more paranasal sinuses	68% to 71%
C	Extension of tumor beyond the sinonasal cavities	41% to 47%

TABLE 3-9 Modified Kadish Staging for Olfactory Neuroblastoma

Stage	Extent of Tumor
A	Tumor confined to the nasal cavity
B	Tumor involves the nasal cavity plus one or more paranasal sinuses
C	Extension of tumor beyond the nasal cavity and paranasal sinuses including involvement of the cribriform plate, base of skull, orbit, or intracranial cavity
D	Tumor with metastasis to cervical lymph nodes or distant sites

all these tumor types rests on the immunohistochemical staining profile for a given tumor (see [Table 3-6](#)).

Treatment and Prognosis

- Complete surgical eradication (craniofacial resection that includes removal of the cribriform plate) followed by full course radiotherapy is the preferred treatment.
- Limited success using chemotherapeutic modalities (concurrent chemotherapy and neoadjuvant chemotherapy) achieved for advanced unresectable tumors and/or for disseminated disease
- The overall 5-, 10-, and 15-year survival rates have been reported to be 78%, 71%, and 68%, respectively:
 - More recent evidence reports a 10-year survival rate for all patients of greater than 80%.
- Five-year disease-specific and recurrence-free survival rates reported to be 83% and 64%, respectively.
- Initial multimodality therapy is associated with 5-year survival of 80% for low-grade tumors and 40% for high-grade tumors.
- The majority of the recurrences occur within the first few years (2 to 4 years) following treatment:
 - Most frequent recurrence is local, with rates around 30%.
 - Late recurrences may occur, necessitating lifelong follow-up with clinical examination and serial imaging (including neck and entire intracranial compartment).
- Prognosis has traditionally been correlated to clinical staging as defined by Kadish ([Table 3-8](#)) with:
 - 5-year survival of 75% for Stage A tumors
 - 5-year survival of 68% for Stage B tumors
 - 5-year survival of 41% for Stage C tumors
- A revision of the Kadish staging system was proposed to include metastatic tumor to cervical lymph nodes or distant sites representing Stage D ([Table 3-9](#)), a good predictor of outcome.
- Complete tumor resection was found to be of more prognostic importance than clinical staging.
- Other factors purportedly implicated in prognosis include:
 - Histologic grading:
 - Histologically lower grade tumors (grades I and II) have been reported to have a better 5-year survival than higher-grade tumors (grades III, IV).
 - Proliferation rate and ploidy:
 - High proliferation indices and high rate of ploidy/aneuploidy have been correlated with increased morbidity (i.e., tumor recurrence, metastasis) and mortality (i.e., decreased survival).
 - Intracranial extension of the disease and positive surgical margins are independent predictors of worse overall, disease-specific, and recurrence-free survival.
- Majority of tumors behave as locally aggressive lesions mainly involving adjacent structures (orbit and cranial cavity).
- Local recurrence and distant metastasis may occur years following the initial diagnosis:
 - Approximately 15% to 70% of patients will experience local recurrence.
 - 10% to 25% will have cervical lymph node metastasis.
 - Approximately 10% to 60% will experience distant metastasis.
- More common sites of metastatic disease include lymph nodes, lungs, and bone:
 - All histologic grades have the capacity to metastasize.

OLFACTORY CARCINOMA

Definition: Rare, little-described variant of ONB characterized by a histologically high-grade ONB confirmed by immunohistochemical staining admixed with foci of carcinoma in the form of squamous or glandular differentiation as seen by light microscopy

and/or diffuse immunohistochemical staining for epithelial markers.

- Origin not clarified but may originate from olfactory epithelium lining the surface of the olfactory mucosa and/or submucosal minor salivary glands present in the olfactory mucosa (i.e., Bowman's glands)
- Absence in the literature of studies detailing clinical features, treatment, and prognosis
- If confronted with a possible diagnosis of olfactory carcinoma:
 - Clinical (e.g., Kadish) staging warranted
 - Complete surgical extirpation to include tumor-free margins indicated
 - Adjuvant therapy (e.g. radiation) may be required.
 - Evaluation for presence of metastatic (nodal and visceral) disease should be undertaken.

NEUROENDOCRINE CARCINOMAS

- Neuroendocrine carcinomas (NEC) represent a heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines.
- For a more complete discussion of NEC see Section 5, Larynx.
- The classification of NEC is to some extent still debated:
 - Some divide these tumors into:
 - Carcinoid tumor
 - Atypical carcinoid tumor
 - Small cell carcinoma
 - Others classify them according to differentiation:
 - Well-differentiated neuroendocrine carcinoma (equated with carcinoid tumor)
 - Moderately differentiated neuroendocrine carcinoma (equated with atypical carcinoid)
 - Poorly differentiated neuroendocrine carcinoma (equated with small cell undifferentiated neuroendocrine carcinoma [SCUNC])
 - Another classification includes an admixture of the above schemes:
 - Carcinoid
 - Moderately differentiated neuroendocrine carcinoma
 - Small cell neuroendocrine carcinoma
 - More recently, the large cell variant of NEC (LCNEC) reported in the head and neck, primarily involving the larynx but also reported in other sites including the sinonasal tract; for more details see Section 5, Larynx.
 - According to the time-honored terminology and to minimize confusion, the terms carcinoid, atypical carcinoid, small cell carcinoma, and large cell carcinoma, as proposed by the World Health Organization, are used in this book, but the “atypical” carcinoid tumor is a fully lethal tumor and the term “atypical” should not lull the clinician into a false sense of security that this tumor is only slightly different in its behavior from the relatively indolent “classic” carcinoid tumor.
- Given the recent identification of the large cell neuroendocrine carcinoma of the head and neck, the classification of head and neck NEC includes:
 - Carcinoid tumor (well-differentiated neuroendocrine carcinoma)
 - Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
 - Small cell (neuroendocrine) carcinoma (poorly differentiated neuroendocrine carcinoma)
 - Large cell neuroendocrine carcinoma
- In general, all subtypes of NEC are uncommon in the head and neck and even more so in the sinonasal tract.
- Most commonly encountered subtype of NEC in the head and neck is the small cell undifferentiated carcinoma (SCUNC) followed by the atypical carcinoid; carcinoid tumor and LCNEC are least common.
- NECs, especially SCUNC, may be identified in virtually all upper aerodigestive tract sites but primarily involve the larynx; less frequently, NECs occur in salivary glands (parotid) and sinonasal tract.
- SCUNC of the sinonasal tract affects men and women equally and occurs over a wide age range from the third to eighth decades of life with a mean of 49 years.
- Sinonasal tract SCUNC most commonly occurs in the superior or posterior nasal cavity, often with extension into adjacent paranasal sinuses (e.g., maxillary and ethmoid sinuses).
- Primary paranasal sinus disease in the absence of nasal cavity involvement may occur.
- Presenting signs and symptoms include nasal obstruction, epistaxis, and pain; local invasion may result in exophthalmos.
- Irrespective of the site of occurrence, the histologic appearance of SCUNC is the same:
 - Foci of squamous differentiation may be present:
 - CK5/6 and p63 positive, which are typically absent in the neuroendocrine component
 - Rhabdomyoblastic differentiation may be present:
 - Cells are desmin and myogenin positive.
- Oropharyngeal SCUNC may be associated with HPV (see Section 3, Pharynx for more complete discussion):
 - In contrast to the relatively favorable prognosis associated with HPV-associated squamous cell carcinomas of the oropharynx, the findings of the HPV-associated NEC of the oropharynx suggest an aggressive behavior despite its association with HPV.

- Differential diagnosis for NEC, especially SCUNC of the sinonasal tract, includes other “small round cell” malignant neoplasms as well as other malignancies:
 - Sinonasal undifferentiated carcinoma
 - Small cell undifferentiated neuroendocrine carcinoma
 - Nasopharyngeal-type undifferentiated carcinoma
 - Sinonasal-based lymphoepithelial carcinoma
 - Squamous cell carcinoma, keratinizing and non-keratinizing types
 - Mucosal malignant melanoma
 - Nasal-type NK/T-cell lymphoma
 - Rhabdomyosarcoma
 - Ewing sarcoma family of tumors
 - NUT midline carcinoma

NOTE: Although differences can be identified by light microscopic evaluation, often the differentiation of all these tumor types rests on the immunohistochemical staining profile for a given tumor (see Table 3-6).

- Preferred treatment for SCUNC is multimodality therapy including (neoadjuvant) chemoradiotherapy; surgery is not considered appropriate therapy due to the high rate of metastatic disease, although treatment protocols vary and some advocate incorporating radical surgery.
- SCUNCs are highly malignant tumors; median survival rates for head and neck SCUNC are reported to be 14.5 months.
- Local recurrence and distant metastasis occur frequently with reported rates of 45% and 35%, respectively.
- Metastases occur to cervical lymph nodes, lung, liver, and bone.

MUCOSAL MALIGNANT MELANOMA (MMM)

(Figs. 3-61 through 3-70)

Definition: Neural crest-derived neoplasm originating from melanocytes and demonstrating melanocytic differentiation.

Clinical

- Approximately 15% to 25% of all malignant melanomas arise in head and neck sites.
- Of the head and neck malignant melanomas more than 80% are of cutaneous origin.
- MMM of the upper aerodigestive tract represents from 0.5% to 3% of malignant melanomas of all sites:
 - Of the noncutaneous head and neck malignant melanomas, the majority are of ocular origin.
 - Most common site of the upper aerodigestive tract is the oral cavity.

- Approximately 6% to 8% originate in the mucous membranes of the upper aerodigestive tract.
- Less common sites of involvement include sinonasal tract, nasopharynx > pharynx, larynx and middle ear.
- Sinonasal tract MMM accounts for less than 5% of all sinonasal tract neoplasms.
- Irrespective of the site of occurrence, upper aerodigestive tract MMMs are more common in men than women.
- Primarily a disease of adults, occurring over a wide age range but most frequently in the sixth to eighth decades of life with a peak incidence in the seventh decade:
 - Rarely if ever occurs in infants and children
- Most examples of upper aerodigestive tract MMM occur in Caucasians, but blacks are also affected.
- Symptoms vary according to the site of occurrence:
 - Sinonasal tract and nasopharynx include airway obstruction, epistaxis, pain, nonhealing ulcer, and dysphagia
- In the sinonasal tract, nasal cavity involvement is more common than that of the paranasal sinuses:
 - In the nasal cavity, the most frequent site of occurrence is the septum (anterior portion) and the lateral nasal wall.
 - In the sinuses, the maxillary sinus is the most common site of occurrence followed by the ethmoid, frontal, and sphenoid sinuses.
 - Concurrent nasal cavity and paranasal sinus melanomas frequently occur either as a result of direct extension or as multicentric tumors.
- No known etiologic agents linked to the development of MMM, but there is consideration that tobacco smoking plays an important factor in the development of (laryngeal) MMM.

Pathology

Gross

- Variety of appearances including polypoid or sessile, brown, black, pink or white, friable to rubbery masses measuring from 1.0 cm to large, resulting in obstructive signs and symptoms

Histology

- In general, surface ulceration is a common finding:
 - In tumors with an intact surface epithelium, continuity of the tumor with the surface epithelium (junctional or pagetoid changes) can be identified.
 - Presence of a junctional or in situ component suggests origin from the surface epithelium.
 - Junctional or in situ melanoma not a requirement for a diagnosis of MMM, as melanocytes are found in the submucosa of the upper aerodigestive tract (in association with seromucous glands



Fig. 3-61. Gross appearances of mucosal malignant melanoma.

Mucosal malignant melanomas of upper aerodigestive tract include (A) the oral cavity (most common nonocular head and neck site) appearing as a discolored palatal mass; (B) nasal cavity appearing as a fleshy mass in the nasal vestibule with widening of the nasal cavity and radiographic evidence (not shown) of destructive growth; (C) nasal septum appearing as an exophytic, black mass in this resection specimen.

- or separate from seromucous glands), potentially giving rise to MMM in the absence of junctional or in situ melanoma.
- Cytomorphologic features include epithelioid or spindled cells; tumors with mixed epithelioid and spindle cells are frequently seen.
- In predominantly or exclusively epithelioid cell MMM:
 - Growth patterns vary and may be solid, organoid, nested, trabecular, alveolar, or any combination of these patterns.
 - Cells are round to oval and tend to be markedly pleomorphic, having increased nuclear-to-cytoplasmic ratio, vesicular to hyperchromatic nuclei, prominent eosinophilic nucleoli, and eosinophilic to clear-appearing cytoplasm.
 - Nuclear pseudoinclusions and nuclear molding are present.
 - Epithelioid cells may have plasmacytoid features with eccentrically located nuclei and eosinophilic cytoplasm, but in contrast to plasma cell proliferations, the nuclear chromatin pattern is more

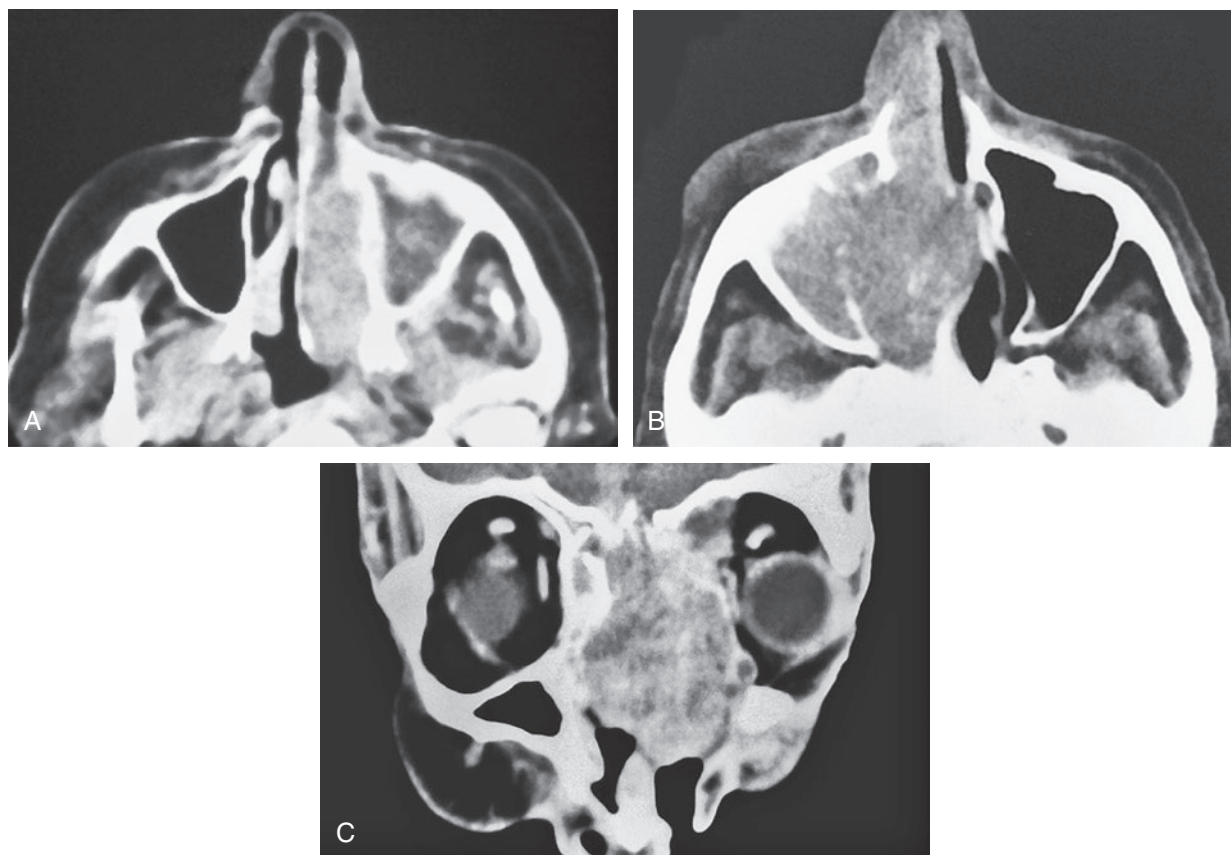


Fig. 3-62. Sinonasal mucosal malignant melanoma.

Axial CT scan (**A**) shows an enhancing, expansile polypoid mass in the left nasal fossa. The left antrum is obstructed. There is virtually no bone destruction associated with this benign-appearing lesion. Axial CT scan (**B**) on another patient shows a primarily expansile right nasal fossa mass that obstructs the right antrum. There is a greater element of bone destruction than in **A**. Coronal CT scan (**C**) on a third patient shows a primarily destructive mass in the nasal fossae, ethmoid sinuses, and left maxillary sinus. The tumor has invaded the left orbit and the floor of the anterior cranial fossa. All of these patients had melanomas. These three cases illustrate the variation of the imaging appearance of this tumor. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 293, Fig. 4-84.)

- densely hyperchromatic and there is no paranuclear clear zone.
- In predominantly or exclusively spindle cell MMM:
 - Growth patterns may be storiform and/or fascicular.
 - Cells are oblong to cigar-shaped and markedly pleomorphic with large vesicular to hyperchromatic nuclei, absent to prominent nucleoli, and scant eosinophilic cytoplasm.
 - Spindle cell MMM may have an associated myxoid stroma:
 - Myxoid stroma may be so prominent as to suggest a myxoid type of sarcoma.
 - In both epithelioid and spindle cell MMM, necrosis (individual cell and confluent foci) and increased mitotic activity, including atypical mitoses, are common findings; uncommon features that may be seen include neoplastic giant cells and glandular or squamous differentiation.
 - By light microscopy, MMM may demonstrate heavy melanin deposition, but approximately one third of cases have only focal, weak pigmentation or are nonpigmented.
 - Histochemistry:
 - Identification of melanin by argentaffin (Fontana) and argyrophilic (Churukian-Shenk) positive staining
 - Intracytoplasmic diastase-sensitive, PAS-positive material indicative of glycogen may be present.
 - Mucicarmine negative

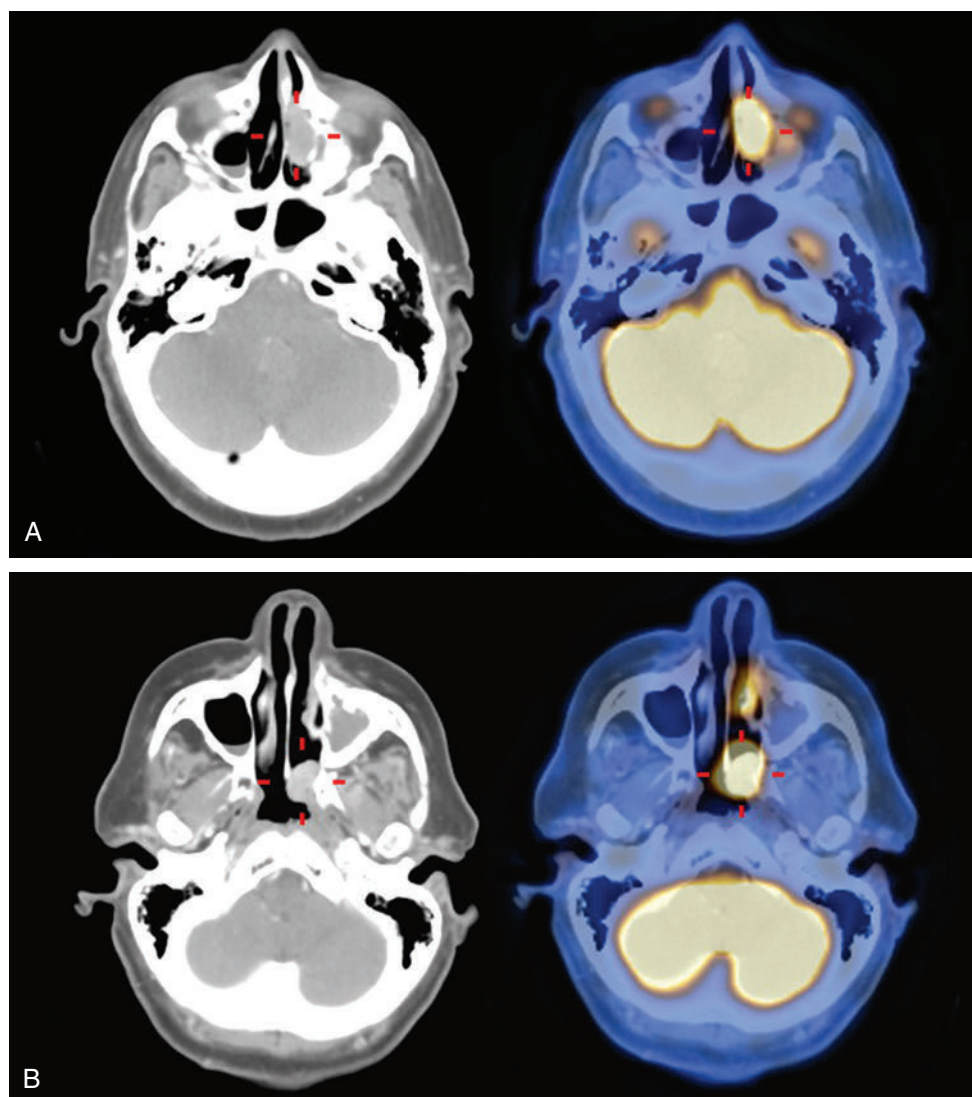


Fig. 3-63. Sinonasal mucosal malignant melanoma.

Axial fluorodeoxyglucose (FDG)-PET/CT scans through the upper (**A**) and mid (**B**) nasal cavity show two distinct, polypoid masses that are intensely avid. This patient had two separate mucosal melanomas. (*Som PM, Curtin HD: Head and neck imaging, ed 5, Philadelphia, 2011, Elsevier, p 295, Fig. 4-88.*)

- Immunohistochemistry:
 - Represents the gold standard for the diagnosis of malignant melanoma irrespective of cell type:
 - S100 protein and vimentin; S100 protein staining is typically diffuse and strong (nuclear and cytoplasmic).
 - HMB-45, melan-A, tyrosinase, microphthalmia transcription factor (MITF); staining is typically diffuse and strong:
 - Exceptions to staining pattern may occur in desmoplastic melanomas in which S100 protein and tyrosinase may be more sensitive than the other melanoma-related markers.
- Sox10:
 - Transcription factor involved in neural crest development and differentiation of neural crest cells into melanocytic and Schwannian differentiation
 - Sensitive marker for melanoma:
 - Diffuse and strong nuclear staining
 - Expression reported in more than 85% to 90% of melanomas
 - Reactivity also present in:
 - Schwannomas (100%)
 - Neurofibromas (greater than 90%)
 - Salivary gland neoplasms, especially those with myoepithelial differentiation

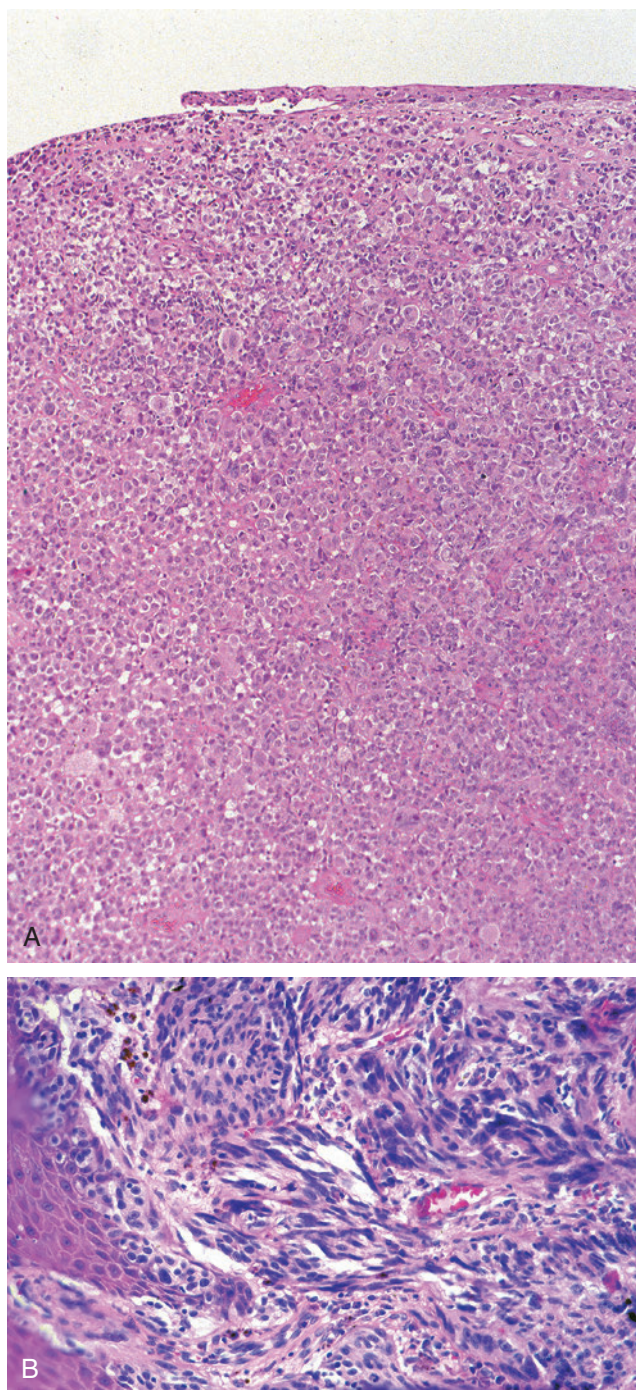


Fig. 3-64. Sinonasal mucosal malignant melanoma.

A, In most examples there is no evidence of junctional activity or evidence of premalignant intraepithelial changes either due to surface ulceration, as seen here, or due to origin from melanocytes localized in the submucosa; a diffuse invasive cellular infiltrate of epithelioid-appearing pleomorphic cells is present. **B**, Occasionally, junctional activity may be present (*left*).

- Malignant peripheral nerve sheath tumors (30% to 50%)
 - Clear cell sarcomas (approximately 60%)
 - Sustentacular cells of paragangliomas and pheochromocytoma
- c-kit expression may be present.
- Generally no immunoreactivity for cytokeratins, epithelial membrane antigen (EMA), p63, neuroendocrine markers, myogenic markers, hematolymphoid markers:
 - Rare examples of MMM reported to be reactive for epithelial markers, including CAM 5.2 (CK8/18) and EMA
- Electron microscopy:
 - Melanosomes and premelanosomes can be seen.
- Molecular genetics:
 - Serine/threonine-protein kinase B-raf (*BRAF*) mutations:
 - Present in 50% to 60% of cutaneous malignant melanoma
 - Uncommon in MMM; present in less than 20% of cases
 - c-kit:
 - Somatic mutations of c-kit with oncogenic point mutations in less than 20% of MMM
 - NRAS mutations:
 - Appear to be relatively more frequent than *BRAF* and c-kit

Intraoperative Consultation (Frozen Section) in Sinonasal MMM

- Intraoperative frozen margins for sinonasal tumors considered reliable for most histologic subtypes except for sinonasal MMM:
 - Overall false-negative rate for all tumor types by intraoperative frozen margins reported to be 6.5%
 - False-negative margin rate for MMM of 25%
 - Implications relate to size of margins required in resection of sinonasal MMM melanomas, which need to be larger than those for other tumors.

Differential Diagnosis

- Metastasis from a separate primary cutaneous or noncutaneous, non-head and neck malignant melanoma:
 - Before a diagnosis of a primary MMM of the upper aerodigestive tract is made, a metastasis from a cutaneous primary malignant melanoma or another malignant melanoma of another primary site must be excluded.
 - Cutaneous malignant melanomas are capable of spontaneous regression, lying dormant for many years only to re-emerge as a metastasis (distant from the primary cutaneous site of occurrence).

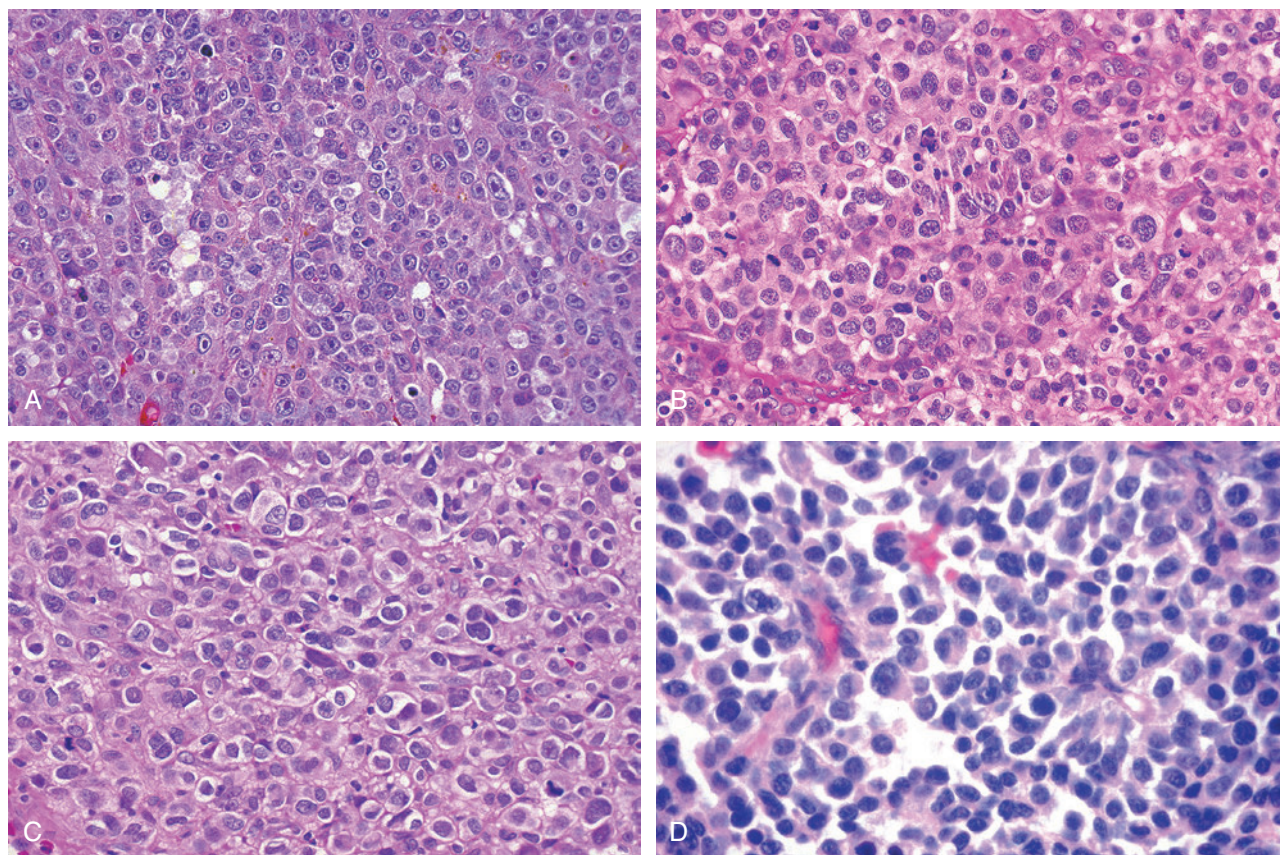


Fig. 3-65. Sinonasal epithelioid mucosal malignant melanoma.

A, The neoplastic infiltrate has a diffuse growth composed of round to oval, markedly pleomorphic cells with increased nuclear-to-cytoplasmic ratio, vesicular to hyperchromatic nuclei, nuclear molding, prominent eosinophilic nucleoli, and eosinophilic cytoplasm; scattered intracytoplasmic fine pigmentation is present consistent with melanin. **B,** In addition, intranuclear pseudoinclusions and increased mitotic activity are present. **C,** Clear cell cytoplasmic changes and **(D)** plasmacytoid-appearing cells may be focally present or represent the dominant cell type in a given case.

- Detailed clinical history to include knowledge of a prior excision (cutaneous and otherwise) is imperative; further, if available, histologic review of all appropriate previous excisions is strongly recommended.
 - In the face of a known history of a prior melanoma and/or histologic review confirming a prior diagnosis of melanoma, the sinonasal tract neoplasm can be considered as representing a metastasis.
 - In the absence of a previous or concurrent malignant melanoma elsewhere, the MMM can be considered as a primary neoplasm.
 - Presence or absence of *BRAF* mutations may have diagnostic utility in differentiating a possible metastatic cutaneous malignant melanoma (*BRAF* mutated) versus a primary sinonasal or other upper aerodigestive tract MMM (*BRAF* nonmutated).
 - Sinonasal undifferentiated carcinoma
 - Small cell undifferentiated neuroendocrine carcinoma
 - Nasopharyngeal-type undifferentiated carcinoma
 - Sinonasal-based lymphoepithelial carcinoma
 - Squamous cell carcinoma, keratinizing and nonkeratinizing types
 - Nasal-type NK/T-cell lymphoma
 - Rhabdomyosarcoma
 - Ewing sarcoma family of tumors
 - NUT midline carcinoma
- NOTE:** Although differences can be identified by light microscopic evaluation, often the differentiation of all these tumor types rests on the immunohistochemical staining profile for a given tumor (see [Table 3-6](#)).

Treatment and Prognosis

- Irrespective of their site of origin, MMMs as a group represent aggressive and highly lethal tumors.
- Radical surgical excision is the preferred treatment.

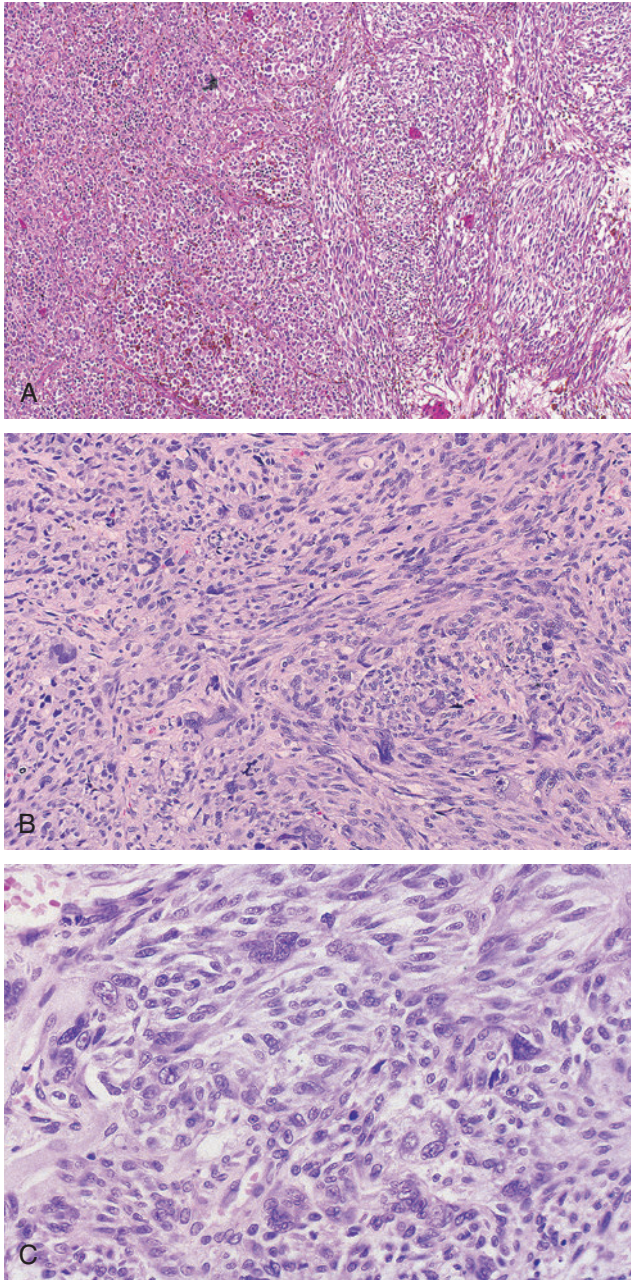


Fig. 3-66. Sinonasal mucosal malignant melanoma.

A, Admixture in a single case of epithelioid and spindle-shaped cells. **B** and **C**, Melanomas may be composed entirely of spindle-shaped cells with a fascicular to storiform growth that in the absence of light microscopic evidence of melanin may be mistaken for a sarcoma or spindle cell squamous carcinoma.

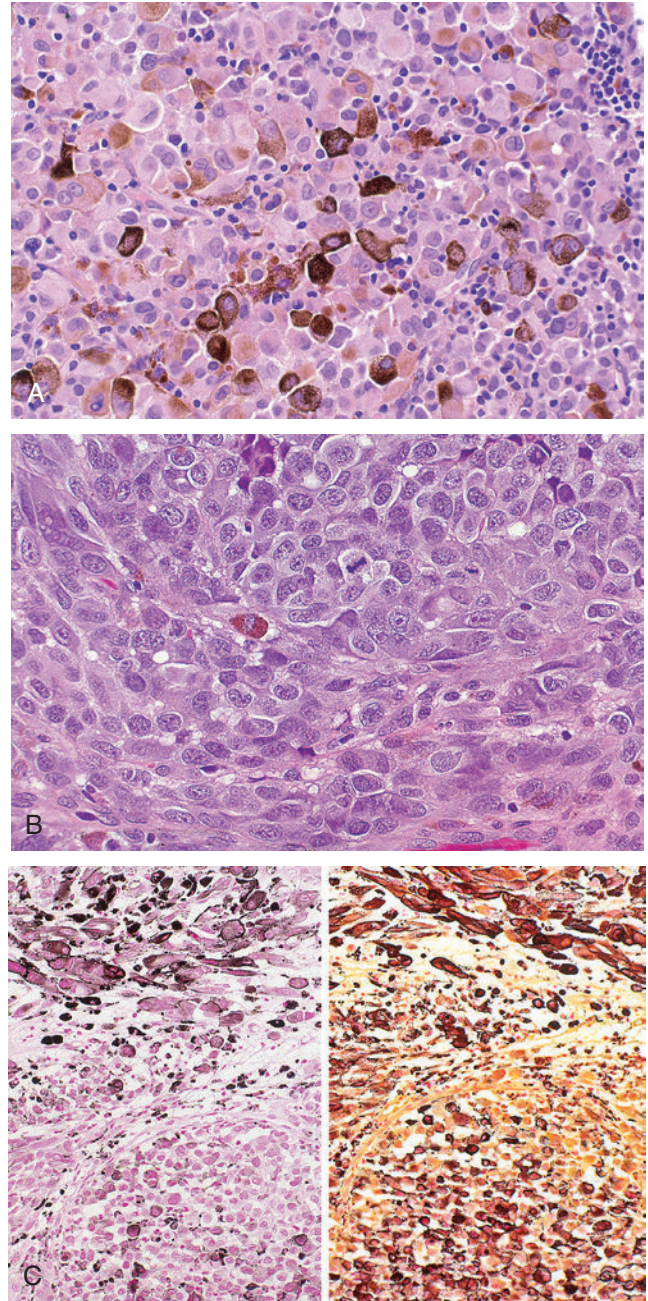


Fig. 3-67. Melanin in mucosal malignant melanomas is variable.

A, Readily identifiable intracytoplasmic melanin may be present. **B**, Not uncommonly, there may be an absence of melanin or the presence of scattered isolated cells with intracytoplasmic pigmentation suggestive of melanin. **C**, Histochemical confirmation of melanin includes (*left panel*) Fontana and (*right panel*) Churukian-Schenk staining. Melanin is present in the epithelioid cells and spindle-shaped cells in both panels.

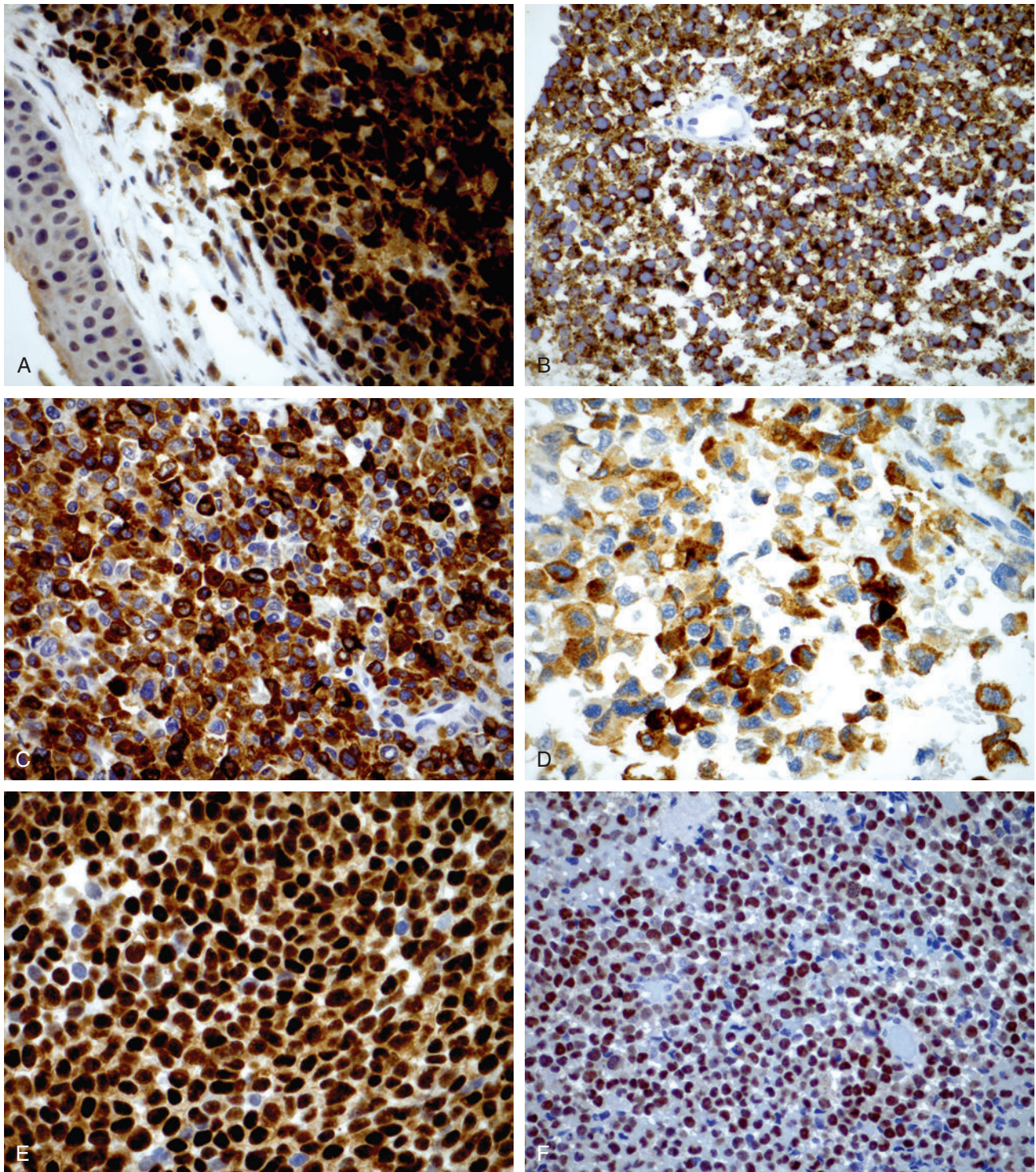


Fig. 3-68. Immunohistochemical staining in mucosal melanoma.

Often a diagnosis of mucosal malignant melanoma requires immunohistochemical confirmation as seen by reactivity for (A) S100 protein (nuclear and cytoplasmic); (B) HMB-45 (cytoplasm); (C) MelanA (cytoplasm); (D) tyrosinase (cytoplasm); (E) MITF (nuclear); and (F) SOX10 (nuclear).

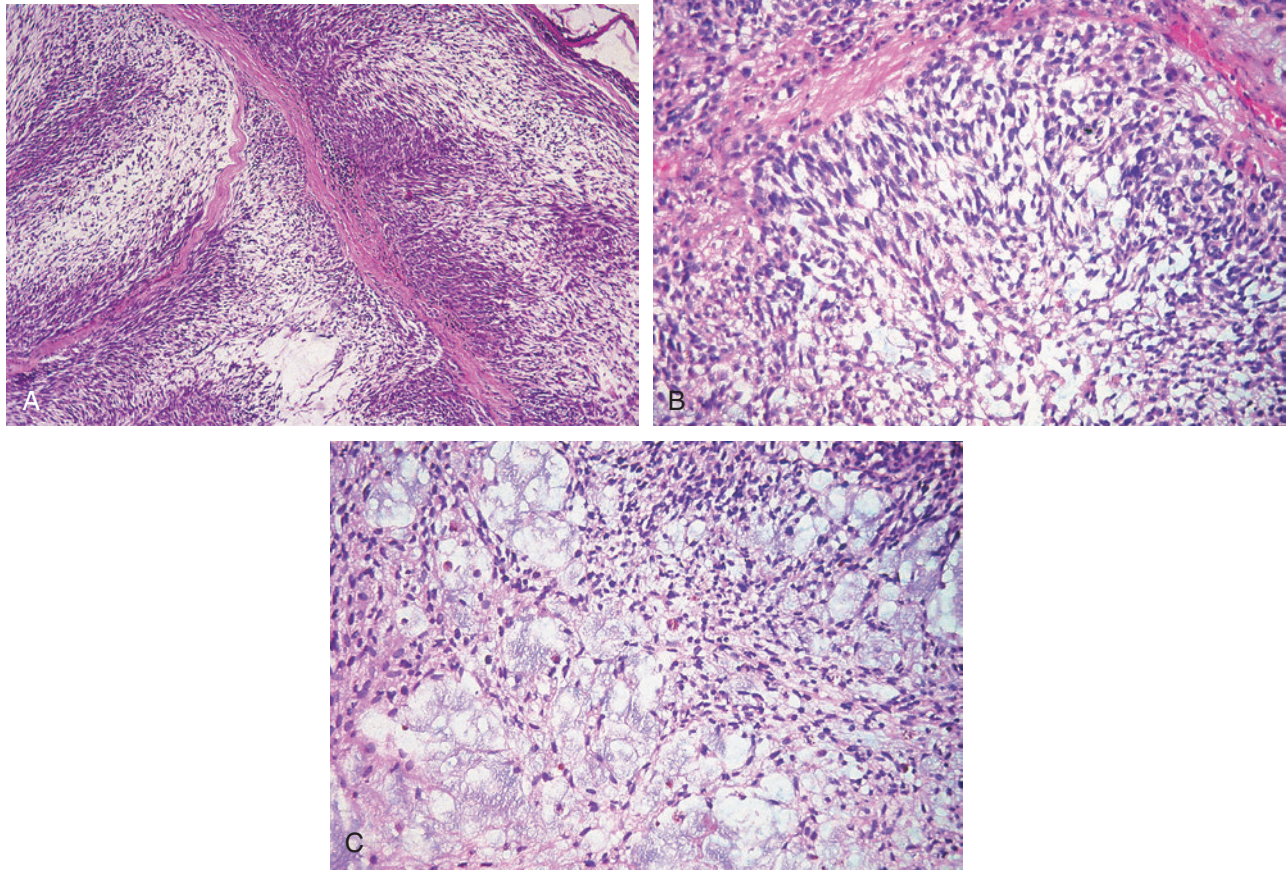


Fig. 3-69. Variant histology of melanoma.

Melanoma is notorious for being the “great masquerader,” simulating by light microscopy the appearance of other tumor types. **A** through **C**, Mucosal malignant melanoma showing a multinodular growth pattern with prominent myxoid stroma and cells with relatively uniform spindle-shaped nuclei; in **C**, scattered melanin was identified and the diagnosis was confirmed by immunohistochemical stains (not shown).

- Adjuvant radiotherapy and chemotherapy are of questionable value in the management of MMM.
- Prolonged palliation (i.e., survival) may be achieved in a limited number of patients following multimodality treatment (surgery and radiotherapy).
- Radiotherapy or chemotherapy in the treatment of MMM is felt to have little effect on local or distant disease, and presently is used as adjuvant therapy.
- Overall, the prognosis for MMM of all upper aerodigestive tract sites is considered poor:
 - 5-year survival rates generally less than 30%
- Targeted therapy:
 - Given the absence of *BRAF* mutations in the majority of MMM cases, targeted therapy used for *BRAF*-mutated cutaneous malignant melanomas is less promising for patients with MMM.
 - Presence of activated c-kit mutations raises possible utility of targeted therapy, with tyrosinase kinase inhibitors found to be effective for tumors with c-kit mutations.
- For sinonasal tract MMM, the 5-year disease-specific survival ranges from 10% to 46%; median survival of 2 years.
- There is no time period after which a patient with MMM should be considered as cured.
- Malignant melanoma is notorious for remaining quiescent for long periods following the initial diagnosis, only to resurface years to decades later.
- Recurrence, metastasis, and death may occur decades after “curative” therapy.
- Metastatic disease occurs most frequently to the lungs, lymph nodes, and brain.
- Histopathologic determination of the anatomic level of invasion (Clark level) and thickness of tumor (Breslow thickness) used for cutaneous malignant melanomas and are not applicable to MMM.

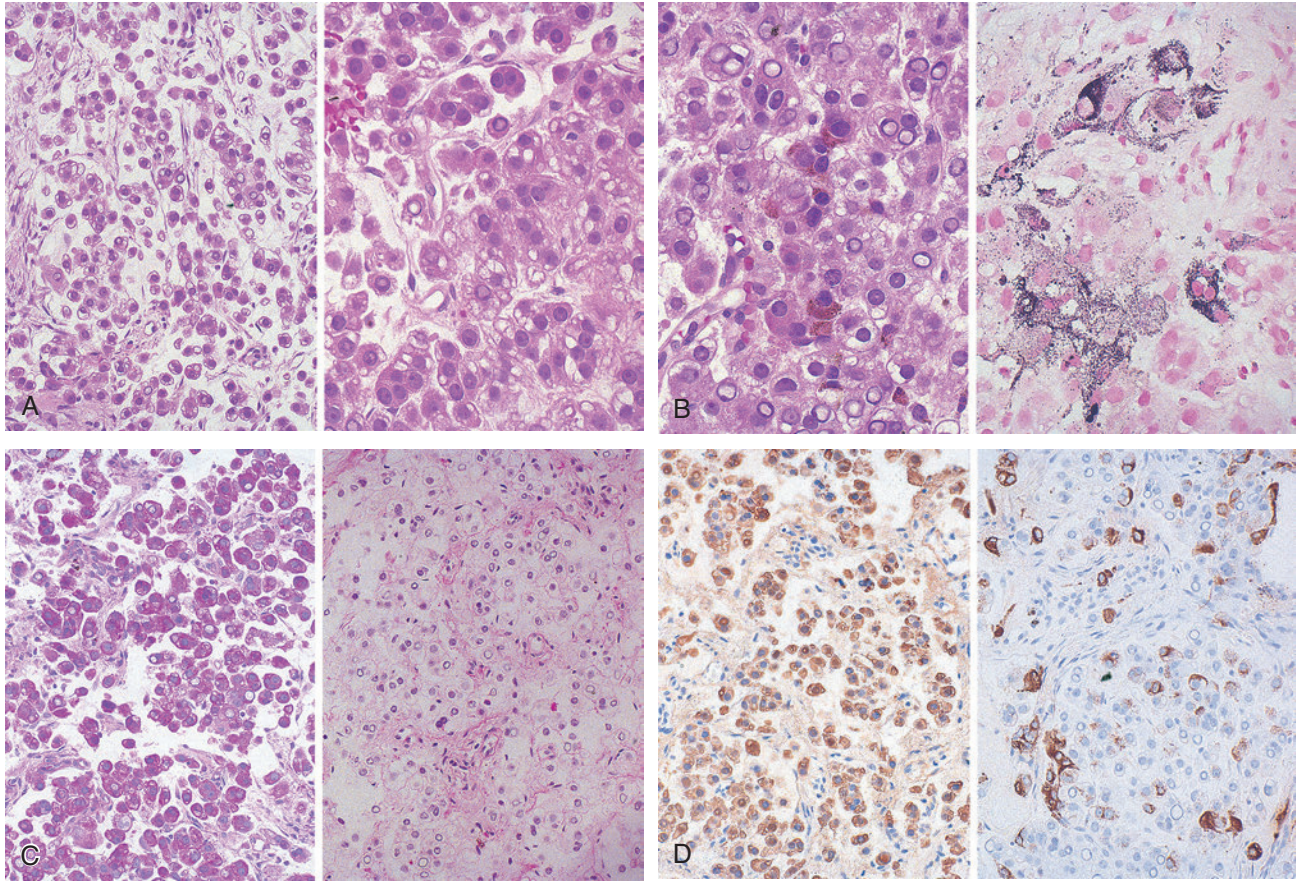


Fig. 3-70. Variant histology of melanoma.

Another example of mucosal malignant melanoma with unusual histology. **A**, Scattered nests of epithelioid cells with cytoplasmic vacuolization; intranuclear pseudoinclusions are present. **B**, *left panel*, intracytoplasmic pigment suggestive of melanin is present confirmed by *right panel* Fontana stain. **C**, The cells contain glycogen as evidence by the presence of diastase-sensitive, PAS-positive intracytoplasmic material (*left panel*, PAS; *right panel*, PAS with diastase digestion). **D**, Immunohistochemical confirmation of melanoma includes (*left panel*) S100 protein and (*right panel*) HMB45 reactivity.

MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY (MNTI)

(Figs. 3-71 through 3-73)

- Rare primitive neuroectodermal tumor occurring most often in infants in the first year of life and primarily arising in head and neck sites (anterior maxilla \gg other craniofacial sites) with evidence of epithelial, neural, mesenchymal, and neuroectodermal differentiation.
- Believed to be of neural crest origin
- Synonyms include melanotic progonoma; congenital melanocarcinoma; retinal anlage tumor; melanotic adamantinoma.
- Rarely, MNTI may occur in sites other than head and neck, including:
 - Mediastinum, brain, anterior fontanelle, mandible, femur, epididymis
- Presents as a rapidly growing soft tissue mass in the area of the upper jaw (canine teeth) with or without bone destruction.
- Radiology:
 - Cystic radiolucent lesion
 - Local destruction may be identified including displacement of teeth.
- Histopathology characterized by an alveolar or pseudoglandular growth composed of a biphasic cell population consisting of:
 - Smaller cells:
 - Small round, lymphocytic-like cells with hyperchromatic nuclei and scant cytoplasm (neuroblastic cells)
 - Neurofibrillary matrix may be present.
 - Neural type rosettes absent
 - Larger cells:
 - Epithelioid cells with vesicular nuclei, prominent nucleoli and eosinophilic cytoplasm
 - Noteworthy for the presence of melanin



Fig. 3-71. Melanotic neuroectodermal tumor of infancy (MNTI).

A, Infant with a lesion of the maxilla protruding from her mouth with a red to black appearance; a tooth is identifiable. **B,** The tumor was completely excised and was oval, firm, and tan-gray to red in appearance; the tooth is seen along one edge of the resection specimen.

- Rhabdomyoblastic differentiation may be identified:
 - Myogenin-positive cells
- Immunohistochemistry:
 - Polyphenotypic expression of epithelial, neural, mesenchymal, and melanocytic cell markers:
 - Both small and large cells: expression of NSE, CD57 (Leu-7); variable reactivity for desmin and muscle specific actin
 - Smaller cell component: variable expression of synaptophysin, GFAP
 - Larger cell component: consistent expression of cytokeratin, HMB-45 and vimentin; variable EMA expression

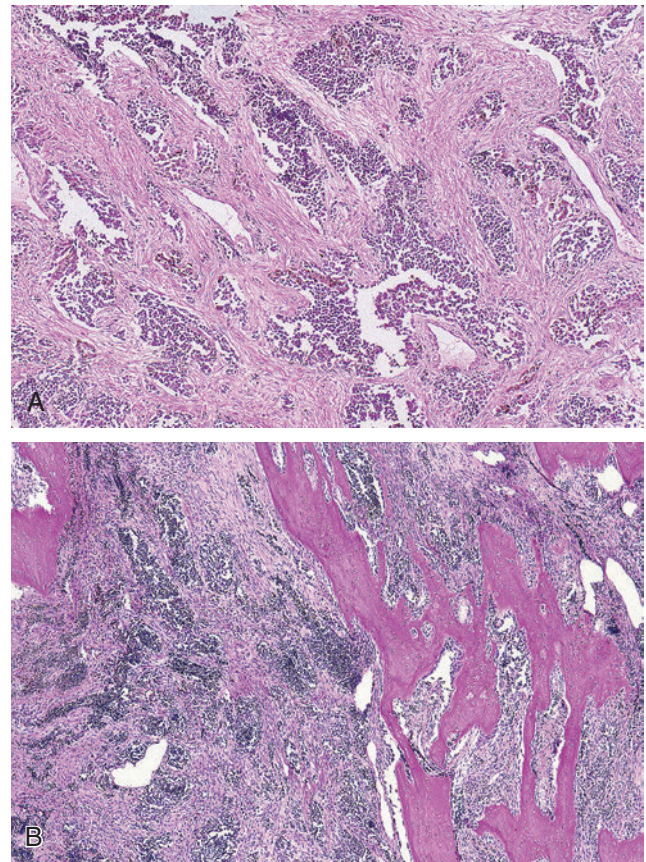


Fig. 3-72. MNTI.

A, The tumor is infiltrative with nests of dark appearing cells separated by fibroconnective tissue. **B,** Infiltration into bone (and other soft tissue structures) may be present.

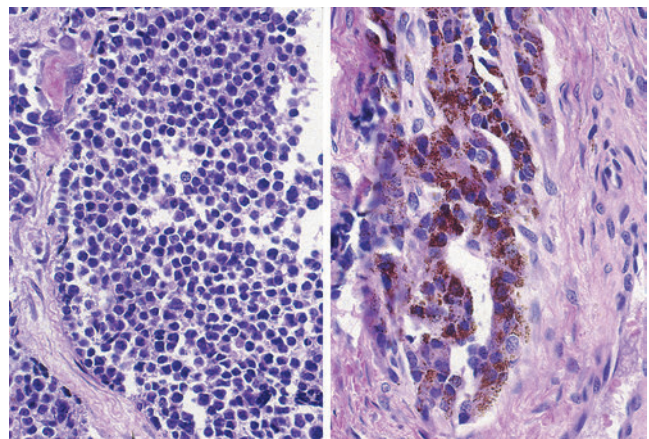


Fig. 3-73.

MNTI comprises a dual cell population, including (*left panel*) small round, lymphocytic-like cells with hyperchromatic nuclei and scant cytoplasm (neuroblastic cells) and (*right panel*) larger epithelioid cells with vesicular nuclei, eosinophilic cytoplasm, and melanin.

- No immunoreactivity in either cell component for S100 protein, neurofilament, CEA
- Cytogenetics:
 - Absence of t(11;22) translocations:
 - In the absence of this translocation MNTI is not considered to be within the same family of tumors as Ewing sarcoma and primitive neuroectodermal tumor (PNET).
- Treatment is surgical but should include tumor-free margins.
- Local recurrence is usually the result of inadequate surgical resection.
- Majority of MNTI are benign:
 - Low rate of recurrence
 - Small percentage behave in a malignant manner (metastatic disease).
- Malignant-behaving MNTI require surgery, radiation therapy, and chemotherapy:
 - Aggressive neoplasms
 - May have widespread dissemination, usually to regional lymph nodes
 - Marked decrease in survival

SINONASAL (MUCOSAL) ADENOCARCINOMA

- Adenocarcinomas of the sinonasal tract represent from 10% to 20% of all primary malignant neoplasms of this region but, exclusive of salivary gland types, represent only 6.3% of all malignant sinonasal tract tumors.
- Malignant salivary gland neoplasms are discussed later in this chapter.
- Two main categories of nonsalivary gland type adenocarcinomas are recognized in the sinonasal tract including:
 - Intestinal type adenocarcinomas
 - Nonintestinal type adenocarcinomas

Intestinal Type Adenocarcinomas (ITAC) (Figs. 3-74 through 3-78)

Definition: Malignant epithelial glandular neoplasm of the sinonasal tract that histologically resembles intestinal adenocarcinoma and adenoma.

Clinical

- More common in men than in women; occur over a wide age range but are most common in the fifth to seventh decades of life
- Most frequently involve the ethmoid sinus followed by the nasal cavity (inferior and middle turbinates) and maxillary sinus; however, may arise anywhere in the sinonasal tract

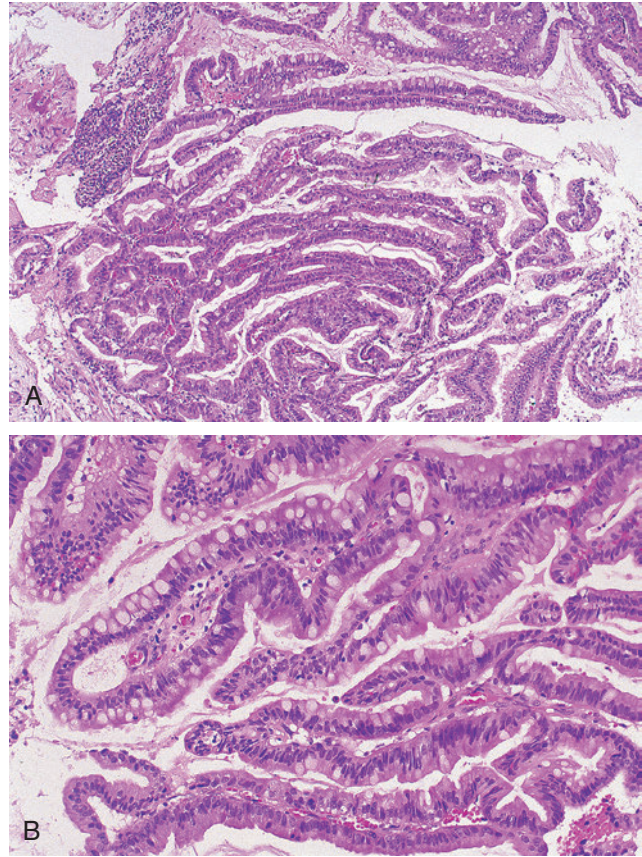


Fig. 3-74. Sinonasal tract intestinal type adenocarcinoma, papillary.

The papillary type shows a predominance of papillary architecture with minimal cytologic atypia.

- Early symptoms tend to be nonspecific and vary from nasal stuffiness to obstruction that, with persistence, may be associated with epistaxis, prompting further clinical evaluation.
- Due to the delay in diagnosis, tumors may reach a large size with extensive invasion at the time of presentation.
- Advanced tumors present with pain, cranial nerve deficits, visual disturbances, and exophthalmos.
- Etiologic factors associated with the development of ITAC include exposure to hardwood dust, leather, and softwood; increased incidences of adenocarcinoma are seen in woodworkers and workers in the shoe and furniture industries:
 - Wood dust exposure shown to be causal factor in the mutagenesis of TP53 possibly caused by reactive nitrogen species generated through a chronic inflammatory process, suggesting a role in the pathogenesis of ITAC

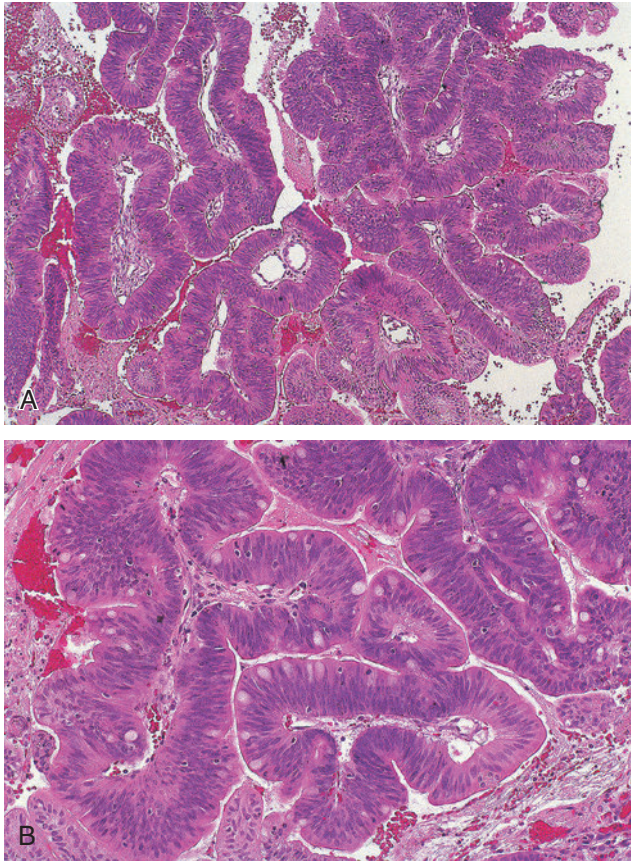


Fig. 3-75. Sinonasal tract intestinal type adenocarcinoma, colonic type.

The colonic type shows tubulo-glandular architecture with increased nuclear pleomorphism and mitotic activity.

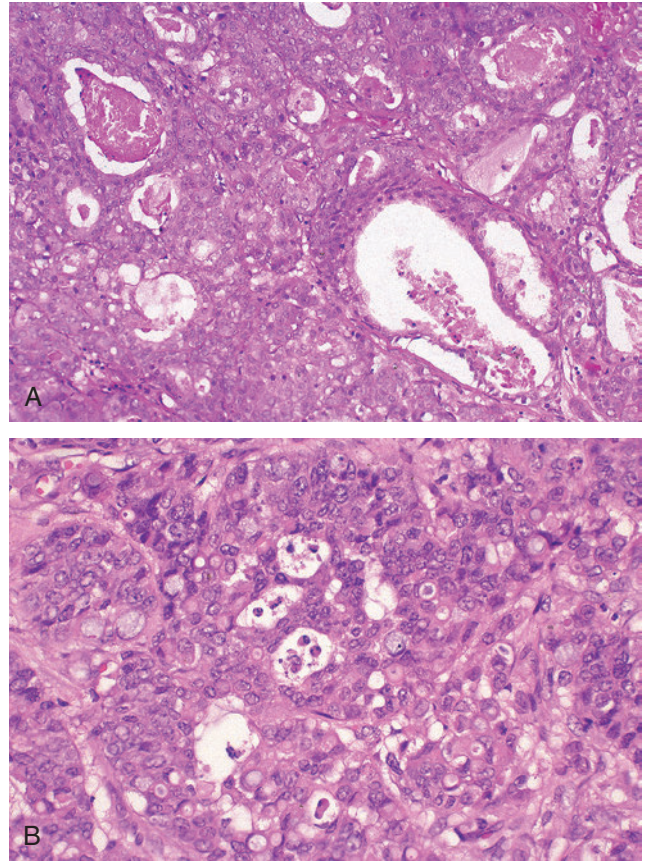


Fig. 3-76. Sinonasal tract intestinal type adenocarcinoma, solid type.

The solid type shows a loss of differentiation characterized by solid growth with tubule formation, nuclear pleomorphism, round vesicular nuclei, prominent nucleoli, and increased mitotic figures.

- Significant association between COX-2 expression with occupational exposure to wood dust, suggesting a role for inflammatory components in the carcinogenesis process
- Sporadic ITAC unassociated with occupational exposure occur and tend to affect women more than men, with most tumors involving the maxillary antrum.

Pathology

Gross

- These tumors have a variable appearance; they may be well demarcated to poorly defined and invasive, flat, to exophytic or papillary growths with a tan/white to pink color and a friable to firm consistency.
- A mucinous or gelatinous quality may be readily identifiable.

Histology

- Invasive tumors with various growth patterns, including papillary-tubular, alveolar-mucoid or alveolar-goblet, signet-ring, and mixed
- Two classifications have been proposed ([Table 3-10](#))
 - Barnes classification divided ITAC into 5 categories, including:
 - Papillary
 - Colonic
 - Solid
 - Mucinous
 - Mixed
 - Kleinsasser and Schroeder classification divided ITAC into four categories, including:
 - Papillary tubular cylinder (PTCC) types I-III (I = well differentiated, II = moderately differentiated, and III = poorly differentiated)
 - Alveolar goblet type

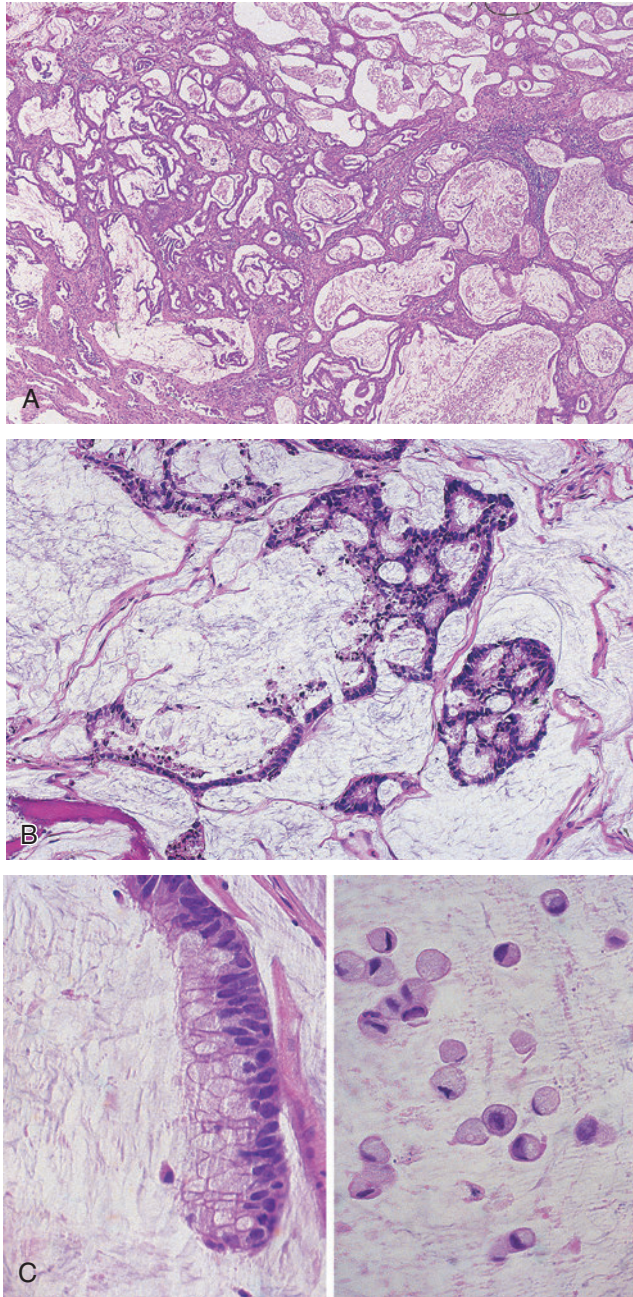


Fig. 3-77. Sinonasal tract intestinal type adenocarcinoma, mucinous type.

A, Large, well-formed glands distended by mucus and extracellular mucin pools. **B**, Clusters of individual glands and signet ring cells. **C**, Intracellular mucin within (*left panel*) columnar cells and (*right panel*) signet ring cells; a prominent mucomyxoid matrix is present.

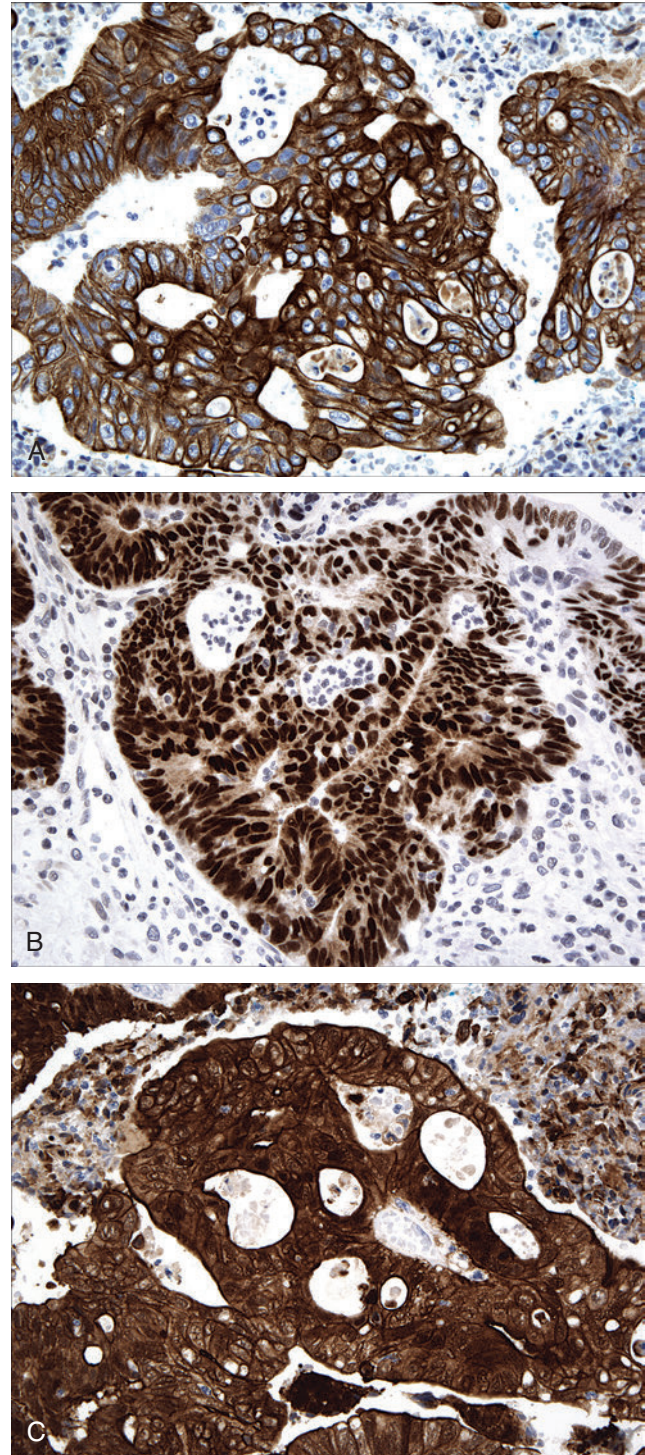


Fig. 3-78. Sinonasal tract intestinal type adenocarcinoma, colonic subtype.

Among the immunomarkers that these tumors are reactive for include (**A**) CD20, (**B**) CDX2, and (**C**) villin.

TABLE 3-10 Classification of Sinonasal Tract Intestinal-Type Adenocarcinoma (ITACs)

Barnes	Kleinsasser and Schroeder	Percentage of Cases	3-Year Cumulative Survival*
Papillary-type	PTCC-I	18%	82%
Colonic-type	PTCC-II	40%	54%
Solid-type	PTCC-III	20%	36%
Mucinous-type	Alveolar goblet	Uncommon	48%
	Signet-ring	Uncommon	0
Mixed	Transitional	Rare	71%

PTCC, Papillary tubular cylinder cell.

*Survival data derived from Kleinsasser and Schroeder.

- Signet-ring type
- Transitional type
- Barnes papillary, colonic, and solid types correspond to Kleinsasser and Schroeder PTCC-I, PTCC-II, and PTCC-III, respectively.
- Either classification is acceptable, but for simplicity the Barnes classification is preferred and is the one used in this section.
- Most common histologic types seen in association with woodworkers as well as in sporadically occurring cases are the papillary and colonic types.
- Papillary type (papillary tubular cylinder I or well-differentiated adenocarcinoma), representing approximately 18% of cases, shows a predominance of papillary architecture with occasional tubular glands, minimal cytologic atypia, and rare mitotic figures.
- Colonic type (papillary tubular cylinder II or moderately differentiated adenocarcinoma) shows a prevalence of tubuloglandular architecture, rare papillae, with increased nuclear pleomorphism and mitotic activity.
- Solid type (papillary tubular cylinder III or poorly-differentiated adenocarcinoma) shows a loss of differentiation characterized by solid and trabecular growth with isolated tubule formation, marked increased in the number of smaller cuboidal cells with nuclear pleomorphism, round vesicular nuclei, prominent nucleoli, and increased mitotic figures.
- Analogous to colonic adenocarcinoma, some ITAC are predominantly composed of abundant mucus production and are classified as mucinous type of ITAC.
- Mucinous type (alveolar goblet cell and signet ring) includes two growth patterns:
 - In one pattern there are solid clusters of cells, individual glands, signet ring cells, short papillary fronds with or without fibrovascular cores; mucin

is predominantly intracellular and a mucomyxoid matrix may be present.

- The other pattern shows the presence of large, well-formed glands distended by mucus and extracellular mucin pools; pools of extracellular mucin are separated by thin connective tissue septa, creating an alveolar type pattern.
- Predominantly cuboidal or goblet tumor cells are present in single layers at the periphery of mucus lakes.
- Mucus extravasation may elicit an inflammatory response that may include multinucleated giant cells.
- Tumors in which the mucus component predominates (>50%), similar to their gastrointestinal counterparts, may be classified as mucinous adenocarcinomas.
- Mixed type (transitional) is composed of an admixture of two or more of the previously defined patterns.
- Irrespective of the histologic type, ITAC histologically simulate normal intestinal mucosa and may include villi, Paneth cells, enterochromaffin cells, and muscularis mucosa.
- In rare instances, the lesion is composed of well-formed villi lined by columnar cells resembling the absorptive cells; in such cases, bundles of smooth muscle cells resembling muscularis mucosae may also be identified under the villi.
- Histochemistry:
 - Stains for epithelial mucins are positive, including intracytoplasmic and extracellular mucicarminophilia.
- Immunohistochemistry:
 - Diffusely positive for epithelial markers including epithelial membrane antigen, B72.3, Ber-EP4, BRST-1, CD57 (Leu-M1), and human milk fat globule (HMFG-2)
 - Strongly reactive with anti-cytokeratin cocktails
 - CEA staining is variable with conflicting results in the literature, including some cases with diffuse staining, some cases with focal staining, and some cases with no staining.
 - CK20 positivity (73% to 86%) and variably CK7 reactivity (43% to 93% of cases)
 - CDX-2, a nuclear transcription factor involved in the differentiation of intestinal epithelial cells and diffusely expressed in intestinal adenocarcinomas, can be found in ITAC.
 - CDX-2 reactivity not limited to ITACs but can also be seen in sinonasal nonintestinal-type neoplasms, including:
 - Sinonasal undifferentiated carcinomas, squamous cell carcinomas (keratinizing and non-keratinizing), salivary-type adenocarcinomas, and small cell carcinoma

- Nonintestinal types of sinonasal tumors are generally CK20 negative.
- CDX-2 and CK20 are highly sensitive sinonasal ITAC, but CK20 is more specific.
- Clear-cut glandular differentiation and CK20 reactivity represent more reliable features for ITACs than CDX-2 staining.
- Expression of villin and MUC2 also present
- Absence of myoepithelial-related markers including p63 and calponin; however, p63 reactivity may be present and does not exclude a diagnosis of adenocarcinoma; in such cases complexity of growth, cytomorphology and/or invasion assist in diagnosis of adenocarcinoma.
- Neoplastic cells may express a variety of hormone peptides, including serotonin, cholecystokinin, gastrin, somatostatin, and leu-enkephalin.
- Chromogranin and synaptophysin-positive cells can be identified.
- Aberrant expression of p53 and p16 commonly present:
 - p53 overexpression less frequent in mucinous subtype
- Cytogenetics and molecular genetics:
 - *k-ras* mutations in up to 25%
 - *h-ras* mutations variably identified present in some studies and absent in other studies
 - Absence of microsatellite instability by PCR
 - CGH analyses have shown a variety of gains and losses.

Differential Diagnosis

- Metastatic adenocarcinoma of gastrointestinal origin:
 - Rare occurrence to the sinonasal tract
 - Clinical history is critical in establishing a diagnosis of ITAC and in excluding a metastasis to the sinonasal tract from a gastrointestinal tract primary neoplasm.
 - Histology, histochemistry, and immunohistochemistry of ITAC and GIT adenocarcinomas are identical.
- Nonintestinal, nonsalivary gland adenocarcinoma:
- Salivary gland-type adenocarcinoma
- Nasopharyngeal low-grade papillary adenocarcinoma
- Papillary sinusitis (see Fig. 2-6, E, F):
 - In limited biopsy material including only superficial tissue fragments showing a papillary epithelial proliferation, differentiation of florid reactive chronic sinusitis with papillary architecture can present diagnostic challenges in differentiation from a papillary type of ITAC:
 - Presence of immunohistochemical staining for CDX2, CK20, villin assists in identifying papillary type of ITAC and differentiating it from papillary sinusitis.
- Sinonasal hamartomas

Treatment and Prognosis

- Treatment includes complete surgical excision, generally via a lateral rhinotomy; depending on the extent and histology of the neoplasm the surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy, and additional exenterations).
- Radiotherapy may be used for extensive disease or for higher grade neoplasms.
- All sinonasal intestinal-type adenocarcinomas are considered as potentially aggressive, lethal tumors.
- Metastasis to cervical lymph nodes and spread to distant sites are infrequent, occurring in about 10% and 20%, respectively.
- 5-year cumulative survival rate is around 40%, with most deaths occurring within 3 years.
- Death results from uncontrollable local or regional disease with extension and invasion of vital structures and/or metastatic disease.
- Sinonasal ITAC are generally locally aggressive tumors with frequent local failure (about 50%):
 - Because most patients present with advanced local disease, clinical staging generally has no relevant prognostic significance.
- Histologic subtype has been identified as indicative of clinical behavior, with the papillary type (grade I) lesions behaving more indolently than the other variants (see Table 3-10).
- Slight differences in survival noted between ITAC occurring in occupational-exposed individuals and sporadically occurring ITAC:
 - Occupational-associated ITAC: 50% 5-year survival
 - Sporadic occurring ITAC: 20% to 40% 5-year survival

Nonintestinal (Nonsalivary Gland) Adenocarcinomas (Figs. 3-79 and 3-80)

Definition: Those sinonasal tract tumors that do not demonstrate histopathologic features of the sinonasal “intestinal” types of adenocarcinoma and are not salivary gland neoplasms.

- These adenocarcinomas are divided into low- and high-grade types.

Clinical

Low-grade

- Predominantly occur in adults but have been identified over a wide age range from 9 to 80 years:
 - Slight male predominance; wide age range from 9 to 75 years, with most occurring in fifth to

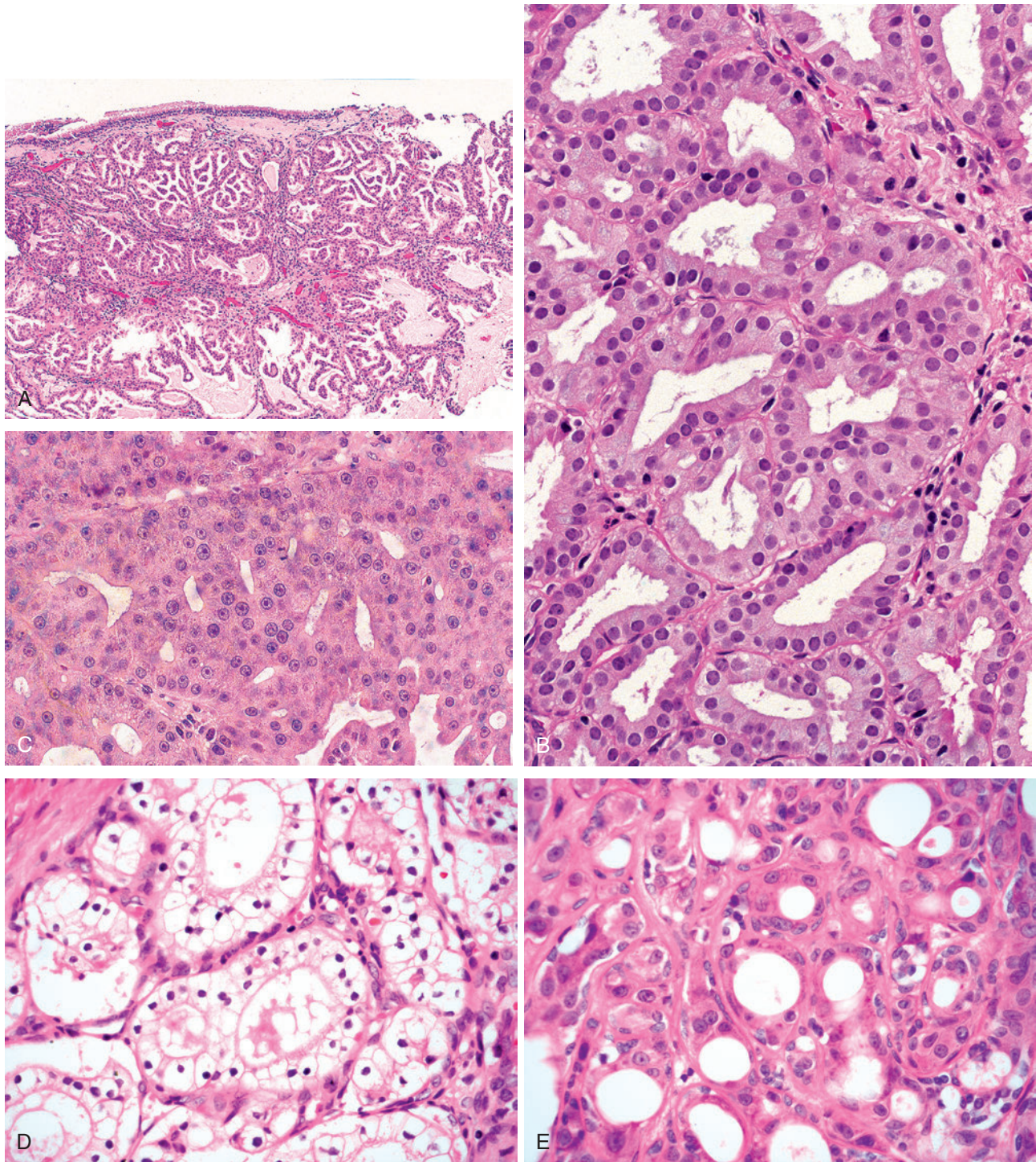


Fig. 3-79. Sinonasal tract nonsalivary, nonintestinal type adenocarcinoma, low grade.

A, Submucosal unencapsulated invasive tumor with complex glandular and papillary growth. **B**, Numerous uniform small glands or acini are present with a back-to-back growth pattern, absence of intervening stroma; the glands are lined by a single layer of nonciliated, cuboidal to columnar cells with uniform, round nuclei, mild pleomorphism, and absence of mitotic figures. **C**, Another example showing complex back-to-back growth with cells showing moderate nuclear pleomorphism, prominent nucleoli, and a mitotic figure; other types of low-grade nonsalivary and nonintestinal types of adenocarcinoma can include (**D**) clear cells and (**E**) oncocytic cells.

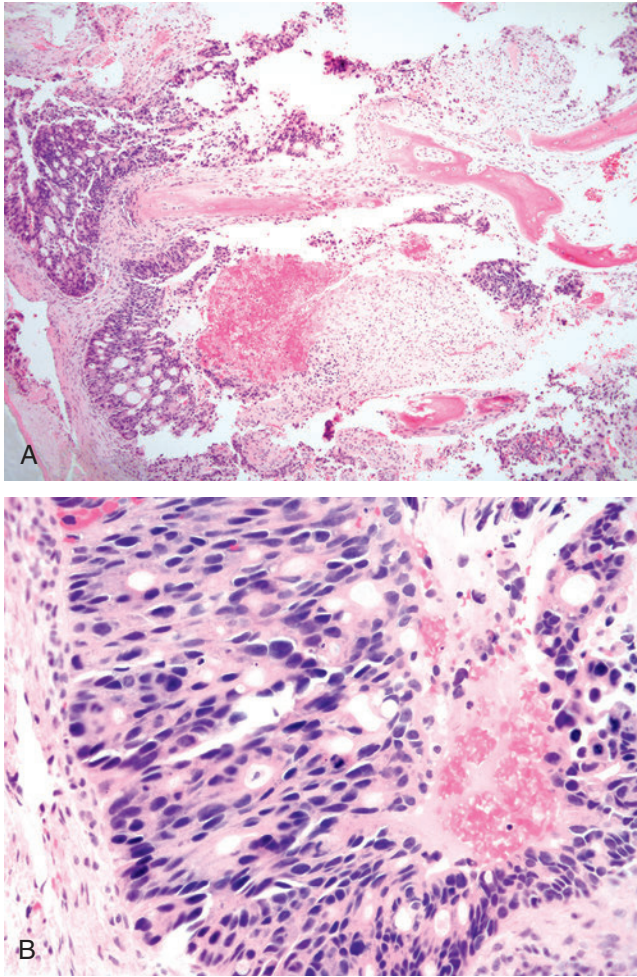


Fig. 3-80. Sinonasal tract nonsalivary, nonintestinal type adenocarcinoma, high grade.

A, The neoplasm invades into bone and shows solid and complex (back-to-back) glandular growth patterns. **B,** At higher magnification glandular differentiation is evident, but the neoplasm is characterized by the presence of cells with moderate to marked nuclear pleomorphism and increased mitotic activity.

seventh decades of life and average age at presentation of 53 years.

- Predilect to the ethmoid sinus (to a lesser extent as compared with the “intestinal” type) followed by nasal cavity > nasal septum > sinuses (multiple) > maxillary antrum
- Primarily present with nasal obstruction and epistaxis; pain is an infrequent feature (less than 10%).
- Duration of symptoms ranges from 2 months to 5 years with a median duration of 5.5 months
- No known etiologic factors such as tobacco, alcohol, occupational, environmental, or genetic

- Some cases reported to be associated with respiratory epithelial adenomatoid hamartoma (REAH), prompting suggestion that REAHs are precursor lesions for a subset of sinonasal low-grade adenocarcinomas.

High-grade

- Male predilection; mean age at presentation of 59 years
- Predilect to the maxillary sinus
- Primary presenting symptoms include nasal obstruction, epistaxis, pain, and facial deformity (e.g., proptosis); the duration of symptoms ranges from 2 weeks to 5 years with a median duration of 2.5 months.
- No known etiologic factors such as tobacco, alcohol, occupational, environmental, or genetic
- May occur in association with Schneiderian papilloma
- Rarely reported in association with high-risk HPV
- Both low- and high-grade types may also originate in the nasal cavity, other paranasal sinuses, or (not infrequently) in multiple sinonasal sites in various combinations.

Pathology

Gross

- These tumors have a variable appearance, including well-demarcated to poorly defined and invasive, flat to exophytic, or papillary growths with a tan/white to pink color and a friable to firm consistency.

Histology

- Either low- or high-grade, may be seen entirely within the submucosa without surface involvement or may involve the overlying ciliated respiratory epithelium

Low-grade

- Glandular or papillary growth and may be circumscribed but are unencapsulated tumors
- Numerous uniform small glands or acini are seen, often with a back-to-back growth pattern without an intervening stroma; occasionally, large, irregular cystic spaces can be seen.
- Glands are lined by a single layer of nonciliated, cuboidal to columnar cells with uniform, round nuclei, which may be limited to the basal aspect of the cell or may demonstrate stratification with loss of nuclear polarity and an eosinophilic cytoplasm.
- Cellular pleomorphism is mild to moderate and occasional mitotic figures are seen, but atypical mitoses and necrosis are absent.
- Despite the relatively bland histology, the complexity of growth, absence of two cell layers, absence of

encapsulation, and presence of invasion into the submucosa confer a diagnosis of adenocarcinoma.

- Variants include papillary, tubulopapillary, clear cell, and oncocytic adenocarcinomas.
- Multiple morphologic patterns may be seen in any one neoplasm.
- Squamous metaplasia not infrequently seen

High-grade

- Invasive tumors predominantly with a solid growth pattern, but glandular and papillary growth patterns can also be seen.
- Characterized by the presence of moderate to marked cellular pleomorphism, increased mitotic activity, including atypical forms, and necrosis
- Immunohistochemistry (both low- and high-grade):
 - Consistently and intensely CK7 reactive
 - Nonreactive for CK20, CDX2, villin, chromogranin, or synaptophysin
 - Myoepithelial-related markers, including p63, calponin, smooth muscle actin, usually (but not always) absent
- S100 protein may be positive.

Differential Diagnosis

- Low-grade adenocarcinoma:
 - Intestinal-type adenocarcinomas:
 - Presence of CK20, CDX2, and villin allow for differentiation.
 - Salivary gland-type adenocarcinomas
 - Papillary sinusitis:
 - In limited biopsy material including only superficial tissue fragments showing a papillary epithelial proliferation, differentiation of florid reactive chronic sinusitis with papillary architecture from low-grade adenocarcinoma with papillary architecture can be virtually impossible:
 - Immunohistochemical staining will not assist in differentiating florid papillary sinusitis from low-grade adenocarcinoma with papillary architecture
 - In a scenario in which limited tissue sampling precludes a definitive diagnosis, a diagnosis of “papillary glandular epithelial proliferation, not further specified” is merited with:
 - Indication that the differential diagnosis includes florid papillary sinusitis versus low-grade adenocarcinoma
 - Recommendation for additional biopsies to include deeper aspects of the lesion or conservative but complete excision to allow for differentiating these lesion types
 - Differentiation is predicated on presence of back-to-back glands, single cell type and infiltrative growth seen in low-grade adenocarcinomas versus absence of complex growth pattern,

presence of two cell layers, and absence of infiltrative growth in papillary sinusitis.

- Sinonasal hamartomas, in particular seromucinous hamartoma
- Nasopharyngeal low-grade papillary adenocarcinoma
- Metastatic adenocarcinoma from gastrointestinal tract, lung, breast, other
- For high-grade adenocarcinoma:
 - Intestinal-type adenocarcinomas
 - Salivary gland-type adenocarcinoma, including salivary duct carcinoma:
 - Androgen receptor reactivity is seen in salivary duct carcinoma but should be absent in sinonasal high-grade adenocarcinoma.
 - Nasopharyngeal low-grade papillary adenocarcinoma
 - Metastatic adenocarcinoma from gastrointestinal tract, lung, breast, other

Treatment and Prognosis

- Treatment for all the histologic variants of nonintestinal, nonsalivary gland sinonasal adenocarcinomas is complete surgical excision generally via a lateral rhinotomy:
 - Depending on the extent and histology of the neoplasm the surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy, and additional exenterations).
- Radiotherapy may be used for extensive disease or for higher grade neoplasms.
- Chemotherapy may be used in high-grade adenocarcinomas.
- Low-grade adenocarcinoma:
 - Excellent prognosis
 - 3-year survival rates of 70% to 89%
 - May recur in up to 30% of patients
 - Low metastatic rate
 - Death due to disease is rare, occurring in less than 5% of cases, and is due to uncontrollable local invasion.
- High-grade adenocarcinoma:
 - Dismal prognosis with approximately 20% 3-year survival rates

MALIGNANT SALIVARY GLAND NEOPLASMS

- Most common malignant salivary gland tumor of the sinonasal tract (and nasopharynx) is the adenoid cystic carcinoma.
- More common malignant neoplasms of major salivary glands, including mucoepidermoid carcinoma and acinic cell adenocarcinoma, are uncommon in the sinonasal tract (and nasopharynx):

- Most acinic cell adenocarcinomas arising outside the parotid gland including the sinonasal tract (and nasopharynx) more likely represent mammary analogue secretory carcinoma.
- For a more detailed discussion see Section 6, Salivary Glands.

Sinonasal Adenoid Cystic Carcinoma

- Adenoid cystic carcinoma (AdCC) is a malignant salivary gland neoplasm characterized by a distinctive histologic appearance, a tendency to invade nerves, and its protracted but nonetheless relentless clinical course.
- Approximately 20% of all AdCCs occur in the sinonasal tract; AdCCs represent approximately 5% of sinonasal malignancies.
- Most common site of involvement is the maxillary sinus (57%) followed by the nasal cavity (24%), ethmoid sinus (14%), and other sites (5%).
- AdCC of the sinonasal tract is a tumor of adults and rarely occurs in the first two decades of life.
- Symptoms may include airway obstruction, epistaxis, and pain.
- Can attain large sizes with extensive infiltrative growth at presentation
- Grossly, may appear circumscribed, solid, rubbery to firm, tan-white to gray-pink mass measuring from 2 to 4 cm in greatest dimension.
- Histologic appearance is identical to AdCC of more common sites; in the sinonasal tract AdCC:
 - Is a submucosal-based, unencapsulated, infiltrating neoplasm
 - Shows varied architecture consisting of cribriform, tubular/ductular, and solid patterns
 - Individual neoplasms may have a single growth pattern, but characteristically they show multiple patterns, any one of which may predominate.
 - Most common pattern is the cribriform type, considered the “classic” pattern, demonstrating arrangement of cells in a “Swiss cheese” configuration with many oval or circular spaces; these spaces contain basophilic mucinous substance or hyalinized eosinophilic material.
 - Tubular type has cells arranged in ducts or tubules; the ducts or tubules contain faintly eosinophilic mucinous material.
 - Cribriform and tubular patterns often occur together.
 - The least common pattern is the solid type, composed of neoplastic cells arranged in sheets or nests of varying size and shape with little tendency to form cystic spaces, tubules, or ducts.
- Irrespective of the growth pattern, the tumors are composed of a combination of abluminal-type myoepithelial cells (the predominant cell) and duct-lining cells.
- In the solid pattern, the cell population is dominated by the basaloid myoepithelial cells.
- Cellular and nuclear pleomorphism, necrosis, and mitotic activity are limited in the cribriform and tubular patterns; these features are more frequently seen in the solid pattern.
- Common to all histologic variants is the proclivity for nerve invasion (neurotropism), including peri- and intraneural invasion; invasion of adjacent soft tissue structures, including skeletal muscle and bone, can also be seen.
- Unlike the HPV-associated carcinoma with adenoid cystic-like features (see previously in this chapter), sinonasal AdCCs:
 - Show expression of the *MYB-NFIB* fusion biomarker
 - Lack intraepithelial dysplasia of the surface epithelium
 - May show p16 immunoreactivity but lack presence of transcriptionally active virus
- Preferred treatment for sinonasal AdCC is wide local excision and postoperative radiotherapy.
- Problems in the surgical removal relate to the infiltrative nature of these neoplasms with their tendency to extend along nerve segments, which is further compounded by their deceptively circumscribed macroscopic appearance.
- Recurrence rates are high, ranging from 75% to 90% and directly related to inadequate surgical excision.
- AdCCs are radiosensitive and radiotherapy is particularly useful in controlling microscopic disease after initial surgery, in treating locally recurrent disease, or as palliation in unresectable tumors.
- Radiotherapy is not curative.
- Sinonasal (and nasopharyngeal) AdCCs have similar biologic behavior to AdCCs at other locations:
 - Short-term prognosis is generally good because tumor growth is slow, but the long-term prognosis is poor.
 - 5-year survival rate (for all head and neck sites) of 75%
 - 20-year survival rate (for all head and neck sites) of 13%
 - Tumor location affects prognosis:
 - AdCCs located in major salivary glands have a better prognosis than their minor salivary gland counterparts.
 - Clinical staging plays a more decisive role than histologic grading in predicting prognosis in AdCC.

NON-HODGKIN LYMPHOMAS OF THE SINONASAL TRACT (NHL-SNT)

Definition: Heterogeneous group of hematolymphoid malignancies in which the bulk of disease is within the sinonasal tract.

- NHL-SNT include lymphomas of B-cell lineage, T-cell lineage, and NK/T-cell lineage.
- Nasal cavity lymphomas are predominantly of NK/T-cell type.
- Majority of B-cell lymphomas occur in the paranasal sinuses:
 - Diffuse large B-cell lymphoma (DLBCL) is the most common type.
 - Less often, other B-cell lymphomas of these sites occur, including Burkitt lymphoma, extranodal marginal B-cell lymphoma of the MALT type, and follicular lymphoma.

Clinical

- NHL-SNT are uncommon and account for only 1.5% of non-Hodgkin malignant lymphomas in the United States:
 - Incidence has been reported to be higher, however, in Asian and South American countries, where the incidence of primary non-Hodgkin malignant lymphoma is approximately 6.7% and 8.0% of all malignant lymphomas.
- Virtually the entire spectrum of morphologic types of lymphoma can be seen.
- Most common type of lymphoma in the sinonasal tract is the extranodal NK/T-cell lymphoma of nasal type.

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE (Figs. 3-81 through 3-86)

Synonyms: Angiocentric NK/T-cell lymphoma of nasal type; angiocentric lymphoma; angiocentric immunoproliferative lesions; peripheral T-cell lymphoma; polymorphic reticulosis; lethal midline granuloma; midline malignant reticulosis; idiopathic midline destructive disease; Stewart's granuloma.

NOTE: Some of these terms have been used over the years synonymously with NHL-SNT; this is categorically incorrect. Non-neoplastic lesions, inflammatory and infectious diseases, as well as numerous benign and malignant neoplasms of the sinonasal tract may result in a destructive process occurring in the midline aspect of this region. Therefore idiopathic midline destructive

disease is not a specific term and should never be used to indicate a diagnosis of a malignant lymphoproliferative neoplasm.

Clinical

- Primarily affects men; disease of adults with a median age in the sixth decade of life
- Most common in Asians and reported with significant frequency in South and Central America and Mexico:
 - In these populations, the disease is seen primarily in individuals of Native American origin.
 - These findings suggest a racial predisposition for the disease.
 - Although uncommon, NK/T-cell lymphomas, nasal type also occur in Western populations and can affect Caucasians.
- Commonly presents as a destructive process of the midfacial region with nasal septal destruction, palatal destruction/perforation, orbital swelling, or with obstructive symptoms related to a mass:
 - A small percentage of cases present with hemophagocytic syndrome with pancytopenia.
- Irrespective of ethnic background, strongly associated with EBV.
- Rarely, patients are iatrogenically immunosuppressed transplant recipients.
- Primary lymph node involvement is extremely uncommon.
- Antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3 (PR3) levels not elevated

Pathology

Gross

- No specific findings; tissue fragments often friable, hemorrhagic, and/or necrotic

Histology

- Sinonasal mucosa often with surface ulceration with associated fibrinoid necrosis, and acute and chronic inflammation:
 - Intact surface mucosa may show squamous metaplasia with or without pseudoepitheliomatous hyperplasia.
- Broad cytologic spectrum is present:
 - Usually cytologically atypical cells are present:
 - Atypical cells may vary from small and medium-sized cells to large, hyperchromatic cells.
 - Atypical cells may have irregular and elongated nuclei, prominent nucleoli, or clear cytoplasm.
 - Increased mitotic activity is often seen.
 - Epitheliotropism may be present.



Fig. 3-81. Extranodal NK/T-cell lymphoma, nasal type.

The clinical picture may include (A) sinonasal, upper lip, and orbital swelling; (B) destruction of the nasal septum with passage of a string between nasal passages. C, Same patient as in B showing not only septal destruction but also palate erosion as evidenced by the ability to pass the string between the nasal cavity and oral cavity. D, Ulcerative palatal lesion with purulent exudates due to a destructive lesion that originated in the floor of the maxillary sinus.

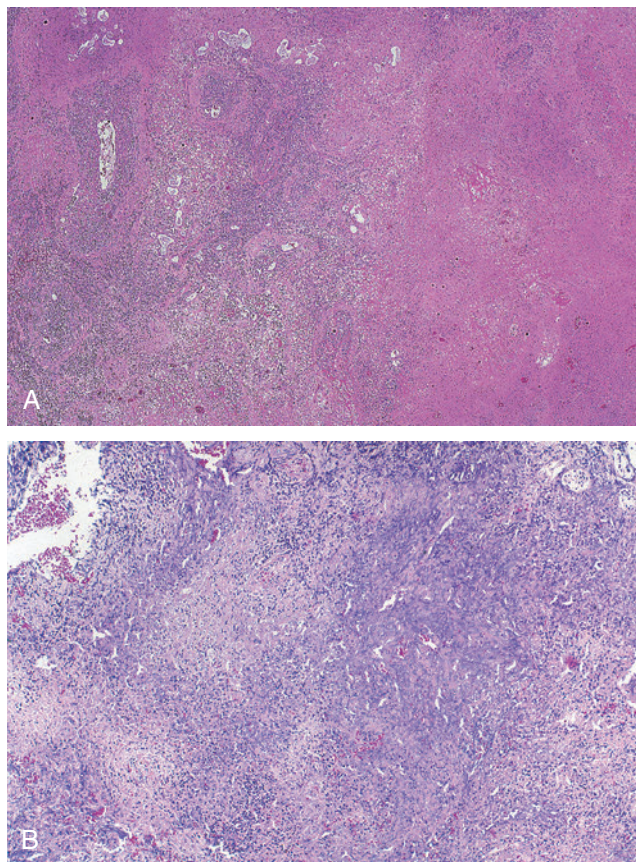


Fig. 3-82. Extranodal NK/T-cell lymphoma, nasal type.

At low magnification areas of geographic necrosis similar to that seen in granulomatosis with polyangiitis (formerly, Wegener granulomatosis) are present.

- In some cases overtly atypical or malignant cells are not evident:
 - Infiltrate has the appearance of a mixed (benign) inflammatory cell proliferation.
 - Presence of EBV would confirm a diagnosis even in the absence of overtly malignant cells; see below.
- An associated prominent admixed inflammatory cell infiltrate may be present:
 - Polymorphous cell population may obscure the atypical cells, causing diagnostic difficulties.
 - Benign inflammatory cell infiltrate may include mature plasma cells, histiocytes, and eosinophils.
 - Multinucleated giant cells and true granulomas are absent.
- In adequately sampled material, low-power appearance includes the presence of geographic (ischemic-type) necrosis characterized by bluish or so-called “gritty” necrosis:
 - Necrosis is a virtually constant (but not pathognomonic) feature.
 - Zonal pattern of distribution suggests a vascular pathogenesis.
 - Atypical cells invade and destroy blood vessels.
 - Vascular invasion and destruction is responsible for the designation “angiocentric lymphomas.”
 - Angiocentricity is defined as the presence of tumor cells around and within vascular spaces with infiltration and destruction of the vessel wall.
 - Perivascular localization is not sufficient for the designation of angiocentricity.
- Histochemistry:
 - Stains for microorganisms are negative.
- Immunohistochemistry:
 - NK-cell immunophenotype is most commonly present, including:
 - Cytoplasmic CD3 positive but surface (membranous) CD3 (by flow cytometry) negative
 - CD2 positive
 - CD56 (neural cell adhesion molecule [NCAM]) positive
 - Markers of cytotoxic granules are positive, including expression of:
 - Granzyme B
 - Cytotoxic granule-associated TIA-1
 - Perforin
 - T-cell markers, including CD43 and CD45RO (UCHL1), are positive.
 - CD4, CD5, CD8, CD20, CD57 (Leu-7) are negative.
 - Some cases may be CD30 positive.
 - p63 usually negative but may be focally positive.
 - T-cell receptor (TCR) and immunoglobulin (Ig) genes are germline (NK lineage):
 - T lineage cases have clonally arranged TCR genes and may express surface CD3.
 - Epstein-Barr virus:
 - Detected in most neoplastic cells in virtually all cases by in situ hybridization for EBER
 - Some cases may express EBV latent membrane protein (LMP).
 - LMP less sensitive than EBER in detecting EBV
 - Tumors that are CD56 negative may still be classified as NK/T-cell lymphomas if they express T-cell markers and cytotoxic markers and are EBV positive.
- Cytogenetics and molecular genetics:
 - NK/T-cell lymphomas are positive for EBV in greater than 95% of cases by in situ hybridization (ISH) for EBER.
 - Because EBV-positive cells are typically absent in the nasal cavity mucosa or in inflammatory diseases of the nasal cavity, the presence of EBV

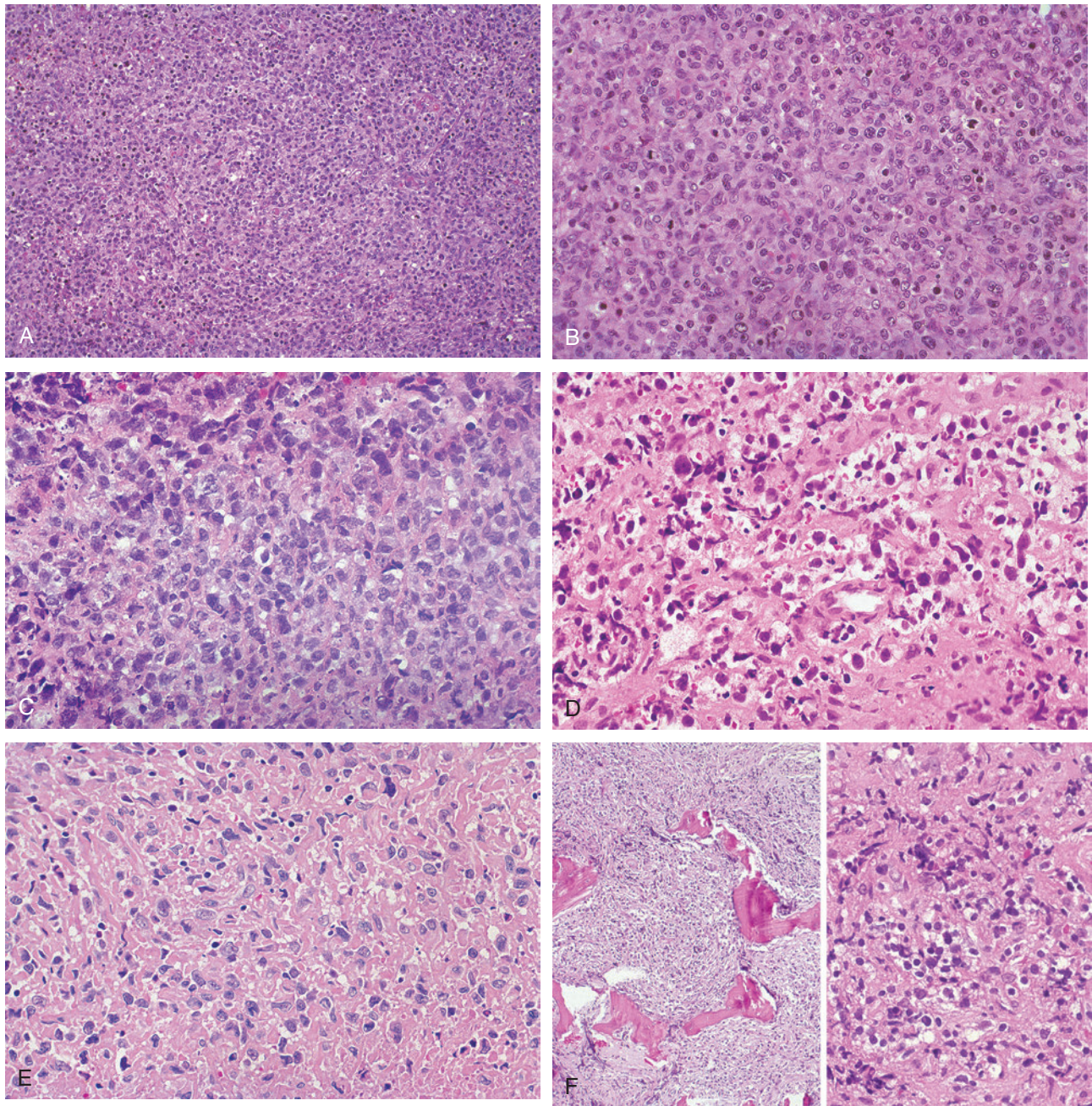


Fig. 3-83. Extranodal NK/T-cell lymphoma, nasal type.

A through **D**, Diffuse dyscohesive cellular proliferation varying from small and medium-sized cells to large cells with round to oval to irregular and elongated nuclei, vesicular to hyperchromatic nuclei, prominent nucleoli, and indistinct eosinophilic to clear cytoplasm; increased mitotic activity can be seen. **E**, Occasionally a collagenized stroma may be present.

F, Tumor infiltration of sinonasal bone

by ISH can be used in conjunction with light microscopy in the diagnosis of nasal cavity NK/T-cell lymphomas:

- Identification of EBV would confer a diagnosis of NK/T-cell lymphoma, nasal type

even in cases without overtly atypical/malignant appearing cells.

- EBV virus may induce the expression of cytokines (e.g., TNF α), which could lead to the presence of necrosis; this may then represent

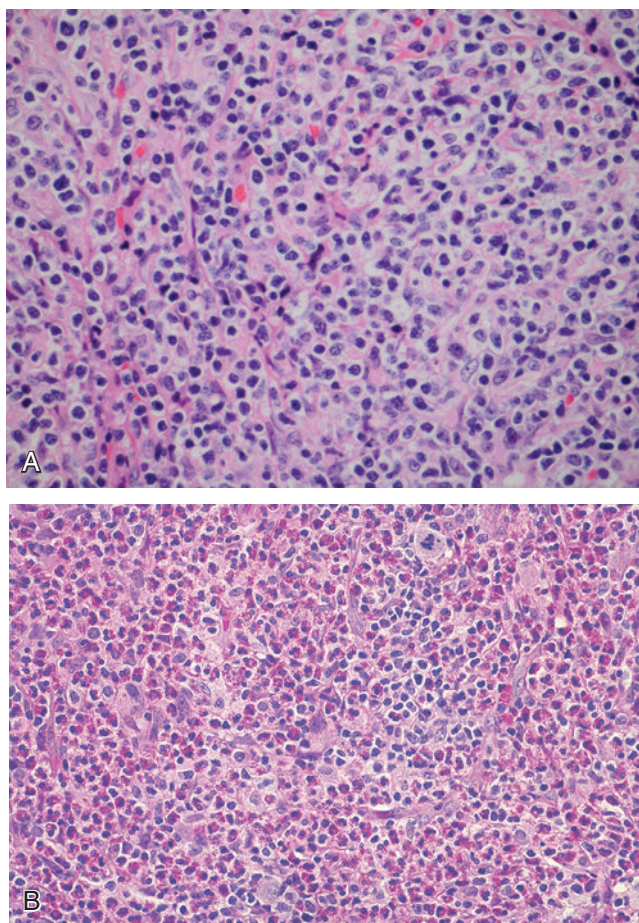


Fig. 3-84. Extranodal NK/T-cell lymphoma, nasal type.

A dense mixed inflammatory cell infiltrate can be seen in association with and at times obscuring the neoplastic cells and includes (A) mature lymphocytes and plasma cells and (B) eosinophils.

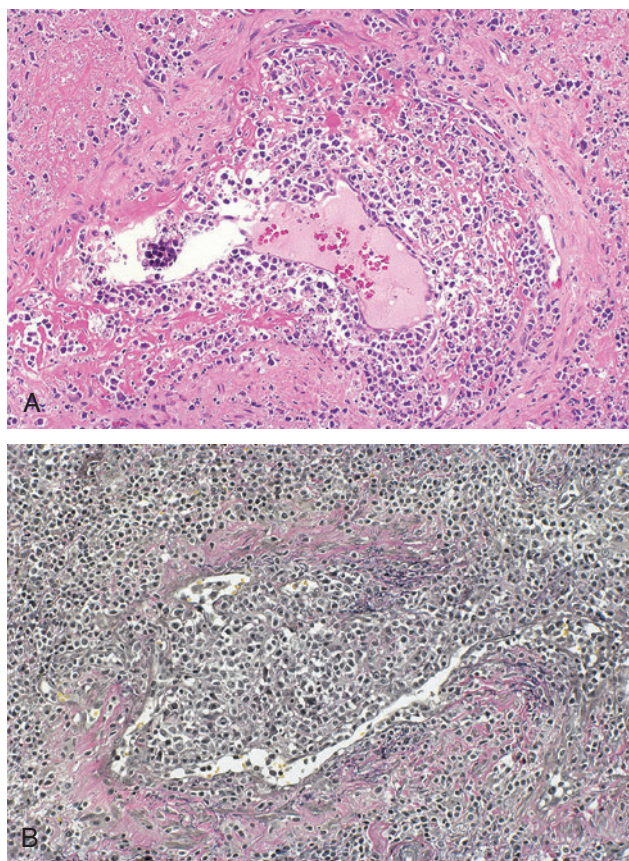


Fig. 3-85. Angiocentricity in extranodal NK/T-cell lymphoma, nasal type.

A, The neoplastic cells surround and invade vascular spaces (angiocentric and angioinvasion). B, Elastic stains shows disruption of the elastic membranes with tumor invasion through the wall with plugging of the vessel lumen.

the pathogenesis for the observed necrosis in those cases without vascular invasion:

- Similar phenomenon can be seen in benign and malignant EBV-positive lymphoproliferative disorders, including infectious mononucleosis, post-transplant lymphoproliferative disorders, and lymphomatoid granulomatosis.
- Immunoglobulin heavy and light chain genes typically not rearranged
- Cytogenetic abnormalities include:
 - p53 mutations from 24% to 63% of cases:
 - Suggests p53 may play a role in the pathogenesis
 - β -catenin mutations in approximately 20% of cases

- *c-kit* and *K-ras* mutations may be identified in a smaller percentage of cases.
- *FAS* mutations are a frequent finding in NK/T-cell lymphomas (50% to 60%) and may account for the presence of necrosis.
- Variety of DNA losses and gains at various loci

Differential Diagnosis

- Infectious diseases (e.g., mucormycosis, aspergillosis)
- Granulomatosis with polyangiitis (GPA) (formerly Wegener granulomatosis) (Table 3-11)
- Mucosal malignant melanoma
- Small cell neuroendocrine undifferentiated carcinoma
- Sinonasal undifferentiated carcinoma

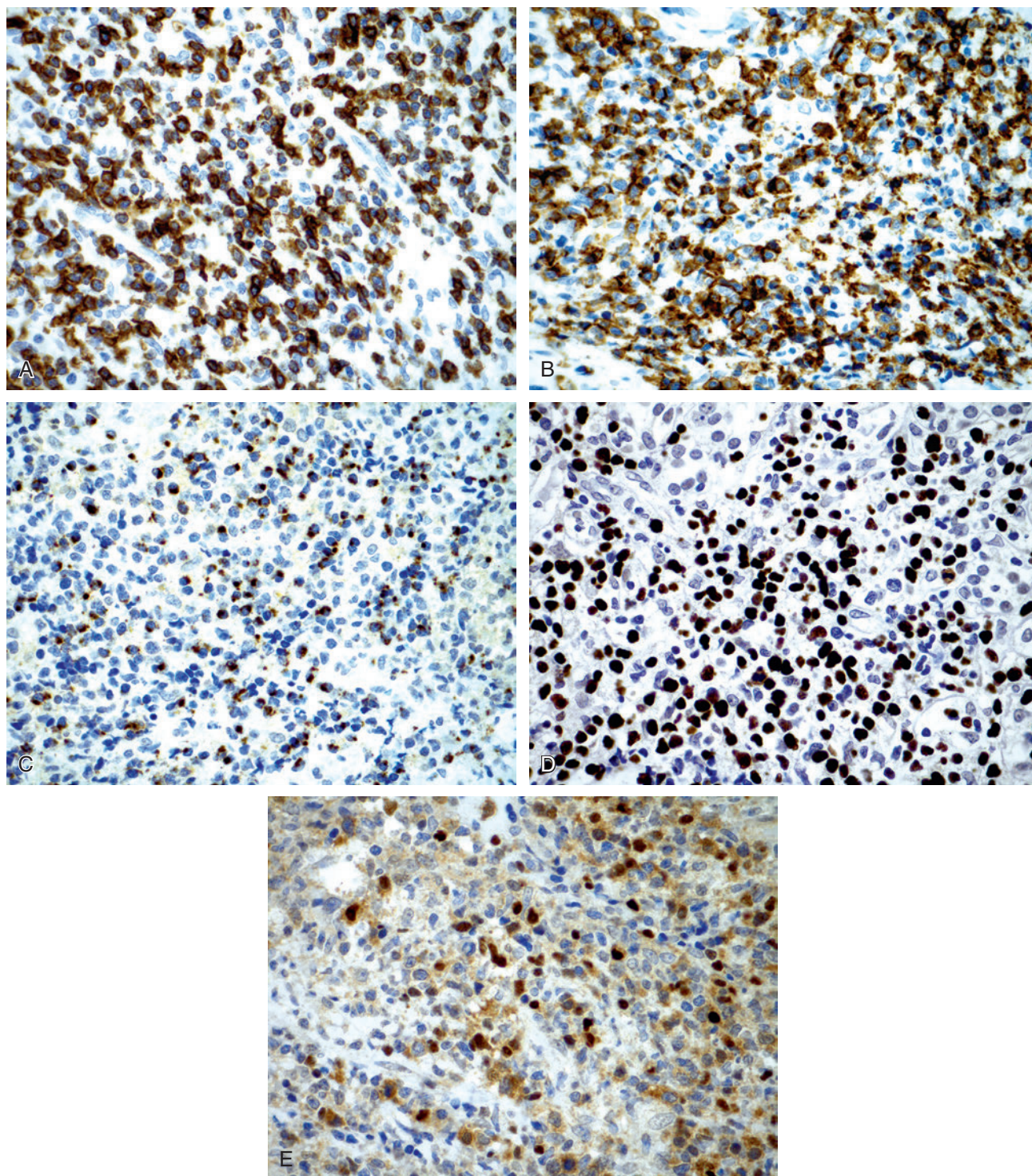


Fig. 3-86. Immunohistochemical staining in extranodal NK/T-cell lymphoma, nasal type.

Lesional cells are immunoreactive for (A) CD3 (cytoplasmic); (B) CD56 (natural killer cell marker); (C) cytotoxic granule-associated TIA-1; and (D) in situ hybridization for EBV-encoded RNA (EBER); (E) scattered neoplastic cells show p63 reactivity.

TABLE 3-11 Clinicopathologic Comparison Between Sinonasal Malignant Lymphomas, Granulomatosis and Polyangiitis (GPA), and Allergic Granulomatosis and Vasculitis*

	Extranodal NK/T- Cell Lymphoma, Nasal Type	DLCBL	GPA	Allergic Granulomatosis and Vasculitis*
Gender/age	M > F; sixth decade; most common in Asians; occurs in Western population but with less frequency	M > F; seventh decade	M > F; fourth-fifth decades; laryngeal GPA affects F > M	M > F; wide age range (third-sixth decades)
Location	Generally limited to the sinonasal region; extra-sinonasal occurs and represents a higher stage tumor	Nasal cavity and one or more paranasal sinuses	Localized UADT GPA most common in nasal cavity > paranasal sinuses; other sites may include nasopharynx, larynx (subglottis), oral cavity, trachea, ear, salivary glands	Multisystem disease including pulmonary, nasal, renal, cutaneous, cardiac, and nervous system involvement
Symptoms	Destructive process of midfacial region: nasal septal perforation, obstruction, palate destruction, orbital swelling	Nonhealing ulcer, epistaxis, facial swelling, pain, cranial nerve manifestations	SNT: sinusitis, with or without purulent rhinorrhea, obstruction, pain, epistaxis, anosmia, headaches Larynx: dyspnea, hoarseness, voice changes Oral: ulcerative lesion Ear: hearing loss, pain	Asthma, allergic rhinitis, evidence of eosinophilia, serum and tissue (e.g., eosinophilic pneumonia, eosinophilic gastroenteritis, other), evidence of vasculitis
Systemic involvement	Majority are localized (stage IE/II/E); may progress to disseminated/systemic involvement	Majority are localized (stage IE/II/E); may progress to disseminated/systemic involvement	ELK Classification: E: ear, nose, throat L: lung K: kidney E, EL = limited form WG ELK = systemic WG	Typically patients have multisystem involvement although limited forms of disease exist
Serology	ANCA and PR3 negative; no specific serologic marker(s)	ANCA and PR3 negative; no specific serologic marker(s)	ANCA positive and PR3: • Increased in primary disease and recurrent disease • c-ANCA more specific than p-ANCA	ANCA and PR3 levels may or may not be present; peripheral eosinophilia
Histology	Overtly malignant cellular infiltrate but in early phases malignant cells may not be overtly identifiable; angiocentricity and angioinvasion; ischemic-type necrosis; no giant cells or granulomas; negative cultures and stains for organisms	Diffuse dyscohesive cellular proliferation of medium to large cells with large round to oval vesicular (noncleaved) nuclei, prominent nucleoli, increased mitotic activity, and necrosis	Polymorphous (benign) cellular infiltrate; vasculitis; ischemic-type necrosis; isolated multinucleated giant cells (not well-formed granulomas); negative cultures and stains for organisms	Polymorphous (benign) cellular infiltrate, predominantly eosinophils; vasculitis that may be a granulomatous vasculitis (multinucleated giant cells in the wall of involved blood vessels); eosinophilic microabscesses; negative cultures and stains for organisms
IHC	CD3 cytoplasmic, CD2, CD56 positive; T cell markers (CD3, others) positive; cytotoxic granule markers (granzyme B, TIA-1, perforin) positive	LCA and B-cell markers (CD20, CD79) positive; p63 may positive (focal to diffuse)	LCA, B- and T-cell markers, kappa and lambda light chains	LCA, B- and T-cell markers
EBV	Strong association	No to weak association	Negative	Negative
Treatment	Radiotherapy for localized disease; chemotherapy for disseminated disease	Radiotherapy and/or chemotherapy	Cyclophosphamide and prednisone	Systemic corticosteroids
Prognosis	5-year survival for Stage I lesions approximately 50%; local recurrence/relapse and systemic failure common	Dependent on stage; 5-year survival rates vary in the literature from 29% to 80%	Limited disease associated with a good to excellent prognosis and occasional spontaneous remissions; mortality related to complications of renal and pulmonary involvement	62% 5-year survival; increased morbidity and mortality due to cardiac involvement resulting in CHF or MI

ANCA, Antineutrophil cytoplasmic antibodies; CHF, congestive heart failure; DLCBL, diffuse large cell B-cell lymphoma; EBV, Epstein-Barr virus; GPA, granulomatosis and polyangiitis (formerly Wegener granulomatosis); IHC, immunohistochemistry; LCA, leucocyte common antigen; MI, myocardial infarction; PR3, proteinase 3; UADT, upper aerodigestive tract.

*Also known as Churg-Strauss syndrome.

- Rhabdomyosarcoma
- Ewing sarcoma family of tumors

NOTE: Although differences can be identified by light microscopic evaluation, often the differentiation of all these tumor types rests on the immunohistochemical staining profile for a given tumor (see [Table 3-6](#)).

Treatment and Prognosis

- Treatment varies depending on the extent of disease.
 - Radiotherapy for localized disease
 - Aggressive chemotherapy in disseminated disease
- Radiosensitive tumors, but prognosis is generally poor once dissemination occurs.
- Majority are localized at presentation (Ann Arbor Stage IE/IIIE):
 - Treated by radiation alone or chemoradiation
- In some patients, surgical resection may be needed for symptomatic relief (e.g., airway obstruction).
- 5-year survival of 46%
- Median survival was 4.2 years
- Local recurrence/relapse and systemic failure is common.
- Systemic failure includes increased risk of dissemination to skin, testes, and GI tract.
- Favorable prognostic factors include:
 - Limited local invasion, low international prognostic index score ([Table 3-12](#)), lack of B symptoms, low proliferation indices (as determined by Ki67 [MIB1]), lower EBV viral load in tumor tissue, lower serum EBV DNA
- Adverse prognostic factors include:
 - Extensive local invasion (to skin, bone), advanced stage disease, poor performance score (Eastern Cooperative Oncology Group [ECOG] of 2 or higher), B symptoms, regional lymphadenopathy, bulky disease, high lactate dehydrogenase level, high proliferation rate
 - Development of hemophagocytic syndrome, an uncommon complication seen in approximately 10% of cases, is considered fatal.

TABLE 3-12 International Prognostic Index Scoring System

Prognostic Factors (1 point each)				
Age > 60 years				
Elevated serum lactate dehydrogenase				
Poor performance status				
High stage (III-IV)				
>1 extranodal site				
Risk Score				
0	1	2	3	4 5
Low	Low-intermediate	High-intermediate	High	

SINONASAL DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) (Fig. 3-87)

Definition: Diffuse proliferation of large or medium-sized neoplastic B-cells with a nuclear size greater than or equal to that of a histiocyte or more than twice the size of a small lymphocyte.

- Primarily affects men with a median age in the seventh decade of life
- Clinical presentations may include aggressive signs and symptoms, including:
 - Nonhealing ulcer, cranial nerve manifestations, facial swelling, epistaxis, or pain
 - High-grade B-cell lymphomas tend to present with soft tissue and osseous destruction and may invade into the orbit and brain, resulting in:
 - Proptosis, diplopia, decreased visual acuity, neurologic abnormalities
 - Low-grade lymphomas may present as a nasal cavity or paranasal sinus mass associated with airway obstructive symptoms.
- Sites of involvement may be one or more paranasal sinuses, or multiple regions within the sinonasal tract:
 - Maxillary sinus > ethmoid sinus, sphenoid sinus, frontal sinus
- Most arise de novo:
 - Some may transform from an underlying low-grade lymphoma.
 - Uncommon (less than 10%) to no association with EBV
- Increased risk associated with immunosuppression, including post-transplantation and human immunodeficiency virus (HIV) infection:
 - Strong association with EBV in immunocompromised patients
- Antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3 (PR3) levels are not elevated in association with DLBCL.

Pathology

- Diffuse submucosal discohesive cellular infiltrate composed of medium to large cells with large round to oval vesicular (noncleaved) nuclei and several membrane-bound small nucleoli or a single centrally located prominent eosinophilic nucleolus
- Mitotic activity, necrosis, and apoptotic figures can be seen.
- Immunohistochemistry is essential in confirming the diagnosis and in differentiating a malignant lymphoma from carcinoma:
 - Immunoreactivity present for leukocyte common antigen (CD45) and pan B-cell markers, including CD20, CD79a, CD22, PAX5

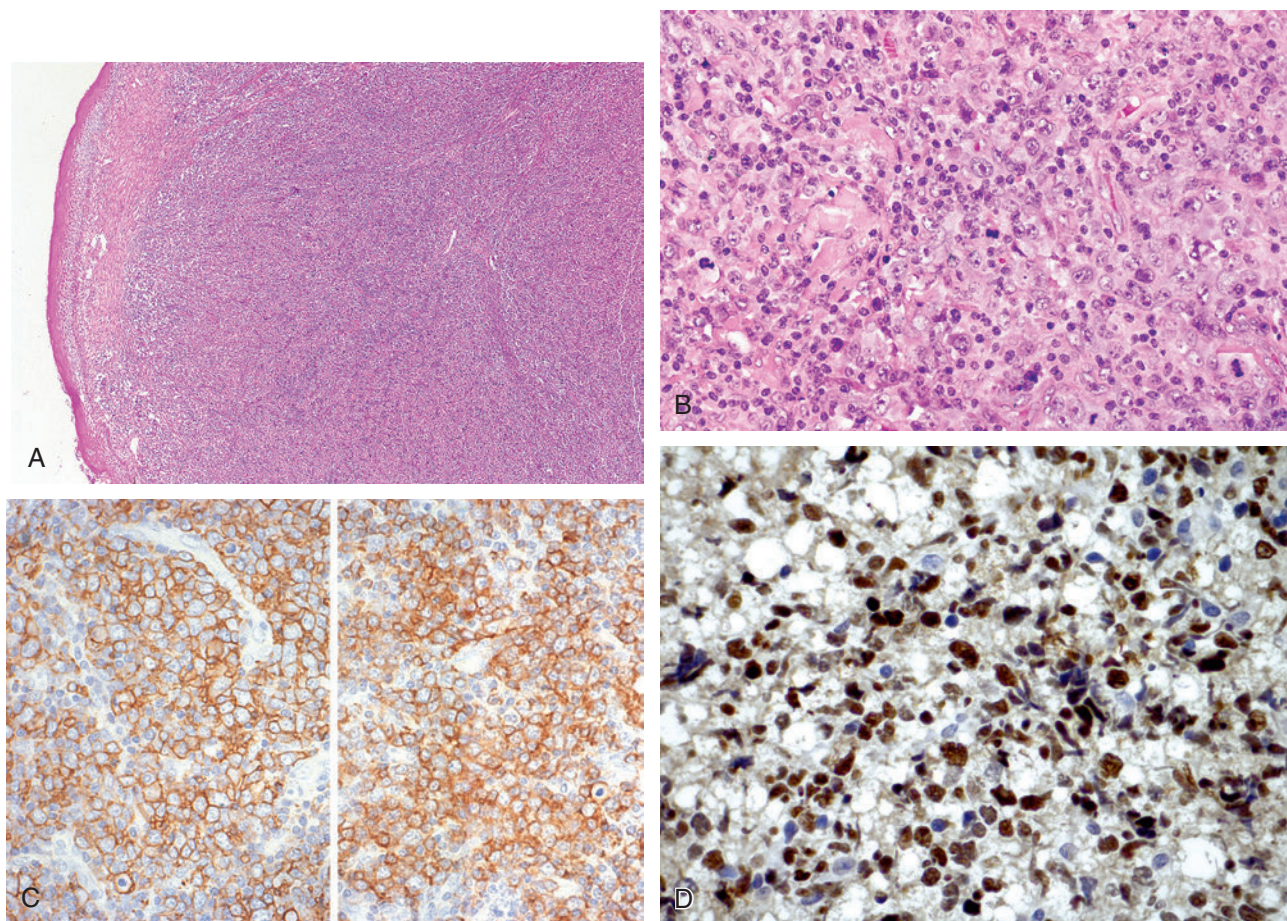


Fig. 3-87. Sinonasal diffuse large cell B-cell lymphoma.

A, Diffuse submucosal dyscohesive cellular infiltrate. **B**, The neoplastic cells are composed of medium to large cells with large round to oval vesicular (noncleaved) nuclei and centrally located prominent eosinophilic nucleoli and smaller membrane-bound nucleoli; increased mitotic activity is present. **C**, This cellular infiltrate is immunoreactive for (*left panel*) leukocyte common antigen and the (*right panel*) B-cell marker CD20. **D**, p63 immunoreactivity may be present. Unless a diagnosis of lymphoma is considered to include evaluation for hematolymphoid markers, the presence of p63 may result in a misdiagnosis of an epithelial malignancy.

- Positive for surface or cytoplasmic immunoglobulin:
 - IgM > IgG > IgA
- Melanoma-associated antigen (MUM1) expression (nuclear staining):
 - MUM1 gene encodes a transcription factor responsible for development of B, T, plasma, dendritic, and myeloid cells.
 - MUM1 expression originally recognized by upregulation in multiple myeloma, however not specific for plasmacytic differentiation and can be seen in a variety of neoplasms, including:
 - DLBCL
 - Follicular lymphoma
 - Burkitt lymphoma
 - Hodgkin's lymphoma
 - Anaplastic large cell lymphoma
 - Lymphoplasmacytic lymphoma
 - Chronic lymphocytic leukemia
 - Marginal zone lymphoma
 - Primary mediastinal large B-cell lymphoma
 - Primary effusion lymphoma
 - Melanoma
- BCL6 in approximately 60%
- CD10 expression occurs in 40%.
- CD5 and CD30 in approximately 10%
- Cyclin D1 (BCL1) negative
- High proliferation index by Ki67 of > 20% and often > 80%
- p53 positive in approximately 40%
- p63 may be positive (usually focal/scattered positive cells):
 - In the setting of a sinonasal small round cell malignancy in biopsy material, the presence of

p63 may suggest an epithelial or myoepithelial lesion, especially if a diagnosis of a lymphoma is not considered.

- Absence of other epithelial markers and presence of immunostaining for hematolymphoid markers (LCA and B-cell markers) results in a diagnosis and prevents misdiagnosis.
- Hans algorithm subclassifies DLBCL into germinal center B-cell type (GCB) versus nongerminal center B-cell type (non-GCB):
 - GCB: CD10+, BCL6+, MUM1-
 - Non-GCB: CD10-, BCL6+, MUM1+
 - GCB DLBCL may have better prognosis than non-GCB DLBCL.
- Cytogenetics and molecular genetics:
 - Clonal rearranged immunoglobulin heavy- and light-chain genes
 - *BCL2* and *BCL6* rearranged in approximately 20% and 30%, respectively
 - *BCL6* mutation in approximately 70%
 - Mutations of *TP53* in approximately 22%
 - *MYC* rearranged in less than 10%:
 - *MYC* rearrangement is a molecular hallmark of Burkitt lymphoma.
 - In DLBCL *MYC* rearrangement more frequent in HIV-infected patients and in extranodal lymphomas
 - Usually EBV negative except in setting of immunodeficiency
 - CGH studies show various chromosomal gains and losses.

Differential Diagnosis

- Carcinoma
- Granulomatosis with polyangiitis (GPA) (formerly Wegener granulomatosis) (see Table 3-10)
- Sinonasal undifferentiated carcinoma
- Nasopharyngeal-type undifferentiated carcinoma
- Mucosal malignant melanoma
- Anaplastic plasmacytoma (Fig. 3-88):
 - Anaplastic variant of extramedullary plasmacytoma is rare.
 - Clinicopathologic features of this uncommon neoplasm are not well established in the literature.
 - Tends to be more common in men than in women; occurs over a wide age range from 37 to 89 years
 - In the upper aerodigestive tract the most common site of occurrence is sinonasal tract; less often occurs in the tonsil and nasopharynx.
 - Most common clinical complaints include nasal obstruction, a mass, or epistaxis
 - All lesions are solitary and extramedullary.
 - No association with previous or concurrent multiple myeloma

- Histologically, the tumors are submucosal and composed of immature-appearing cells with round nuclei, prominent nucleoli, vesicular to dispersed nuclear chromatin, and a variable amount of eosinophilic cytoplasm:
 - Nuclear pleomorphism, mitotic activity, and necrosis are consistently present.
- Foci of differentiated plasma cells and Dutcher bodies can be identified.
- Immunohistochemistry:
 - Light chain restriction ($\kappa > \lambda$)
 - Consistent reactivity in the majority of cases for CD138 (Syndecan-1), vimentin, and CD79a
 - Minority of cases show epithelial membrane antigen (EMA), CD30, CD45 reactivity
 - No immunoreactivity for CD20, cytokeratin, S100 protein, melanocytic markers, neuroendocrine markers, and myogenic markers
- Radiation therapy is preferred treatment and may be supplemented by surgical resection and/or chemotherapy.
- Variable prognosis, some patients alive with no evidence of disease or dead of unrelated causes, some patients alive with recurrent disease, and a minority of patients who develop multiple myeloma.

Treatment and Prognosis

- For B-cell lymphomas, including DLCL, the prognosis is dependent on the clinical stage.
- Majority (approximately 75%) of sinonasal DLCL are localized/low clinical stage disease (Ann Arbor IE/IIIE).
- Treatment primarily includes radiotherapy and chemotherapy.
- Surgical resection may be needed for symptomatic relief.
- Five-year survival rates vary in the literature from 29% to 80%.
- Systemic failure includes increased risk of dissemination to nodal and extranodal sites below the diaphragm (e.g., para-aortic lymph nodes, GI tract).

EWING FAMILY OF TUMORS (EFT) (Figs. 3-89 through 3-91)

Definition: Group of high-grade primitive small round cell sarcomas with (variable) neuroectodermal differentiation and defined by the presence of translocation between Ewing sarcoma (*EWS*) gene on chromosome 22 and the *FLI-1* gene on chromosome 11.

- EFT includes Ewing sarcoma (EWS) and primitive (peripheral) neuroectodermal tumor (PNET); recently the designation PNET was dropped as a synonym for EWS to minimize confusion with

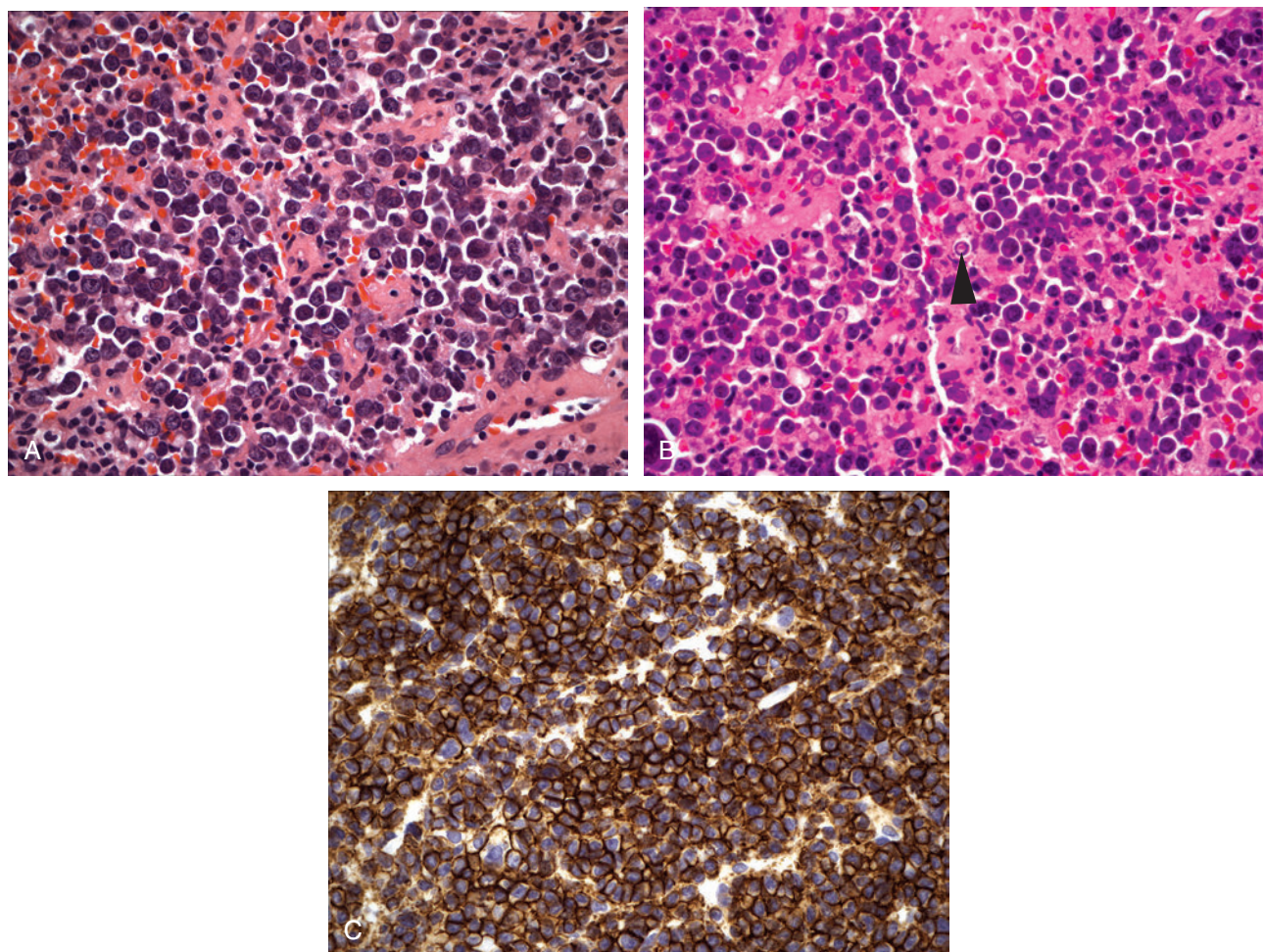


Fig. 3-88. Anaplastic plasmacytoma.

A, This neoplastic infiltrate was located within the submucosa of the maxillary sinus and is composed of immature-appearing cells with pleomorphic round nuclei, prominent nucleoli, vesicular to dispersed nuclear chromatin, variable amount of eosinophilic cytoplasm, and scattered mitotic figures; scattered mature plasma cells including the presence of a paranuclear clear zones are seen. **B,** Cells with intranuclear hyaline inclusions (Dutcher bodies) are present (arrowhead). **C,** Immunoreactivity is present for CD138; in addition, kappa light chain restriction, CD79, vimentin, and EMA reactivity was present (not shown).

similarly named lesions in the central nervous system and female genital tract, which consistently lack *EWSR1* gene rearrangement.

Synonyms: Peripheral neuroectodermal tumor; peripheral neuroepithelioma; peripheral neuroblastoma; adult neuroblastoma; peripheral primitive neuroectodermal tumor

Note: Ewing sarcoma is generally considered a malignant primary bone tumor but may occur outside bone, including in soft tissues referred to as extraosseous (or extraskeletal) Ewing sarcoma.

- EWS and PNET share the common cytogenetic abnormality $t(11;22)(q24;q12)$, supporting the notion that these two tumors are histogenetically related:

- Previously differentiation of EWS from PNET was based on the presence (PNET) or absence (EWS) of neural differentiation.
- Now considered to represent a single type of tumor grouped as members of the EWS/PNET family instead of separate although related tumor types with attempted differentiation predicated on presence or absence of neural differentiation
- Undifferentiated (Ewing-like) sarcoma: the designation undifferentiated/unclassified sarcoma recently introduced for a subset of sarcomas that cannot be classified into any presently defined categories lacking any apparent definable line of

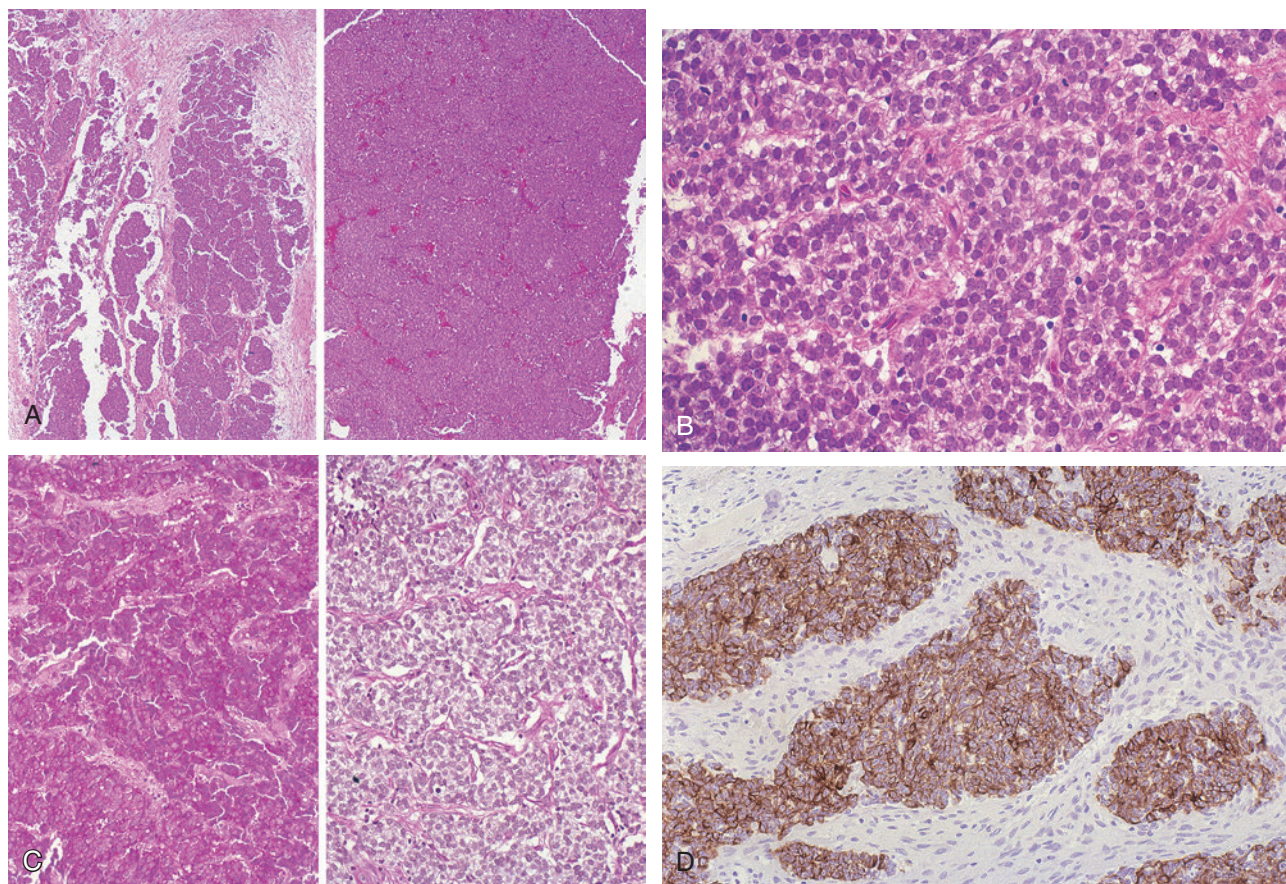


Fig. 3-89. EWS/PNET of the sinonasal tract.

A, Markedly cellular tumor with (*left panel*) sheetlike and (*right panel*) lobular growth with little stromal component. **B**, Densely cellular infiltrate composed of uniform small round cells with round to oval nuclei, fine-appearing (powdery) nuclear chromatin, distinct nuclear membrane, inconspicuous to small nucleoli, scanty pale to vacuolated (clear-appearing) cytoplasm, and indistinct cell borders. **C**, Intracytoplasmic glycogen as seen by the presence of diastase-sensitive, PAS-positive material (*left panel*, PAS; *right panel*, PAS with diastase digestion). **D**, CD99 immunoreactivity.

differentiation by available technologies. These undifferentiated/unclassified sarcomas may have spindle cell, pleomorphic, round cell, and epithelioid cytomorphology. Within the round cell category, there are genetic subsets characterized by *CIC-DUX4* gene fusion resulting in t(4;19) or t(10;19) chromosome translocation. This translocation results in upregulation of a group of genes in the Ewing family of tumors that are similar to genes upregulated in conventional EWS, suggesting a close molecular biologic relationship and the suggested designation of undifferentiated (Ewing-like) sarcoma.

Clinical

- Primarily a tumor of areas other than head and neck sites, including:
 - Thoracopulmonary (Askin tumor) > extremities, abdominal and pelvic regions
- Rare tumor of the head and neck:
 - 2% to 10% occur in the head and neck
 - Most common sites of involvement include the skull and jaws
 - Less common sites of involvement include the sinonasal tract, orbit, and various mucosal sites
- Slightly more common in men than in women
- Predominantly but not exclusively a tumor of children and young adults; occasionally may occur in older adults
- In the sinonasal tract, most commonly occurs in the maxillary sinus and nasal fossa
- Symptoms include pain, a mass lesion, and nasal obstruction:
 - Dural, orbital, or brain involvement may occur.
- Laboratory findings:
 - No specific findings
 - In contrast to neuroblastoma, catecholamine levels are not elevated.

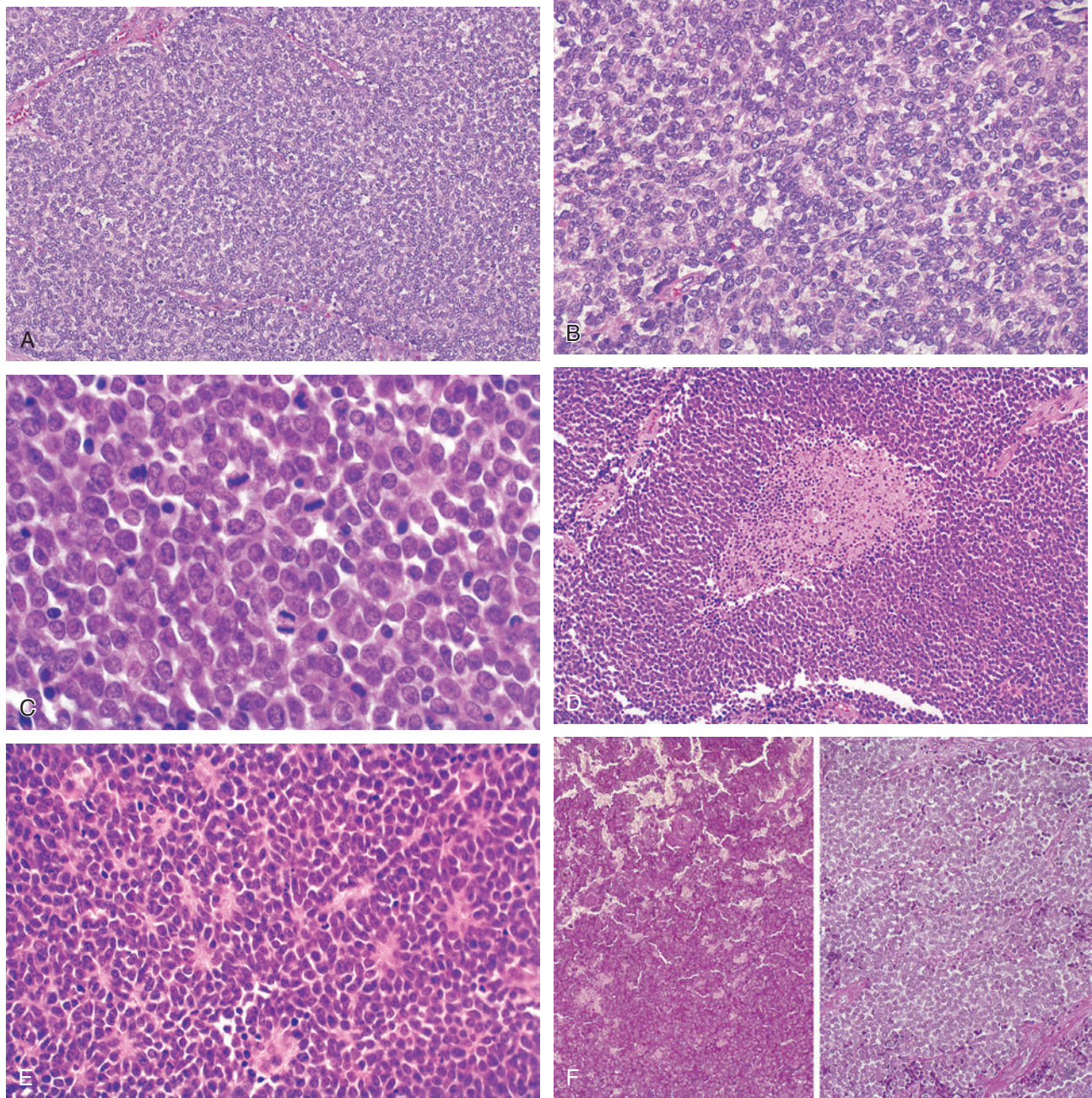


Fig. 3-90. EWS/PNET of the sinonasal tract.

A, Densely cellular composed diffuse (sheetlike) growth with little stromal component. **B**, Neoplastic cells lack cohesiveness and are small and round with irregular-appearing round to oval nuclei with coarse (clumped) nuclear chromatin, variably prominent nucleoli, and scant cytoplasm. **C**, Increased mitotic activity is present. **D**, Necrosis may be present. **E**, Pseudorosettes (Homer Wright) can be identified. **F**, Intracytoplasmic glycogen as seen by the presence of diastase-sensitive, PAS-positive material (*left panel*, PAS; *right panel*, PAS with diastase digestion). Immunoreactivity is present for **G**, CD99 (membranous staining);

Continued

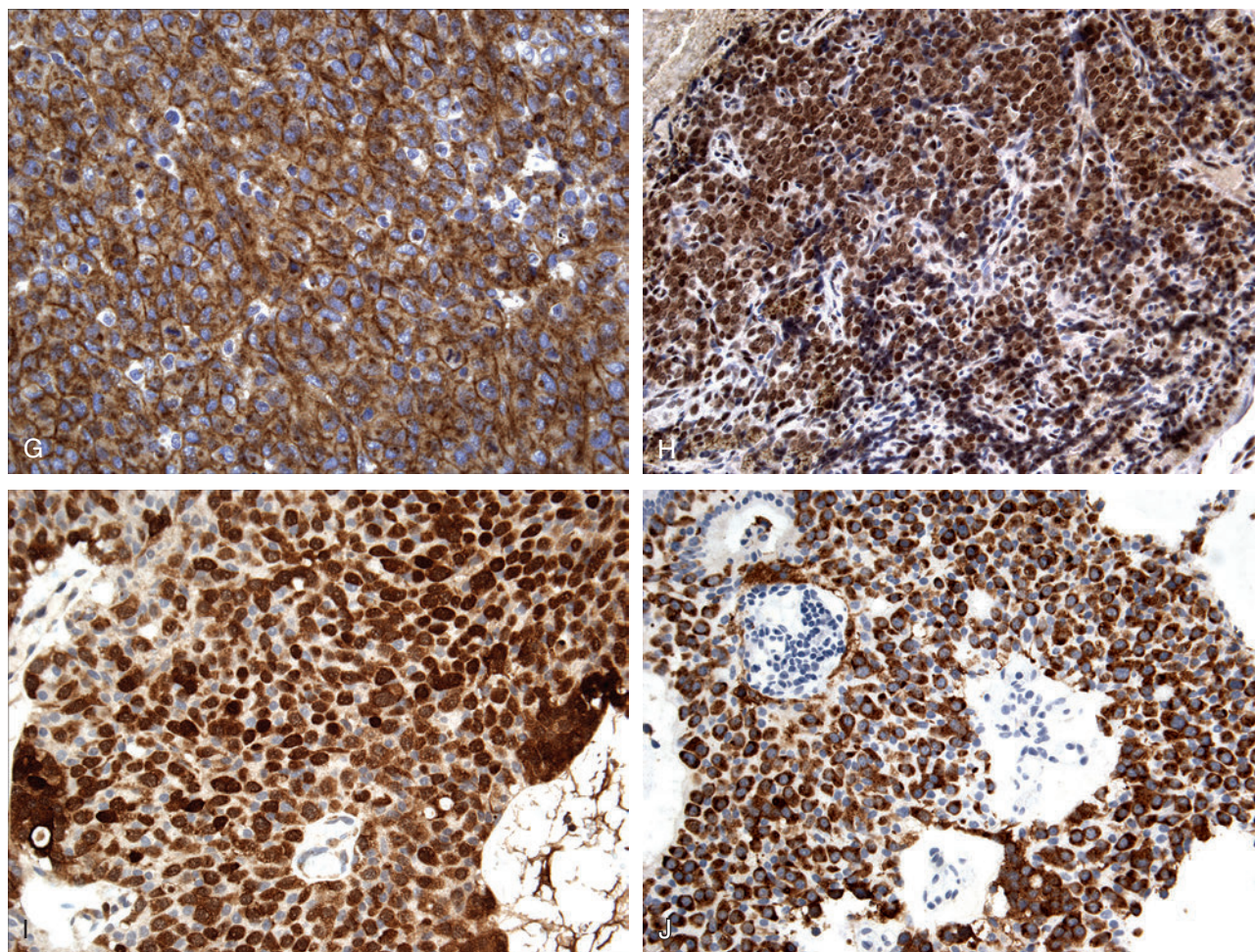


Fig. 3-90, cont'd

H, Fli-1 (nuclear); **I**, neuron specific enolase (nuclear and cytoplasmic); **J**, Synaptophysin (cytoplasmic).

- Radiology:
 - Bony erosion may or may not be present.
- Site for the Ewing sarcoma gene is 22q12.
- Heritable retinoblastoma may predispose to ES and perhaps to a subset of poorly differentiated neuroectodermal tumors in the sinonasal region that may be related to olfactory neuroblastoma.

Pathology

Gross

- In the sinonasal tract, these tumors can be polypoid.
- Multilobular, grey-white, and glistening with associated hemorrhage; ulceration is often present.

Histology

- Markedly cellular with a diffuse (sheetlike) or lobular growth with little stromal component; when present the stromal component includes thin fibrous strands separating tumor lobules:

- Trabecular or cordlike growth may occasionally be present.
- Composed of uniform small round cells with round to oval nuclei, fine-appearing (powdery) nuclear chromatin, distinct nuclear membrane, inconspicuous to small nucleoli, scanty pale to vacuolated (clear-appearing) cytoplasm, and indistinct cell borders
 - Vacuolated (clear-appearing) cytoplasm is due to glycogen deposition, which may result in nuclear indentation.
 - Occasionally spindle cell foci may be present.
- Mitotic activity is variable but can be high, ranging from 5 to 10 mitoses per 10 high-power fields.
- Prominent intratumoral vascularity but the presence of thin-walled vessels may be compressed and obscured by the densely cellular proliferation.
- Degenerative changes and/or necrosis may result in a pseudoalveolar pattern, suggesting a possible diagnosis of rhabdomyosarcoma.

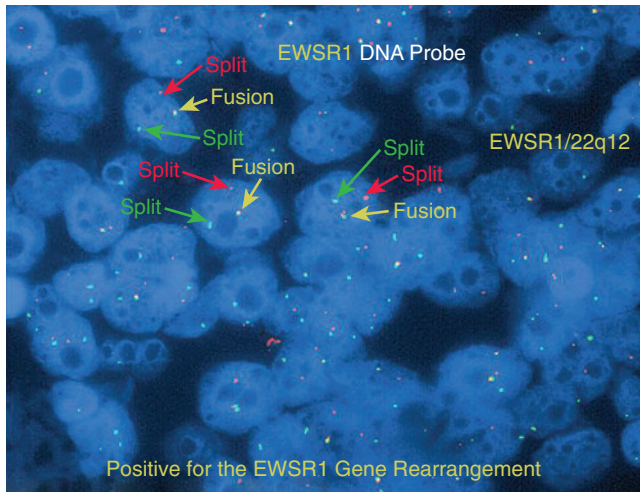


Fig. 3-91. EWS/PNET break-apart fluorescent in situ hybridization (FISH).

Normal *EWSR1* gene is represented by the overlapping red and green signals; separate red and green signals represent the split of the *EWSR1* gene as a result of the translocation. (From Dabbs: *Diagnostic immunohistochemistry*, ed 4, Philadelphia, 2014, Saunders, Fig. 8-2, C.)

- Pseudorosettes (Homer Wright) present in most cases, and less often true neural rosettes (Flexner-Wintersteiner) can be found.
- Histologic variants of EFT include:
 - Atypical variant, also referred to as large cell variant, characterized by larger nuclei with atypical features as compared with “conventional” EWS/PNET
 - Clear cell variant
 - Hemangioendothelioma-like
 - Adamantinoma-like:
 - Rare variant representing approximately 5% of cases
 - Nested, epithelioid growth pattern with stromal desmoplasia
 - Tumor nests show peripheral nuclear palisading and contain large polygonal cells with irregular contours, hyperchromatic nuclei, prominent nucleoli, and moderate amount of cytoplasm.
 - Squamous pearls may be seen.
 - Cells show strong pancytokeratin and focal high molecular weight cytokeratin staining.
 - Sclerosing variant
- Histochemistry:
 - Abundant glycogen as seen by the presence of diastase-sensitive, PAS-positive, intracytoplasmic material
- Immunohistochemistry:
 - CD99 (MIC2) reactivity (membranous) seen in nearly all cases:
 - Gene product of MIC2 is a membranous glycoprotein detected by a number of antibodies (MIC2; O13; HBA-71, p30/32, and 12E7).
 - Represents the monoclonal antibody to the *EWS/FLI1* fusion product
 - CD99 is highly sensitive but lacks specificity, as a wide variety of tumor types express CD99, including (but not necessarily limited to) T-lymphoblastic lymphoma, synovial sarcoma (poorly differentiated), small cell osteosarcoma, rhabdomyosarcoma, desmoplastic small round cell tumor, small cell undifferentiated neuroendocrine carcinoma, Merkel cell carcinoma, mesenchymal chondrosarcoma, neuroblastoma.
 - CD99 must be used in conjunction with a broad panel of antibodies in the diagnosis and differential diagnosis of EWS/PNET.
 - Friend leukemia integration-1 (FLI-1) reactivity (nuclear) seen in a large percentage of cases; staining for vascular endothelial markers including CD31, ERG, others is negative.
 - Vimentin positive
 - Cytokeratin (AE1/AE3, CAM5.2) staining may focally be present in up to a third of cases:
 - Staining is typically focal and dot-like but may be strong and diffuse:
 - Adamantinoma variant typically has strong cytokeratin (AE1/AE3) staining and may show reactivity with high molecular weight cytokeratins
 - Typically, do not express high molecular weight cytokeratins
 - c-kit (CD117) may be present in approximately 25% of cases.
 - Reactivity for at least one neural marker, including NSE, S100 protein, synaptophysin chromogranin, CD56, neurofilament protein (NFP), or GFAP, may be present.
 - Absence of desmin, myoglobin, myogenin (myf-4), leukocyte common antigen, and calretinin reactivity
- Electron microscopy:
 - Presence of dense core (neurosecretory) granules, neurotubules, or neuritic processes
 - Neuritic processes contain intermediate filaments, microtubules
 - Poorly defined desmosomes and tight junctions
- Cytogenetics and molecular genetics:
 - Majority of cases (90% to 95%) show consistent reciprocal translocation between chromosome 11 and chromosome 22:
 - Most common translocation involves *EWSR1* gene (chromosome 22) and *FLI-1* gene (chromosome 11).

BOX 3-2 Tumors with EWSR1 Gene Rearrangements**Soft Tissue Tumors**

- Ewing family of tumors
- Desmoplastic small round cell tumor
- Myxoid liposarcoma
- Extraskeletal myxoid chondrosarcoma
- Angiomatoid fibrous histiocytoma
- Clear cell sarcoma of soft tissue
- Clear cell sarcoma-like tumors of the gastrointestinal tract
- Primary pulmonary myxoid sarcoma
- Extrasalivary myoepithelial tumors
- Sporadic examples of low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma
- Mesothelioma

Non-Soft Tissue Tumors

- Hyalinizing clear cell carcinoma of the salivary gland

- Variant translocations may occur, all involving *EWSR1* gene on chromosome 22.
- A number of tumors other than EFT have *EWSR1* gene rearrangement (Box 3-2).
- *EWS/FLI-1* fusion transcript detected by a variety of molecular techniques, including (but not limited to) fluorescent in situ hybridization (FISH) and reverse transcription-polymerase chain reaction (RT-PCR):
 - FISH and RT-PCR can be performed on formalin-fixed paraffin-embedded tissue.
 - Break-apart probe for *EWSR1* commercially available

Differential Diagnosis

- Olfactory neuroblastoma
- Rhabdomyosarcoma
- Melanotic neuroectodermal tumor of infancy
- Hematolymphoid malignancies
- Small cell neuroendocrine carcinoma
- Mucosal malignant melanoma
- Sinonasal undifferentiated carcinoma
- NUT midline carcinoma
- Mesenchymal chondrosarcoma
- Synovial sarcoma, poorly differentiated
- Small cell osteosarcoma
- Desmoplastic small round cell tumor

NOTE: Although differences can be identified by light microscopic evaluation, often the differentiation of many of these tumor types rests on the immunohistochemical staining profile for a given tumor (see Table 3-6).

Treatment and Prognosis

- Combined multimodality therapy including (multia-gent) chemotherapy, radiation, and surgery (for local disease control) is the preferred treatment.

- Five-year survival rate of sinonasal ES/PNET of 50% to 75%:
 - Represents better overall prognosis as compared with ES/PNET of other sites
- Five-year survival rate for patients with advanced disease of less than 25%
- Local recurrence and distant metastases may occur within 2 years even in patients with localized disease.
- When metastases occur, most common sites include the lungs and bone; lymph node metastasis is less common, occurring in approximately 20% of cases.
- Prognosis has been found to be linked to:
 - Tumor stage:
 - Staging follows that of the Intergroup Rhabdomyosarcoma Study (IRS)
 - Marked improvement in the prognosis with nonmetastatic disease
 - Outcome for patients with recurrent or metastatic disease remains poor.
 - Tumor size:
 - >8 cm associated with adverse behavior
 - p53 alteration:
 - Appears to define a small clinical subset of patients with ES/PNET with a markedly poor outcome
 - Some studies have shown that the presence of type I *EWS/FLI-1* fusion is thought to have a better prognosis than those tumors with other fusion transcripts with:
 - Longer disease-free survival
 - Respond better to chemotherapy
 - Lower proliferation rates
 - Poor histologic/radiologic response at the site of the primary tumor
 - Incomplete radiologic remission of lung metastases after primary chemotherapy
- Targeted therapy:
 - Potential novel targets for therapy are under investigation and may prove beneficial for patients with recurrent or metastatic disease.
- Given the treatment with radiation early in life, there is an increased incidence of radiation-induced sarcoma in these patients in later life.

SINONASAL TRACT SARCOMAS

- In general, sarcomas of the sinonasal tract are uncommon.
- Although uncommon, virtually all types of sarcomas may occur in the sinonasal tract.
- Although also uncommon, among one of the more common sarcomas of the sinonasal tract is rhabdomyosarcoma; see Section 3, Pharynx, and Section 7, Ear and Temporal Bone, for complete discussion.



Fig. 3-92. Sinonasal undifferentiated pleomorphic sarcoma.

The tumor is seen protruding from the left nasal vestibule and invading into the subcutaneous compartment resulting in facial deformity.

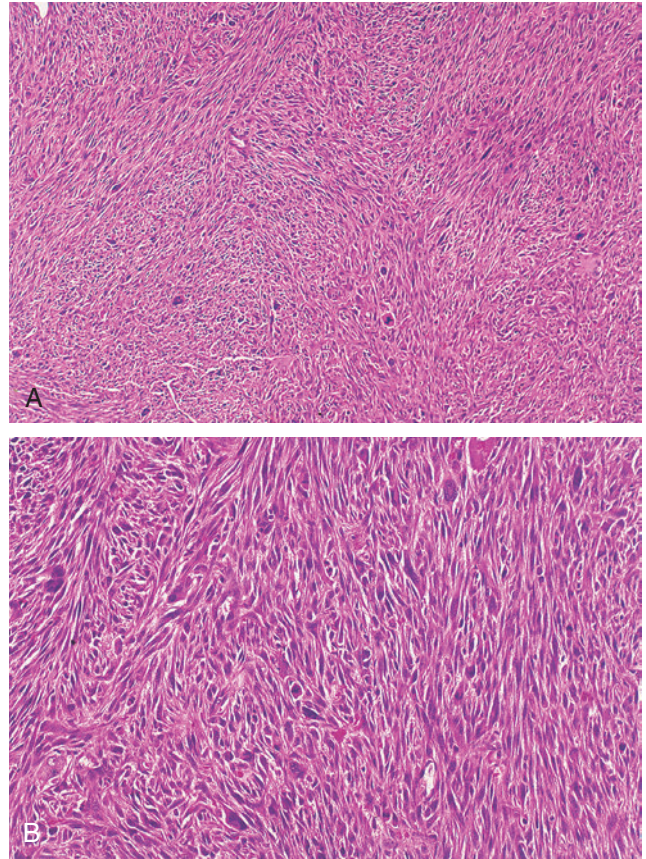


Fig. 3-93. Sinonasal undifferentiated pleomorphic sarcoma.

The tumor is characterized by a densely cellular infiltrate with fascicular and storiform growth composed spindle-shaped cells with marked nuclear pleomorphism, hyperchromasia, and increased mitotic activity, including typical and atypical forms; multinucleated giant cells are present.

- Rarely, osteosarcoma, chondrosarcoma, malignant peripheral nerve sheath tumors, liposarcoma, synovial sarcoma, chordoma, and alveolar soft part sarcoma may occur in the sinonasal tract; see Sections 2, Oral Cavity, 3, Pharynx, 4, Neck, and 5, Larynx, for complete discussion of these tumor types.

Undifferentiated Pleomorphic Sarcoma, Not Otherwise Specified (Figs. 3-92 through 3-95)

Definition: High-grade, pleomorphic malignant neoplasm without specific differentiation and not associated with differentiated sarcoma:

- Undifferentiated pleomorphic sarcoma is the current terminology used for sarcomas previously diagnosed collectively as malignant fibrous histiocytoma (MFH).
- MFH was once considered one of the more common soft tissue sarcoma of late adult life primarily affecting the soft tissues of the lower extremity, but with more advanced diagnostic techniques (e.g., immunohistochemistry, molecular analyses) the recognition that MFH was a “wastebasket” diagnosis for lesions more accurately classified into a specific class of sarcomas (e.g., liposarcoma, others) has decreased its incidence and raised question about the validity of its existence.
- Now classified by the WHO under category designated undifferentiated/unclassified sarcoma

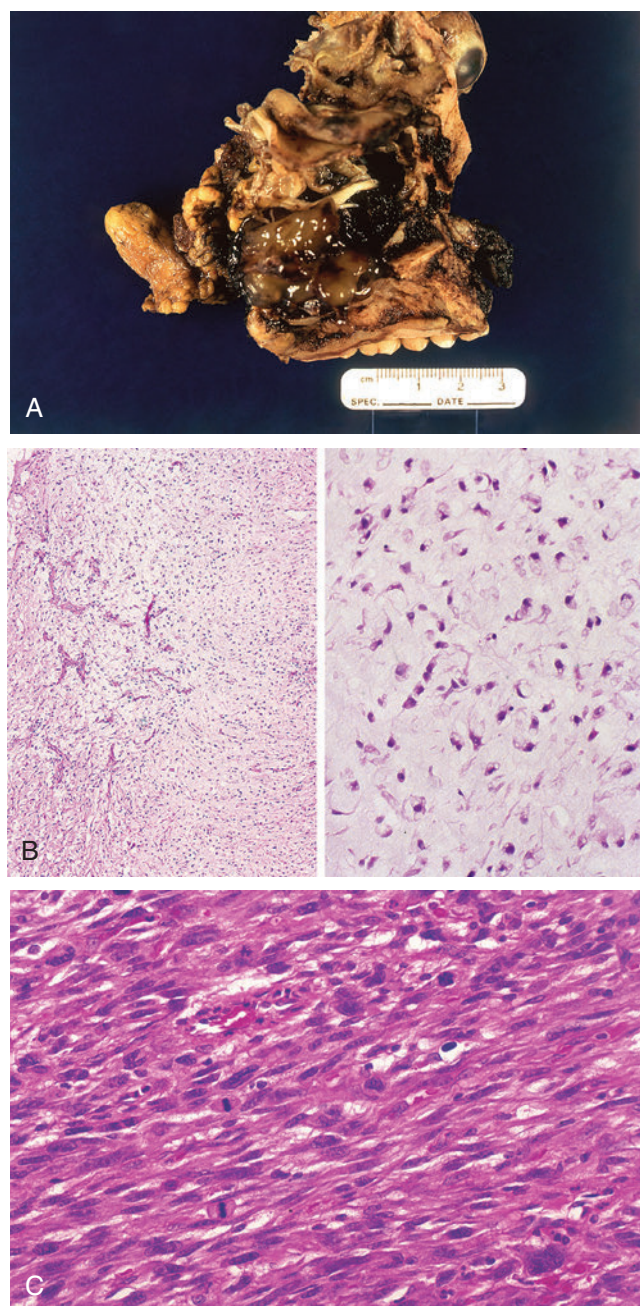


Fig. 3-94. Myxofibrosarcoma.

A, Radical resection specimen that included an orbital exenteration showing a mass with gelatinous/mucoid appearance; more solid nongelatinous foci were present.
B, left panel, Histology includes prominent myxoid stroma with associated curvilinear blood vessels and (*right panel*) cells with hyperchromatic nuclei and vacuolated cytoplasm.
C, Cellular areas showing features of the storiform-pleomorphic type were present but represent the minority of the tumor type.

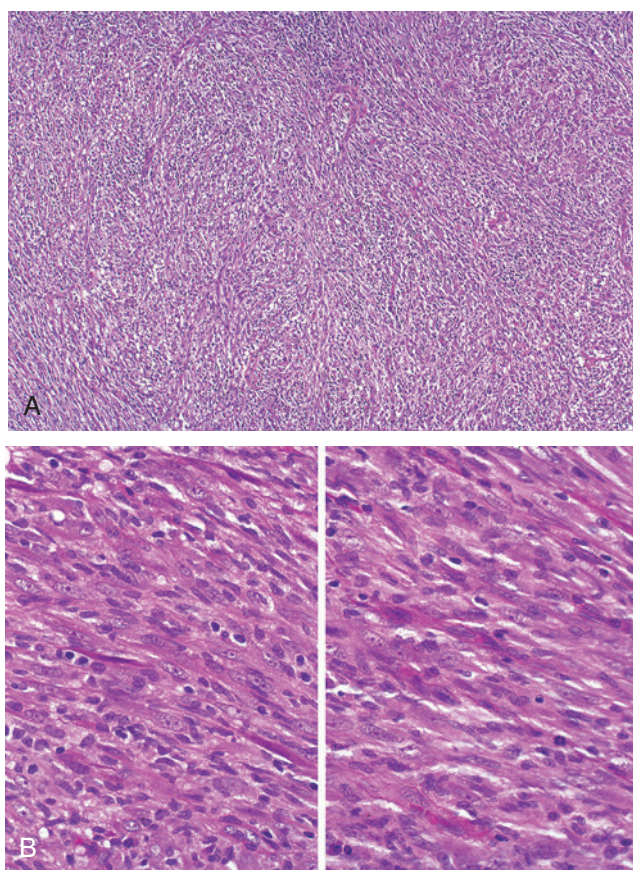


Fig. 3-95. Sinonasal undifferentiated pleomorphic sarcoma, inflammatory fibrosarcoma.

A, Admixture of spindle-shaped and inflammatory cells.
B, At higher magnification malignant cells, including mitotic figure (*right panel*), are seen in association with inflammatory cells.

Clinical

- Uncommon neoplasm in the head and neck:
 - Approximately 3% occur in the head and neck, with the sinonasal tract representing the most common site of occurrence (approximately 31% of cases)
 - The neck is the second most common site of occurrence (approximately 13% of cases).
 - Rare in all other sites of the head and neck, including oral cavity and larynx
- More common in men than in women; occurs over a wide age range but most commonly seen in adults
- In the sinonasal tract the more common sites of occurrence include: maxillary sinus > ethmoid sinus and nasal cavity; rare occurrence in the frontal and sphenoid sinuses
- Symptoms vary and include a mass with or without associated pain, nasal obstruction, epistaxis, facial asymmetry, and proptosis.

- Radiology:
 - Sinus opacification
 - Soft tissue mass with or without osseous destruction/invasion
 - May be entirely intraosseous and in this setting is osteolytic with expansion and erosion of the cortex
- Majority occur de novo; however, evidence supports that some of these tumors are radiation-induced:
 - In association with prior radiation, the latency period is usually a decade or longer from the time of irradiation to the development of the malignancy.

Pathology

Gross

- Nodular- or multinodular-appearing tan-white to gray lesion of varying size; necrosis and hemorrhage may be apparent.
- Myxoid variant appears translucent or gelatinous.

Histology

- Storiform-pleomorphic features are most common:
 - Fascicular and storiform growth patterns:
 - Storiform growth is characterized by neoplastic cells forming short fascicles in a “pinwheel” or “cartwheel” configuration.
 - Hypercellular neoplasm consisting of spindle-shaped to epithelioid-appearing cells marked by nuclear pleomorphism and increased mitotic activity, including typical and atypical forms
 - Multinucleated giant cells, bizarre giant cells with multiple hyperchromatic nuclei are identified
 - Necrosis is commonly seen.
 - Heterologous (metaplastic) bone and cartilage may be present.
- Variable amount of chronic inflammatory cell infiltrate that may include mature lymphocytes, plasma cells, xanthoma (foam) cells with variable numbers of neutrophils and eosinophils; granulomas may be identified.
- Stromal findings include variable fibrosis, hyalinization, myxoid change, and vascularity.
- Histochemistry:
 - Special stains are of little assistance in the diagnosis.
- Immunohistochemistry:
 - Vimentin positive
 - Smooth muscle actin may be focally positive.
 - Giant cells may show CD68 reactivity.
 - Usually there is an absence expression for epithelial markers (e.g., cytokeratins), melanocytic markers (e.g., S100 protein, HMB45, melan-A, tyrosinase), myogenic markers (desmin, myoglobin, myf-4), hematolymphoid markers (LCA, B- and T-cell).

Histologic Variants

- Myxoid variant (myxofibrosarcoma) (see Fig. 3-93):
 - Previously referred to as myxoid malignant fibrous histiocytoma:
 - Defined as tumor with myxoid stroma in at least 50% of the tumor, but prior to considering this diagnosis a myxoid variant of another defined sarcoma type must be excluded.
 - Tend to be multinodular, characterized by cells with low nuclear grade morphology and low mitotic rate
 - Cells are spindle- or stellate-shaped with hyperchromatic nuclei, limited pleomorphism, slightly eosinophilic cytoplasm, and indistinct cell borders.
 - Cellular foci showing features of the storiform-pleomorphic type may be seen but usually are haphazardly arrayed.
 - Myxoid foci may be hypocellular.
 - A variant with predominantly epithelioid morphology described
 - Cells may show features suggestive of lipoblasts, including vacuolated cytoplasm with indentation of the nuclei.
 - Stromal vasculature may include delicate vessels arranged in a curvilinear fashion; tumor cells tend to align along the vessel periphery.
 - Myxoid stroma is rich in acid mucopolysaccharides that are sensitive to hyaluronidase digestion.
 - Overall prognosis thought to be better than that of storiform-pleomorphic type
- Inflammatory variant (see Fig. 3-94):
 - Admixture of histiocytic-appearing cells, xanthomatous cells, and inflammatory cells
 - The inflammatory cells include neutrophils, which:
 - Typically are not associated with necrosis
 - May be intense and obscure the neoplastic cell infiltrate
 - Patients may have constitutional symptoms including fever and peripheral granulocytosis.
- Giant cell variant:
 - Nodular or multinodular growth but may also demonstrate a diffuse growth without nodularity
 - Characterized by the presence of multinucleated giant cells containing numerous (up to 100) round to oval nuclei with vesicular chromatin, identifiable nucleoli, and eosinophilic cytoplasm:
 - Multinucleated giant cells are admixed with mononuclear cells and spindle-shaped cells.

- Diagnosis of giant cell variant requires that the multinucleated giant cells and mononuclear cells represent more than 50% of the tumor.
- Angiomatoid variant (angiomatoid fibrous histiocytoma):
 - Previously referred to as angiomatoid MFH
 - Soft tissue neoplasm of low malignant potential, typically occurring in the superficial soft tissues of the extremities in children and young adults
 - Tendency to locally recur and rarely may metastasize
 - Histology characterized by:
 - Irregular solid masses of histiocytic-like cells:
 - Histiocytic-like cells are usually uniform with round to oval nuclei and slightly eosinophilic cytoplasm.
 - Nuclear atypia and/or hyperchromatic giant cells may be seen.
 - May contain hemosiderin
 - Cystic areas of hemorrhage:
 - Not lined by endothelial cells
 - Outer shell of chronic inflammatory cells, including abundant lymphocytes and plasma cells
 - Uncommonly a prominent myxoid stroma may be present.
 - Unusual features that may be focally seen include clear cells, rhabdomyoblast-like cells, pulmonary edema-like pattern, and tumor cell cords lying in a myxoid stroma.
 - Immunohistochemistry:
 - Reactivity for the epithelial membrane antigen, desmin, smooth muscle actin, muscle specific actin, CD68, and CD99
 - Cytogenetics and molecular genetics:
 - t(12;22)(q13;q12) and t(2;22)(q33;q12) identified
 - *EWSR1-CREB1* and *EWSR1-ATF1* gene fusions identified but also present in:
 - Conventional clear cell sarcoma (of tendons and aponeuroses), clear cell sarcoma-like tumor of the gastrointestinal tract, soft tissue myoepithelial carcinoma, hyalinizing clear cell carcinoma of the salivary gland, primary pulmonary myxoid sarcoma

Differential Diagnosis

- Nodular fasciitis
- Inflammatory myofibroblastic tumor
- Dermatofibrosarcoma protuberans
- Fibrosarcoma
- Spindle cell squamous carcinoma
- Malignant melanoma
- Rhabdomyosarcoma
- Liposarcoma
- Leiomyosarcoma

- Synovial sarcoma, monophasic type
- Malignant peripheral nerve sheath tumor
- Hematolymphoid malignancies

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
- Radiotherapy may be used for those tumors with positive surgical margins or close surgical margins.
- Chemotherapy is employed in the presence of metastatic disease.
- Lymph node metastasis occurs in less than 15% of cases and unless clinically suspect, neck dissection is of limited value.
- For high-grade lesions:
 - A high recurrence and metastatic rates:
 - Metastases occur to the lung > lymph nodes > liver and bone.
 - Death from disease is common:
 - Reported in more than 75% of patients
 - Median time of 13.5 months
- Prognosis depends on:
 - Depth of tumor:
 - Deep soft tissue tumors more likely to metastasize as compared with tumors of the subcutis
 - Size of tumor:
 - Smaller tumors (less than 2.5 cm) less likely to metastasize as compared with larger tumors
 - Inflammatory cell component:
 - Tumors with increased numbers of acute and chronic inflammatory cells are less likely to metastasize as compared with tumors lacking a significant inflammatory cell infiltrate.

Fibrosarcoma (Figs. 3-96 through 3-98)

Definition: Malignant tumor of fibroblasts and myofibroblasts lacking evidence of other types of cellular differentiation.

Clinical

- Found predominantly in the soft tissues of the lower extremities (thigh and knee area)
- Up to 10% may occur in the head and neck region.
- No gender predilection; may affect all age groups, with the majority of cases occurring in the fourth through sixth decades of life:
 - Not limited to adults and may occur in children
- Common head and neck sites include the nasal cavity and paranasal sinuses; less often may occur in other head and neck sites, including the larynx and neck.

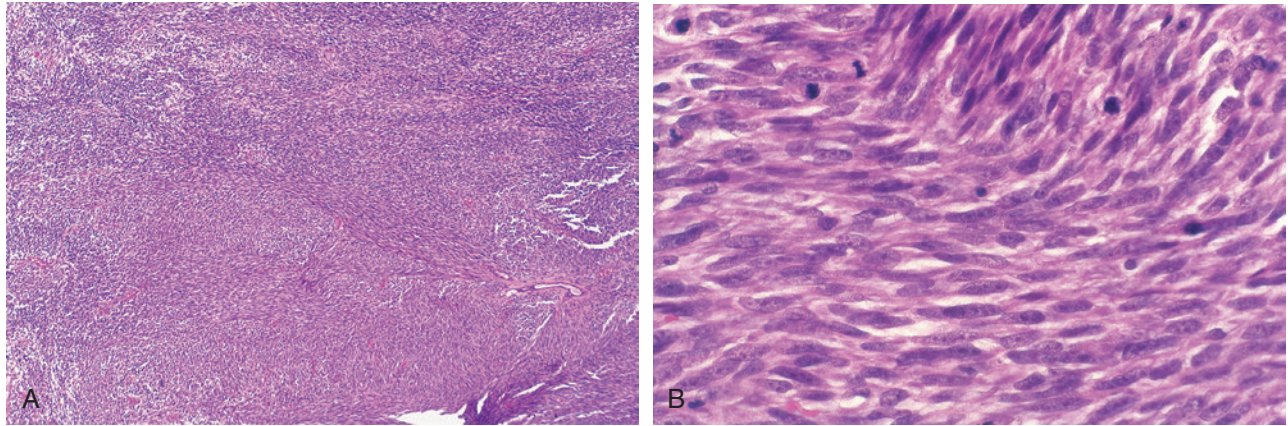


Fig. 3-96. Sinonasal fibrosarcoma, high grade.

A, The tumor is characterized by a fasciculated growth pattern with long sweeping fascicles and a dense spindle-shaped cellular infiltrate; **B**, The cells are pleomorphic with elongated to spindle-shaped hyperchromatic nuclei, scanty cytoplasm, indistinct cell borders, and multiple mitotic figures.

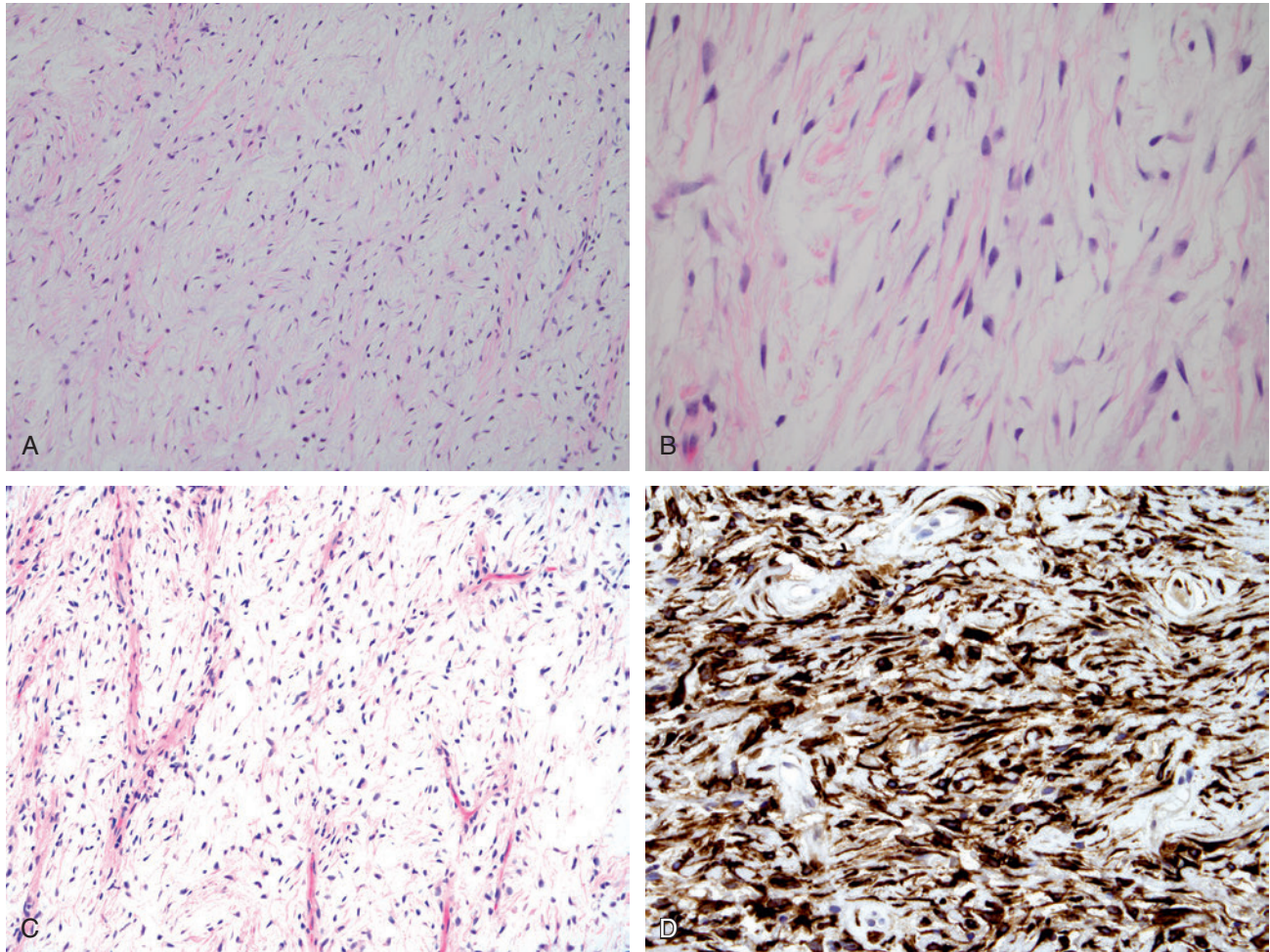


Fig. 3-97. Low-grade fibromyxoid sarcoma.

A, Variably cellular neoplastic proliferation with low to moderate cellularity and a variably myxoid to fibrous-appearing stroma. **B**, Deceptively bland-appearing spindle-shaped cells with small hyperchromatic nuclei and indistinct eosinophilic cytoplasm. **C**, Network of curvilinear and branching capillary-sized blood vessels. **D**, MUC4 immunoreactivity considered sensitive and specific for LGFMS. Additional stains that may be present include vimentin, smooth muscle actin, and muscle specific actin (not shown).

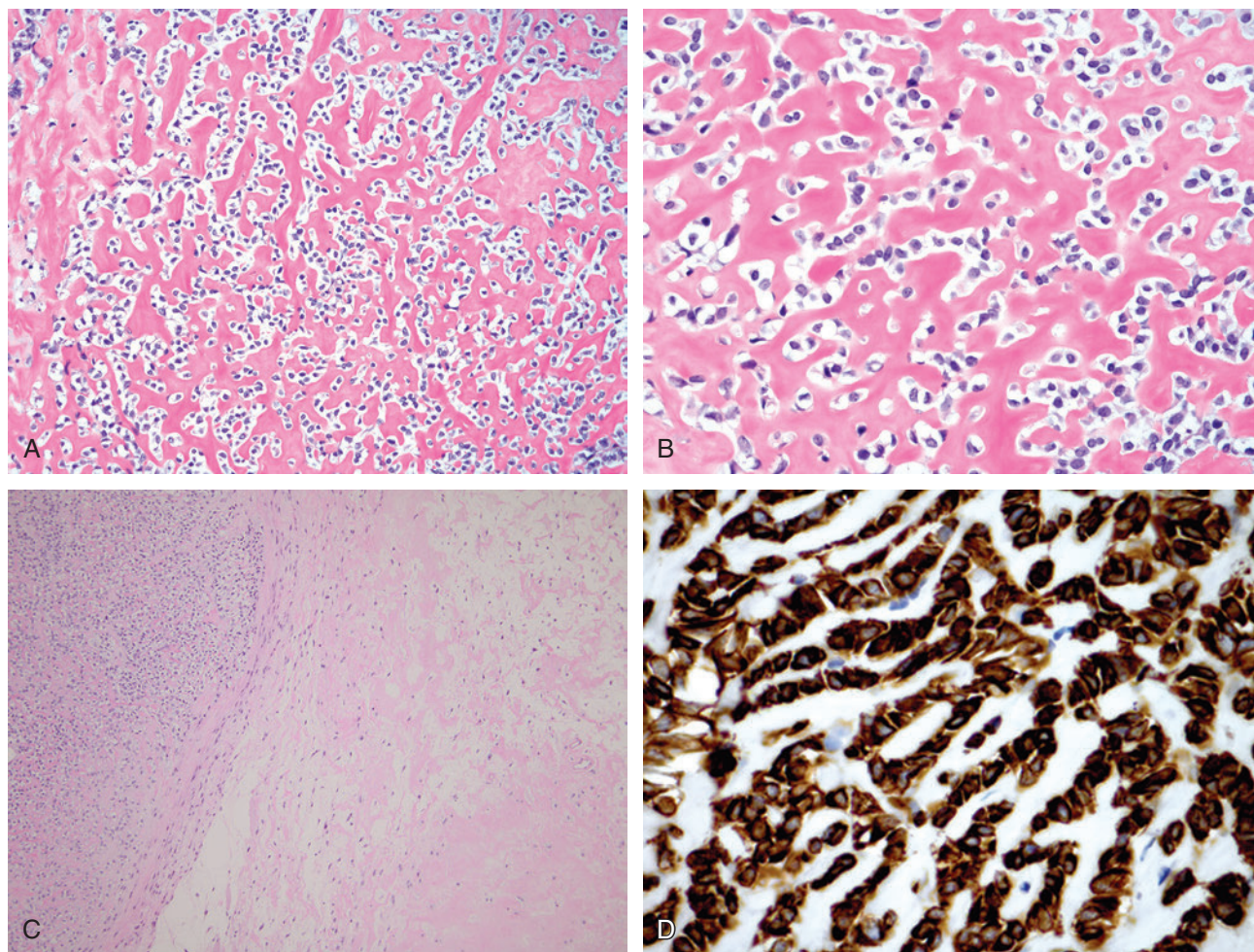


Fig. 3-98. Sclerosing epithelioid fibrosarcoma.

A, Epithelioid cells arranged in nests, cords, and strands embedded in a dense collagenous stroma. **B**, At higher magnification the bland-appearing epithelioid cells have round to oval nuclei, stippled to vesicular chromatin, and scanty clear to eosinophilic cytoplasm. **C**, Hybrid tumor showing foci of sclerosing epithelioid fibrosarcoma (*left*) and low-grade fibromyxoid sarcoma (*right*). **D**, MUC4 staining seen in a majority of cases. The presence of morphologic and molecular overlap between sclerosing epithelioid fibrosarcoma and low-grade fibromyxoid sarcoma suggests a relationship between these tumor types.

- Symptoms vary according to site and include nasal obstruction, epistaxis, pain, dysphagia, or as a solitary mass with or without associated pain.
- Radiology:
 - Soft tissue mass
 - Bone destruction is commonly identified.
- Generally arise de novo but may be linked with prior radiation treatment or in association with old burn scars:
 - In association with prior radiation the latency period is usually a decade or longer from the time of irradiation to the development of the malignancy.

Pathology

Gross

- Unencapsulated, polypoid, or sessile tan-white, firm tumor usually measuring less than 10 cm in diameter
- Sinonasal fibrosarcomas are often associated with bone erosion and/or destruction.

Histology

- Fasciculated growth pattern composed of spindle-shaped cells with scanty cytoplasm and indistinct cell borders

- May be histologically classified as low-grade or high-grade based on tumor cellularity, cellular maturity, and the amount of collagen production:
 - Histologic grading schema has been proposed based tumor differentiation:
 - Low grade = well differentiated
 - High grade = poorly differentiated

Low-grade Fibrosarcoma

- Cellular neoplasm with uniform spindle cells, absence of nuclear hyperchromasia, scattered mitoses, and variable amount of collagen
- Fasciculated growth pattern is distinct.
- Invasive growth is present.

High-grade Fibrosarcoma

- Hypercellular neoplasm with pleomorphism, hyperchromatic, rounded to oval nuclei, increased mitotic activity, necrosis, and less collagen production
- Loss or indistinct fasciculated growth
- Both low- and high-grade neoplasms lack the marked pleomorphism or multinucleated giant cells more typically seen in undifferentiated pleomorphic sarcoma.
- Heterologous metaplastic elements (bone and cartilage) may be seen particularly in the low-grade type.
- Myxoid stromal changes may be focally seen and may be prominent (see below under “variants”).
- Invasive growth is present including osseous invasion.
- Histochemistry:
 - Special stains of limited assistance in the diagnosis
- Immunohistochemistry:
 - Vimentin positive
 - Actin may be focally positive.
 - Usually absent expression for epithelial markers (e.g., cytokeratins), melanocytic markers (e.g., S100 protein, HMB45, melan A, tyrosinase), myogenic markers (desmin, myoglobin, myf-4), hematolymphoid markers (LCA, B- and T-cell), vascular endothelial markers (CD31, CD34)
- Fibrosarcoma variants include:
 - Low-grade fibromyxoid sarcoma (LGFMS; see Fig. 3-96):
 - Also referred to as Evans tumor
 - Generally a tumor of deep soft tissues
 - Tumors are characterized by deceptively bland-looking morphology with low to moderate cellularity composed of relatively bland spindle-shaped cells with small hyperchromatic nuclei and indistinct eosinophilic cytoplasm
 - Mild nuclear pleomorphism and low mitotic rate
 - Variably fibrous and myxoid stroma is present with tendency of these tumors to be more

fibrous; transition between fibrous and myxoid areas may be seen.

- Network of curvilinear and branching capillary-sized blood vessels seen in myxoid areas
- Overall deceptively bland histomorphologic appearance with difficulty in determining malignancy in primary tumor; tendency for recurrence and/or metastasis:
 - Recurrence(s) and metastasis may show similar bland histomorphology as the primary tumor or may show increased cellularity and mitotic activity
- Immunoreactivity:
 - MUC4 immunoreactivity (cytoplasmic) considered sensitive and specific for LGFMS
 - Vimentin, smooth muscle actin, muscle specific actin may be present.
 - p63 staining may be present (weak focal).
- Cytogenetic and molecular genetics:
 - Characterized by the specific translocation t(7;16)(q33;p11) and corresponding fusion gene *FUS-CREB3L2*
 - Alternative *EWSR1-CREB3L1* gene fusion identified:
 - Expands spectrum of gene fusions that characterize LGFMS
 - Suggest *EWSR1* gene may substitute for the function of *FUS* in gene fusions of sarcoma
- Sclerosing epithelioid fibrosarcoma (SEF, see Fig. 3-97):
 - Unusual aggressive fibroblastic neoplasm composed of cords of bland epithelioid cells embedded in a dense collagenous stroma
 - Cells arranged in nests, cords, strands, and occasional acini and alveoli
 - Cells have round to oval nuclei, stippled to vesicular chromatin, and scanty clear to eosinophilic cytoplasm
 - Some SEF cases show morphologic and molecular overlap with low-grade fibromyxoid sarcoma (hybrid tumors), suggesting a relationship between these tumor types.
 - Immunohistochemistry:
 - MUC4 staining (cytoplasmic) seen in a majority of cases
 - *FUS* rearrangement
 - Vimentin positive
 - Epithelial membrane antigen (up to 50% of cases) with membranous staining
 - S100 protein and NSE may be focally positive.
 - No reactivity for desmin, smooth muscle actin, HMB-45, CD68 (KP-1), and leukocyte common antigen

- Cytogenetic and molecular genetics:
 - Characterized by the translocation t(11;16) (p13;p11) and corresponding fusion gene *FUS-CREB3L1*:
 - MUC4-positive SEFs with FUS rearrangement are likely closely related to low-grade fibromyxoid sarcoma.
 - MUC4-positive SEFs that lack FUS rearrangement may be related to low-grade fibromyxoid sarcoma but could have alternate fusion partners, including EWSR1.
 - SEF without MUC4 expression may represent a distinct group of tumors.

Differential Diagnosis (for Fibrosarcoma)

- Nodular fasciitis
- Fibromatosis
- Inflammatory myofibroblastic tumor
- Undifferentiated pleomorphic sarcoma
- Spindle cell squamous carcinoma
- Spindle cell malignant melanoma
- Malignant peripheral nerve sheath tumor
- Synovial sarcoma, monophasic type

Treatment and Prognosis

- Surgical excision to include tumor-free margins is the preferred treatment:
 - Lymph node metastasis is rare; therefore, radical neck dissection is not warranted.
- Adjunctive radiotherapy may be of assistance, but there is no definitive proof as to its efficacy in treating fibrosarcomas.
- Radiotherapy may be used for those tumors with positive surgical margins or close surgical margins and/or for high-grade tumors.
- Prognosis is primarily related to the adequacy of surgical excision.
- Local recurrence likely the result of inadequate resection has been reported to occur in from 50% to 72% of patients:
 - Local recurrence usually occurs within the first 2 postoperative years but may be latent and occur many years following resection.
- Metastatic disease primarily occurs to the lungs and bone.
- Overall 5-year survival rates range from 50% to 70%
- Factors affecting prognosis include:
 - Tumor grade:
 - Low grade associated with high cure rate
 - High grade associated with very low cure rate
 - Tumor size:
 - Worse prognosis associated with tumors greater than 5 cm in greatest dimension

- Adverse prognosis associated with:
 - Positive surgical margins
 - Extension into contiguous anatomic compartments (skin, sinuses)
 - Osseous and neural invasion

Additional Notes

Infantile Fibrosarcoma

- More common in males than in females
- Most common in the upper and lower extremities but up to 15% may occur in the head and neck
- Histologically similar to fibrosarcomas of adults
- Distinctive *ETV6-NTRK3* gene fusion is present.
- Overall have a better prognosis as compared with adult fibrosarcomas with less likelihood of local recurrence or distant metastasis:
 - Applicable to children 5 years or younger
 - Children 10 years and older have a prognosis similar to those of adults.
- Overall 5-year survival of 85% to 95%
- Gains in chromosomes 8, 11, 17, 20 reported in children less than 2 years old

Leiomyosarcoma

(Figs. 3-99 through 3-103)

Definition: Malignant tumor of smooth muscle.

NOTE: Given the relative absence of smooth muscle in the head and neck region, the histogenesis appears to arise from vascular structures.



Fig. 3-99. Sinonasal leiomyosarcoma.

Large, firm polypoid mass with a tan-white appearance.

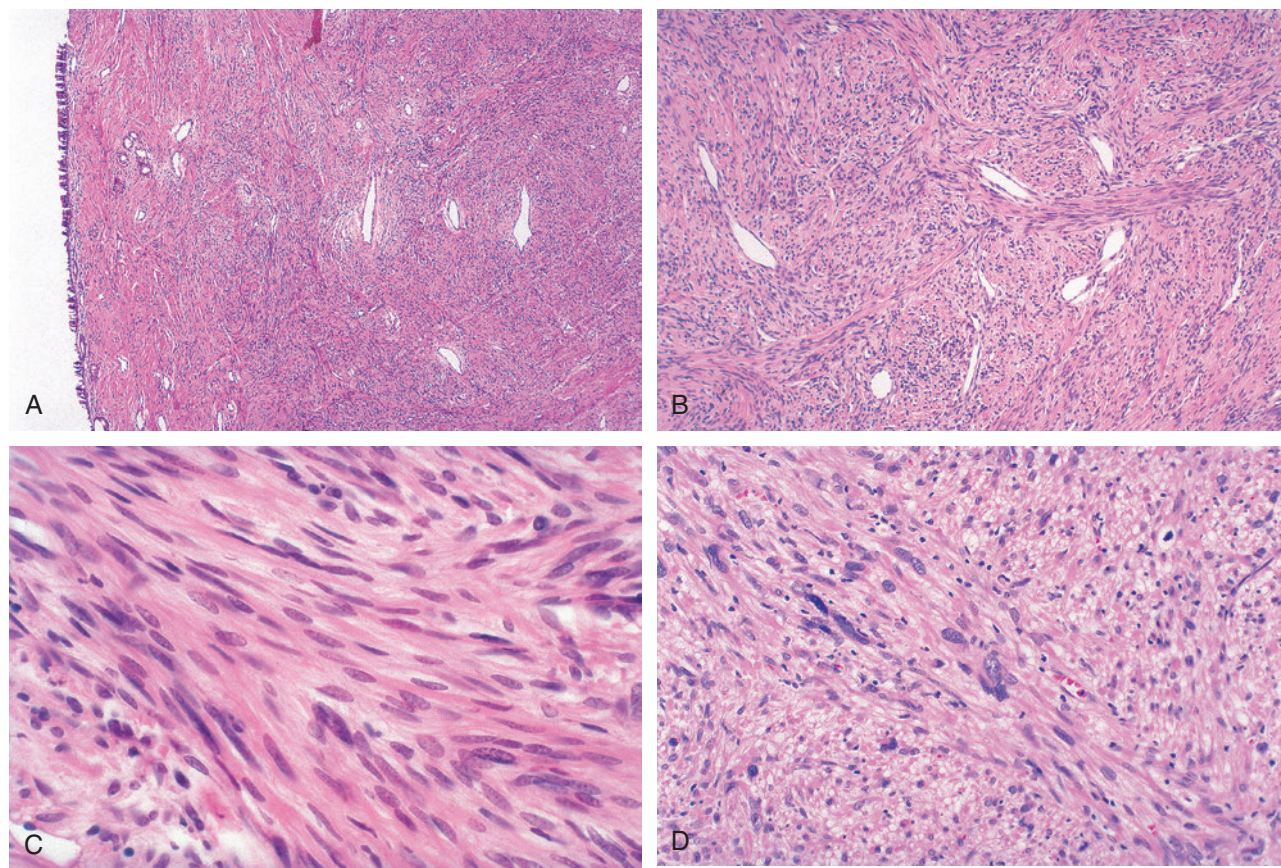


Fig. 3-100. Sinonasal leiomyosarcoma, low grade.

A, Submucosal cellular infiltrate with a fascicular growth. **B**, Cellular neoplasm composed of interlacing bundles intersecting at right angles. **C**, The neoplastic cells are uniform with elongated, centrally located, blunt-ended, cigar-shaped nuclei and indistinct eosinophilic cytoplasm. **D**, Nuclear pleomorphism, hyperchromasia, and a mitotic figure (*upper right*). The overall mitotic count was 4 mitoses per 10 high-power fields that in conjunction with infiltrative growth (not shown) conferred the diagnosis of a low-grade leiomyosarcoma.

Clinical

- Approximately 4% of all leiomyosarcomas arise in the head and neck.
- No gender predilection; occurs in a wide age range but most common in the sixth decade of life
- In the head and neck, the most common sites of occurrence are:
 - Oral cavity (buccal mucosa, gingiva, tongue, floor of mouth) > sinonasal tract > skin and subcutaneous tissue
 - Less common sites of occurrence include larynx, trachea, neck, hypopharynx, orbit, external auditory canal.
- Most common symptoms are dependent on site:
 - Sinonasal tract: nasal obstruction, pain, and epistaxis
 - Oral cavity: painless mass, ulceration
 - Duration of symptoms usually is over extended periods of time.
- Radiology:
 - Soft tissue density
 - Sinus opacification
 - Bone erosion and/or invasion
- Majority occur de novo, but some sinonasal tract tumors reported to occur following irradiation or cyclophosphamide exposure
- Greater frequency of occurrence of leiomyosarcomas (in general, not necessarily those of the head and neck) in the immunocompromised patient, including:
 - Post-transplantation (e.g., renal, cardiac, liver)
 - AIDS
 - Tendency to occur in children
 - Tendency to occur in relationship to viscera (e.g., gastrointestinal tract, lung, other)

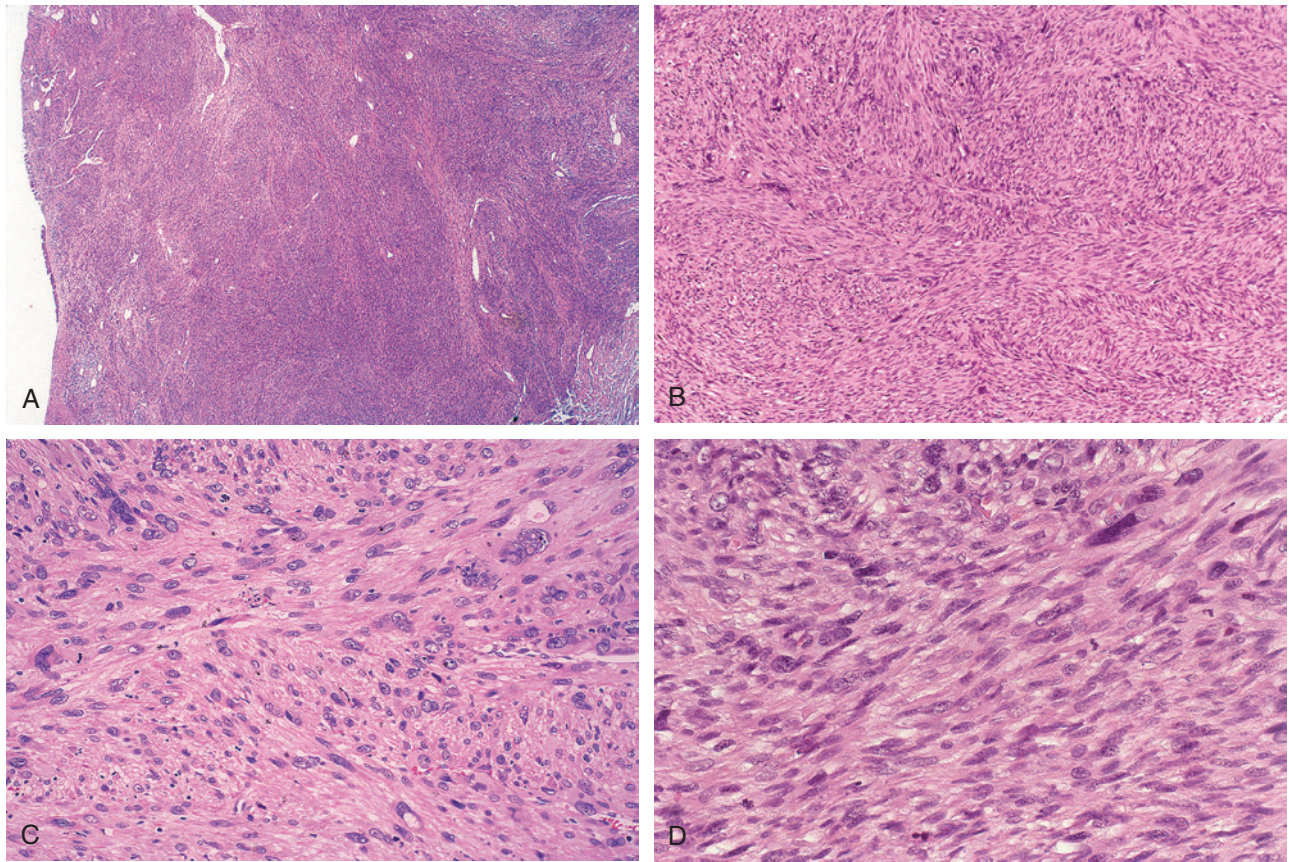


Fig. 3-101. Sinonasal leiomyosarcoma, high grade.

A, Submucosal cellular infiltrate with a fascicular growth; the degree of cellularity in this tumor even at low magnification is greater than that seen in the previous illustration. **B**, Cellular neoplasm composed of interlacing bundles intersecting at right angles with markedly pleomorphic nuclei. **C** and **D**, The neoplastic cells are pleomorphic, hyperchromatic with prominent nucleoli and increased mitotic activity. The overall mitotic count was 10 mitoses per 10 high-power fields that in conjunction with infiltrative growth (not shown) conferred the diagnosis of a high-grade leiomyosarcoma.

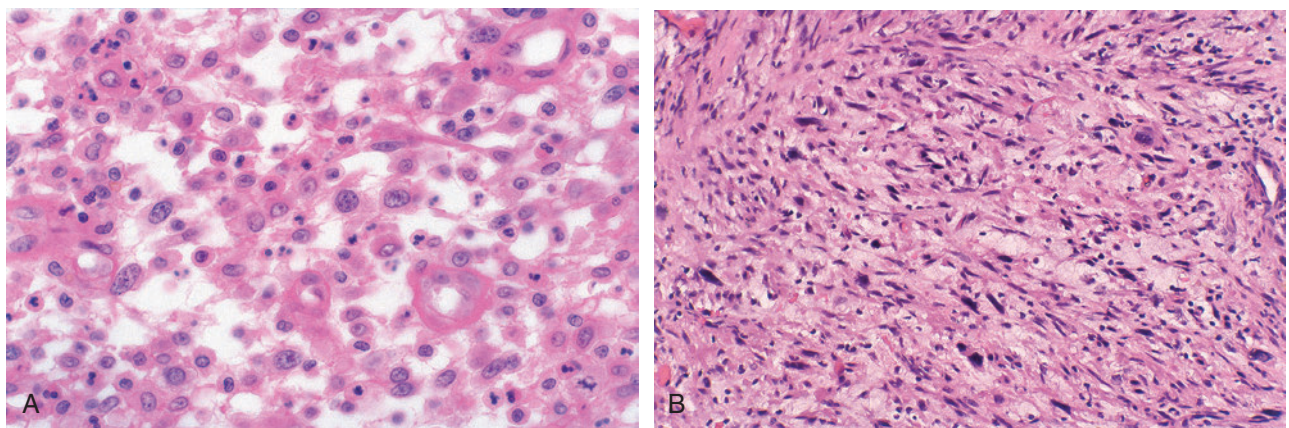


Fig. 3-102. Leiomyosarcoma histologic variants.

Histologic variants of leiomyosarcoma include **(A)** epithelioid and **(B)** inflammatory.

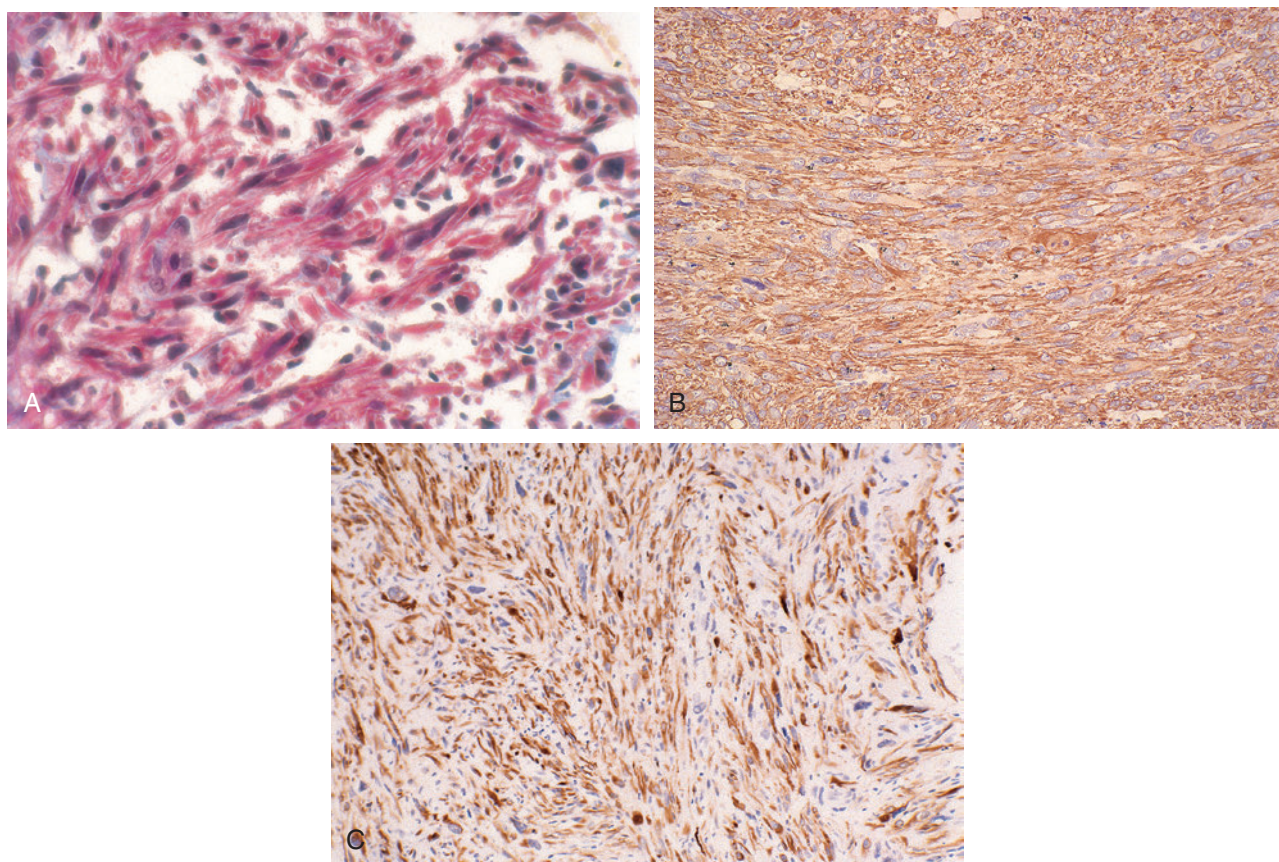


Fig. 3-103. Special stains in leiomyosarcoma.

Special stains that may assist in the diagnosis of leiomyosarcoma include (A) Masson trichrome showing deep red, longitudinal lines consistent with cytoplasmic myofibrils; (B) smooth muscle actin; (C) desmin.

- May be multifocal
- May disseminate and be lethal
- EBV found in these tumors by immunohistochemistry, in situ hybridization, and/or PCR:
 - Referred to as EBV-associated smooth muscle tumors

Pathology

Gross

- Circumscribed but not encapsulated, tan-white to pink-red, rubbery to firm, polypoid or sessile lesion usually measuring >5 cm in diameter
- Ulceration, hemorrhage, necrosis, and invasion of adjacent structures are often identifiable.

Histology

- Cellular neoplasm composed of interlacing bundles of spindle-shaped cells; typically the interlacing bundles intersect at right angles:
 - Fascicular growth similar to that seen in fibrosarcoma may be present.
- Neoplastic cells are elongated with centrally located, blunt-ended, cigar-shaped nuclei and eosinophilic cytoplasm:
 - Perinuclear vacuole or clear halo may be seen, giving the nucleus an indented or concave contour.
- Variable degree of cellular anaplasia with nuclear pleomorphism, nuclear hyperchromasia, and increased mitotic activity (typical and atypical forms) can be seen.
- Infiltrative growth can be seen and is indicative of malignancy.
- Multinucleated giant cells are common.
- Nuclear palisading may be prominent, which may suggest a diagnosis of a peripheral nerve sheath tumor.
- Stroma tends to be richly vascular with close apposition of the tumor with the vascular structures.
- Given the relative dearth of smooth muscle in the sinonasal tract (and oral cavity), the presumed origin

for many leiomyosarcomas of these sites (as well as other mucosal sites of the upper aerodigestive tract) is from vascular smooth muscle:

- Tumors can be seen originating from or in close association with blood vessels (arteries and veins, arterioles and venules).
- Other than relationship to vascular walls, the histology is similar to nonvascular-derived leiomyosarcoma.
- Epithelioid cells and myxomatous change may be seen and occasionally may predominate, giving rise to so-called epithelioid leiomyosarcoma and myxoid leiomyosarcoma, respectively:
 - Myxoid leiomyosarcoma:
 - Extensive myxoid change may create a gelatinous appearance.
 - A prominent myxoid stroma that is rich in hyaluronic acid is present in between the spindle neoplastic cells.
 - Overall, appears relatively hypocellular, and in the presence of low mitotic rate the overall histology may not be suggestive of a malignant neoplasm.
 - Even mitotic rates of two or less mitotic figures should prompt consideration for a malignancy.
 - Inflammatory leiomyosarcoma:
 - Characterized by the presence of a leiomyosarcoma with prominent inflammatory cell infiltrate including xanthoma cells, lymphocytes, and occasionally neutrophils
 - Not associated with systemic (constitutional) symptoms
 - Other cell types may include:
 - Epithelioid (epithelioid LMS), granular eosinophilic cytoplasm (granular cell LMS), multinucleated osteoclast-like giant cells are unusual findings and may be seen in only a part of a tumor when identified.
- Histochemistry:
 - Cytoplasmic myofibrils can be seen in better differentiated tumors as deep red, longitudinal lines by Masson trichrome stain and purple by phosphotungstic acid-hematoxylin (PTAH) stain.
 - Glycogen is demonstrable as diastase-sensitive, PAS-positive material.
- Immunohistochemistry:
 - Actins (smooth muscle and muscle-specific) positive
 - Desmin reactivity (70% to 80%) present
 - Caldesmon positive (60% to 65%)
 - Usually no immunoreactivity for epithelial markers (e.g., cytokeratins), melanocytic markers (e.g., S100 protein, HMB45, melan A, tyrosinase), myogenic markers (myoglobin, myf-4), vascular endothelial markers (CD31, CD34):

- Cytokeratin expression may occur:
 - usually in a perinuclear localization
 - usually seen in association with desmin reactivity
- S100 protein may be positive.

- Electron microscopy:

- Deeply indented nuclei, numerous well-oriented myofilaments (6 to 8 nm), pinocytotic vesicles, intercellular connections, and a basal lamina enveloping the entire cell membrane

Criteria for Malignancy in Smooth Muscle Tumors

- Criteria for malignancy in distinguishing benign from malignant smooth muscle tumors are not always straightforward and can present challenges in determining benignancy from malignancy:
 - Not true relative to high-grade tumors
- Most important pathologic diagnostic parameter is mitotic activity; to a lesser degree tumor size affects the diagnosis, and the location of the tumor affects the diagnosis.
 - Criteria for malignancy relative to uterine smooth muscle tumors are unique and are not applicable to soft tissue (and head and neck sites).
 - Relative to soft tissue and head and neck:
 - Tumors with one to four mitoses per 10 high-power fields are considered as potentially malignant, especially in conjunction with large tumor size, nuclear atypia, and necrosis.
 - Five or more mitoses per 10 high-power fields is malignant.
 - If tumors have no mitoses or very few mitoses and an absence of nuclear atypia, then the tumor is likely benign, especially if there is significant hyalinization or calcification.

Differential Diagnosis

- Leiomyoma
- Spindle cell squamous carcinoma
- Malignant peripheral nerve sheath tumors
- Fibrosarcoma
- Rhabdomyosarcoma

Treatment and Prognosis

- Radical surgical excision is the preferred treatment.
- Radiation and chemotherapy are of questionable utility.
- Prognosis depends on the site and extent of tumor and is not necessarily contingent on the histology:
 - Tumors limited to the nasal cavity are associated with a good prognosis and are cured following complete removal.
 - Tumor involving both the nasal cavity and paranasal sinuses results in an aggressive neoplasm associated with increased recurrence (70% of

- patients), morbidity, and mortality rates (45% of patients with death occurring within 2 years of the diagnosis).
- Local recurrence occurs frequently and is usually associated with extensive uncontrollable local infiltration.
- Metastases (hematogenous) occur infrequently, approximately 17% of patients:
 - Usually involving the lung
 - Lymph node metastases are infrequent early but can occur late in the disease course.
- Cutaneous leiomyosarcoma:
 - May be separated into tumors confined to the dermis and those that involve the subcutis:
 - Dermal-based:
 - Tend to be small (less than 2 cm)
 - Tend to be histologically low grade
 - May recur but do not metastasize; this is true even for histologically higher-grade tumors.
 - Favorable prognosis

- Subcutaneous tumors:
 - Up to 40% may metastasize.
 - Metastasis most often occurs to the lungs; nodal metastasis is uncommon.
 - Prognosis comparable to soft tissue leiomyosarcomas
- Wide surgical resection is indicated.

Angiosarcoma (AS)

(Figs. 3-104 through 3-107)

Definition: Malignant tumor of endothelial cell origin.

Synonyms: Hemangiosarcoma; lymphangiosarcoma

Clinical

- In general, angiosarcoma is a rare neoplasm accounting for up to 3% of all sarcomas:
 - In contrast to other sarcomas, angiosarcomas have a predilection for cutaneous and superficial soft tissue sites.

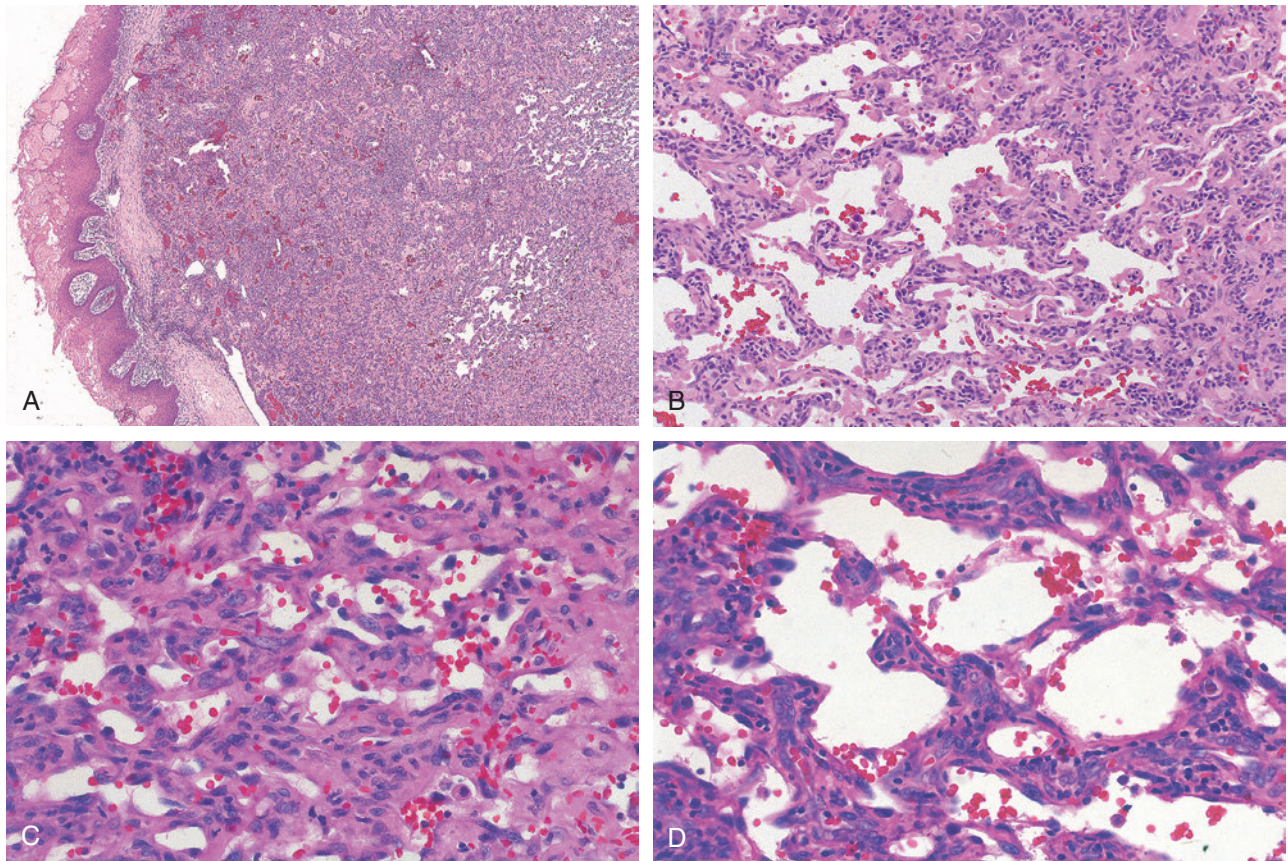
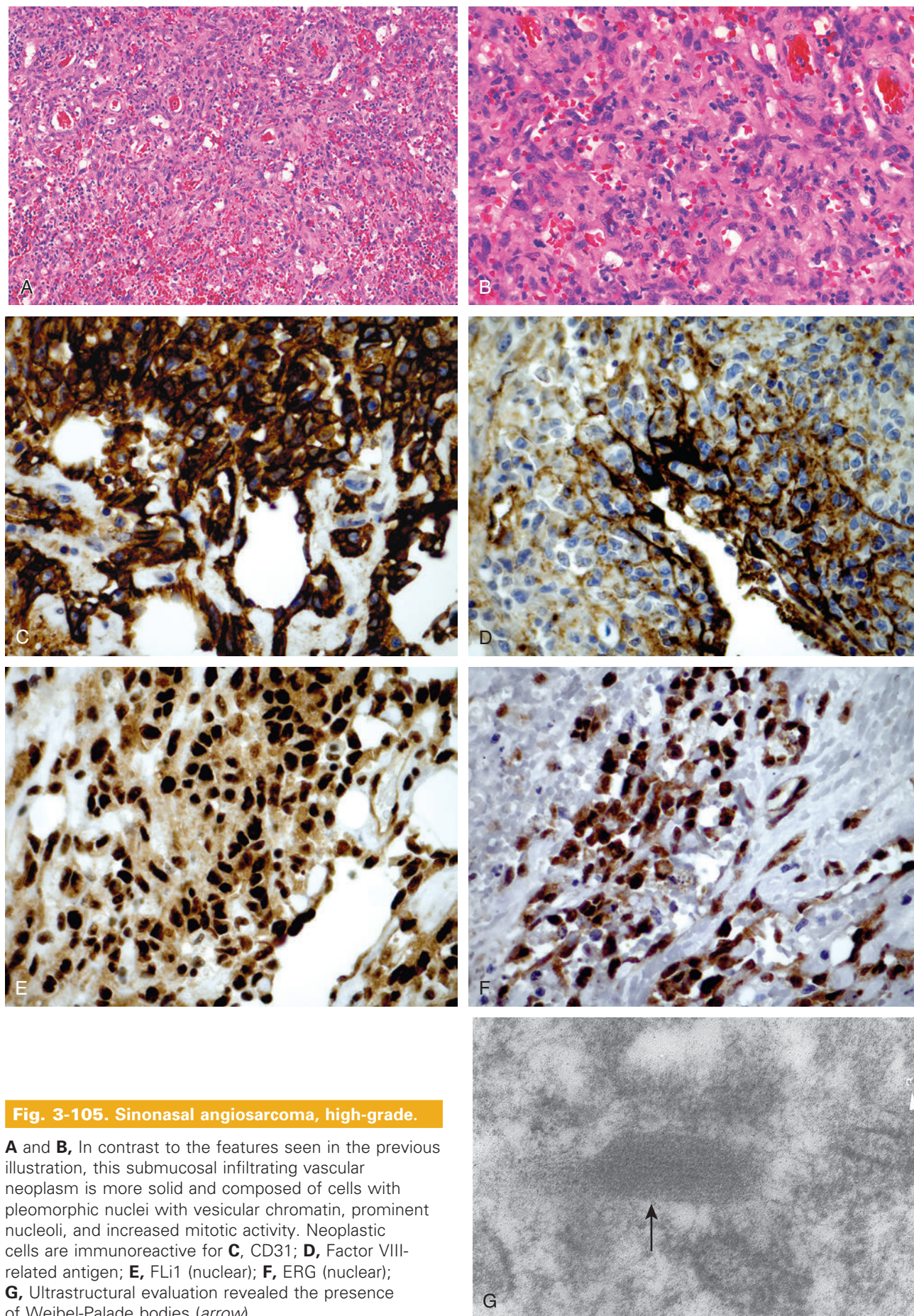


Fig. 3-104. Sinonasal angiosarcoma, low-grade.

A and B, Infiltrative submucosal cellular proliferation characterized by proliferation of ramifying and anastomosing vascular channels. **C and D,** Endothelial cells lining the interconnecting lumens are hyperchromatic with endothelial tufts.



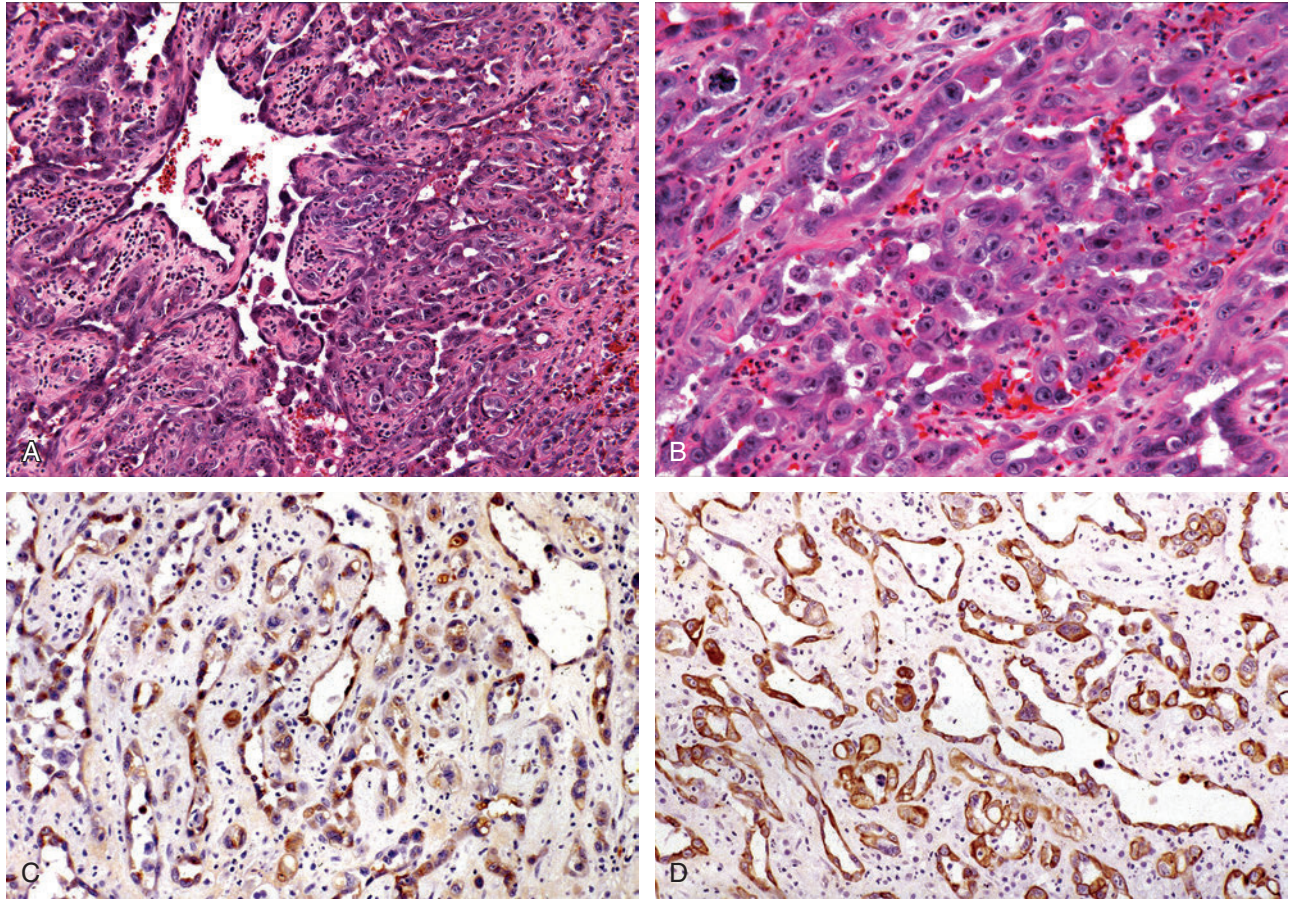


Fig. 3-106. Sinonasal angiosarcoma, epithelioid.

A and **B**, This tumor type, rare in the head and neck, is characterized by the presence of pleomorphic epithelioid-appearing cells with round to oval nuclei and prominent nucleoli lining vascular channels as well as in more solid areas; immunoreactivity can be seen for **C**, Factor VIII-related antigen and **(D)** cytokeratin. The epithelioid appearance coupled with the presence of cytokeratin may result in an erroneous diagnosis of a carcinoma.

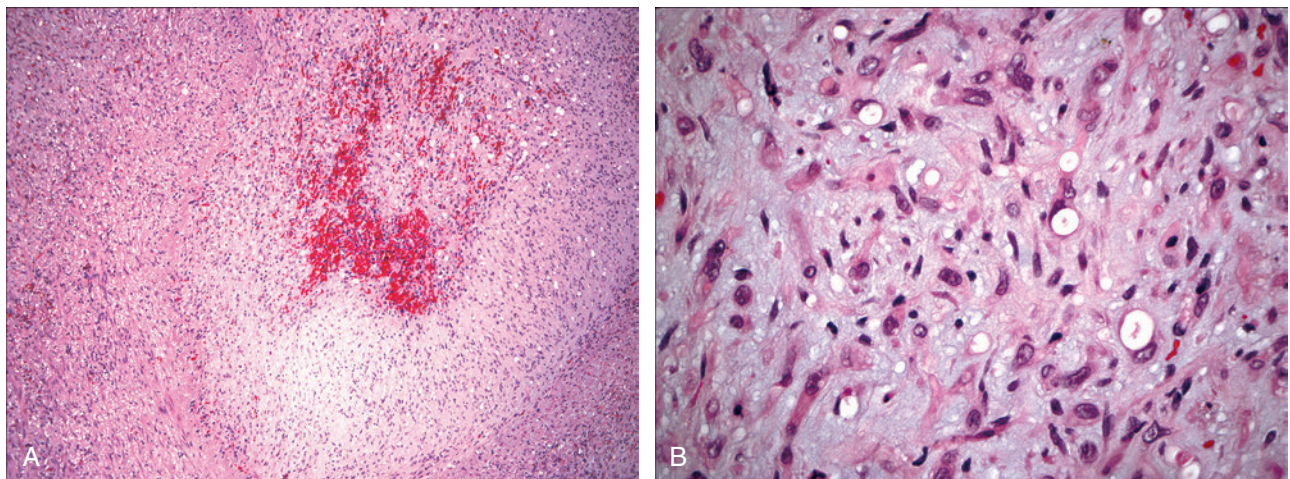


Fig. 3-107. Epithelioid hemangioendothelioma.

A, The tumor is arising in close association with a vascular space with vascular expansion and luminal obliteration by the neoplastic proliferation. **B**, Neoplastic cells appear as strands with identification of intracellular lumens seen as vacuoles or clear spaces. Immunoreactivity for CD31 and CD34 was present (not shown).

- Angiosarcoma of head and neck mucosal sites is uncommon.
 - In the head and neck, the most common site of occurrence is in the skin and subcutaneous tissue, particularly the scalp, but may occur as a primary tumor of the mucosa of the upper aerodigestive tract, including the sinonasal tract.
- Cutaneous angiosarcomas:
 - More common in men than in women; most often seen in the seventh and eighth decades of life
- Noncutaneous (head and neck) angiosarcomas:
 - No gender predilection; occur in a younger age population as compared with their cutaneous counterparts with the average age of occurrence in the fifth decade of life
 - Most common in sinonasal tract > oral cavity (gingiva, buccal mucosa, palate, tongue, tonsil) > nasopharynx and larynx > other sites
- Symptoms vary according to the site of occurrence and include a mass lesion, epistaxis, nasal obstruction, and headaches.
- Majority of mucosal-based head and neck angiosarcomas arise de novo.
- Secondary angiosarcomas represent those angiosarcomas that occur as a consequence of:
 - Radiation therapy and/or chronic lymphedema:
 - Most commonly seen in breast cancer patients
- Low-grade angiosarcoma:
 - Might be better considered epithelioid (histiocytoid) hemangioma or epithelioid hemangioendothelioma
 - True low-grade angiosarcoma may exist but should show complex anastomosing vascular channels with infiltrative growth composed of hyperchromatic atypical endothelial cells with intraluminal papillae.
- High-grade angiosarcoma
- An epithelioid subtype (epithelioid angiosarcoma) characterized by round to oval pleomorphic cells may rarely be present in head and neck sites.
- Histochemistry:
 - Reticulin stains delineate the vascular lumina with the endothelial cells identified on the luminal side of the reticulin of framework (this contrasts with the reticulin staining seen in hemangiopericytomas).
- Immunohistochemistry:
 - CD31, CD34, Factor VIII-related antigen, and *Ulex europaeus* positive
 - Fli-1 positive (nuclear):
 - Nuclear transcription factor identified in greater than 95% of vascular tumors
 - Also expressed in Ewing sarcoma family of tumors, melanoma, lymphoblastic leukemia, others.
 - ERG positive (nuclear):
 - ETS family transcription factor identified in greater than 95% of vascular tumors
 - Sensitive endothelial marker of vascular differentiation
 - Claudin-5 positive:
 - Tight junction protein expressed in endothelial cells and in some epithelial cells
 - Newer marker potentially useful for angiosarcoma and Kaposi sarcoma, but its complete expression in nonvascular tumors yet to be defined
 - Vimentin positive and actins may be positive.
 - HHV-8 is negative.
 - In general, no immunoreactivity is seen for epithelial markers or melanocytic markers.
 - Epithelioid angiosarcomas may be immunoreactive for cytokeratins.
- Electron microscopy:
 - Partial envelopment of basal lamina along the antiluminal border, pinocytotic bodies, tight junctions between cells, and occasional identification of rod-shaped microtubulated bodies (Weibel-Palade bodies)
- Cytogenetics and molecular genetics:
 - Upregulation of vascular-specific receptor tyrosine kinases, including TIE1, KDR, TEK, and FLT1

Pathology

Gross

- Unifocal to multifocal, nodular, polypoid or ulcerative, ill-defined lesion with a bluish color sometimes surrounded by an erythematous ring; tumor size varies and can reach large sizes.
- Hemorrhage and necrosis may be seen.

Histology

- Characterized by the presence of:
 - Ramifying, interconnecting, or anastomosing vascular channels, which “dissect” through surrounding structures
 - Channels lined by atypical endothelial cells, which are increased in number and characterized by nuclear pleomorphism, hyperchromasia, and increased mitotic activity
 - Endothelial cells pile up along the lumen, creating papillations.
 - Endothelial cells may appear spindle, epithelioid, or polygonal.
- Depending on the cellularity, pleomorphism, mitotic activity, and extent of necrosis, angiosarcomas are divided in two histologic grades:

- High percentage of secondary AS show distinct 8q24 chromosomal gains due to MYC amplification and in 25% coamplification of FLT4 (encoding VEGFR3) identified:
 - Not found in primary AS
 - Not found in postradiation atypical vascular lesions
- 11p13, 13q14, and 17p13 allelic losses

Differential Diagnosis

- Angiolymphoid hyperplasia with eosinophilia
- Hemangioma and lobular capillary hemangioma
- Nasopharyngeal angiofibroma
- Papillary endothelial hyperplasia; may be present in association with:
 - Sinonasal inflammatory polyps, particularly antrochoanal polyps due to infarction
 - Vocal cord polyps
- Epithelioid hemangioendothelioma (EHE) (see Fig. 3-106):
 - Vascular neoplasm with biologic behavior intermediate between hemangioma and angiosarcoma
 - Rare tumor type in head and neck sites
 - Angiocentric tumor arising from or in close association with a blood vessel (usually a vein)
 - Histologically, composed of short strands or solid nests of rounded to slightly spindle (endothelial) cells
 - Definitive light microscopic evidence of vascular differentiation (e.g., distinct vascular channels) is uncommonly seen; tumor cells form small intracellular lumens seen as vacuoles or clear spaces that may contain erythrocytes
 - Cytologically, cells are usually bland with mild pleomorphism and limited to no mitotic activity.
 - Minority of cases show atypical features including nuclear pleomorphism with cytologic atypia, spindling, increased mitotic activity (more than 1 mitotic figure per 10 high-power fields), and necrosis:
 - Cases with atypical features have a more aggressive course with higher rate of metastases.
 - Some authorities prefer to designate these atypical epithelioid hemangioendotheliomas as malignant epithelioid hemangioendothelioma.
 - Immunoreactivity present for:
 - CD31, CD34, FLI1, and ERG
 - Podoplanin (D2-40) positive with uniform cytoplasmic reactivity
 - Cytokeratins (7, 8, 18) and EMA positive in 25% to 40%
 - Weibel-Palade bodies may be seen by electron microscopy.
 - Cytogenetics and molecular genetics:
 - t(1;3)(p36.3;q25) chromosomal translocation that is characteristic of EHE

- WWTR1-CAMTA1 gene fusion:
 - Apparently represents disease-defining gene alteration
 - Present in virtually all EHEs
 - Absent from all other vascular neoplasms
- Due to the low-grade nature of epithelioid hemangioendothelioma, therapy includes surgical resection in a conservative manner to ensure complete excision (i.e., tumor-free margins) without adjuvant radiation or chemotherapy.
- Prognosis:
 - Soft tissue EHE with increasing mitotic activity (>3 mitoses per 50 high-power fields) and large size (>3.0 cm) associated with decreased survival:
 - Patients with high-risk tumors reported to have 5-year disease-specific survival of 59%.
 - Patients with low-risk tumors less likely to develop metastasis (15%) and more likely to survive for longer periods of time.
 - EHE of the head and neck is:
 - Low-grade malignancy with a tendency for local recurrence and regional lymph node metastasis
 - Complete excision with negative margins is the preferred treatment for localized disease.

- Sinonasal glomangiopericytoma
- Kaposi sarcoma
- Malignant melanoma
- Poorly differentiated carcinoma
- Fibrosarcoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment, especially with well-delineated and solitary tumors.
- Surgery and radiotherapy may be of benefit in multifocal, ill-defined tumors.
- Prognosis is generally poor, with 10% to 15% 5-year survival rates.
- Recurrences are common and tend to occur within 2 years of surgery and are likely due to the facts that:
 - The extent of the tumor is often difficult to determine.
 - Angiosarcomas often extend beyond their apparent macroscopic limits, which must be accounted for in therapeutic management of these tumors.
- Metastases are uncommon, and when they occur the common metastatic sites include lungs and lymph nodes.
- Prognosis correlates with:
 - Tumor size:
 - Tumors <7 cm in diameter having a better prognosis than tumors measuring >7 cm

- Upper respiratory tract angiosarcomas may have a better prognosis than their cutaneous counterparts and may relate to:
 - Tendency to occur at a younger age
 - Lower incidence of persistence, recurrence, or metastasis
 - Higher salvage rate
 - Greater percentage of patients with no evidence of disease on follow-up
 - Lower morbidity and mortality rates

Low-Grade Sinonasal Sarcoma with Neural and Myogenic Differentiation (LGSSNMF) (Figs. 3-108 and 3-109)

Definition: Recently described distinct spindle cell sarcoma of the sinonasal region characterized by concomitant neural and myogenic differentiation.

NOTE: Whether in fact LGSSNMF truly represents a bona fide independent neoplasm instead of a neoplasm that should be subsumed in another defined tumor category (e.g., neurogenic, fibrohistiocytic, other) remains to be determined, requiring the identification of more cases reported in the literature. For the purposes of this text, LGSSNMF is described as an independent entity with the proviso that classification may or may not change in the future.

Synonym: Biphenotypic sinonasal sarcoma (may eventually represent preferred terminology).

Clinical

- Fewer than 50 cases reported in the literature
- More common in women than men; occur over a wide age range from 24 to 85 years (mean, 52 years):
 - Striking predilection for women in the fifth decade of life (30% of cases)
- Presenting symptoms include difficulty breathing, facial pressure, and congestion:
 - Facial pain and mild epiphora occasionally present
 - Some patients reported to have had a history of sinonasal surgery for apparently benign processes.
- Most tumors involved multiple sites in the sinonasal region:
 - Nasal cavity (54%) and ethmoid sinus (57%) were the most commonly involved areas, either singly or in combination.
 - Tumors may extend to orbit, cribriform plate, or into cranial vault.
- Imaging:
 - Heterogeneously enhancing, destructive lesion
- No known etiologic factors
- No evidence of association with neurofibromatosis

Pathology

Gross

- No distinct gross features:
 - Described as multiple polypoid red/pink to tan or gray fragments measuring up to approximately 4 cm in greatest dimension
 - Tissue fragments described as somewhat more firm than typical inflammatory nasal polyps

Histology

- Poorly circumscribed and unencapsulated cellular spindle cell neoplasm with uniform, elongate nuclei, and an infiltrative growth pattern:
 - Overall, cellularity very high with only a mild degree of variability within a given tumor
 - Tumor cells showed highly uniform, elongate nuclei, focally wavy to buckled in a minority of instances
 - Despite the cellularity, only rare mitotic figures seen; spindle cells were organized into medium-to-long fascicles.
 - Areas of classic “herringbone” pattern identified in most cases
 - Interstitial collagen typically scanty to moderate and arrayed in delicate strands
 - Absence of dense or ropey collagenous matrix
 - Infiltrative growth appreciated at low power, including infiltration of sinonasal bones
 - A striking and characteristic finding in the majority of cases include concomitant, apparently benign epithelial proliferation:
 - Composed of surface-type respiratory epithelium, forming invaginations of small glands or cystic spaces beneath the mucosal surface
 - Glandular structures were intimately admixed with neoplastic spindle cells, imparting a morphologic picture reminiscent of adenocarcinoma of the female genital tract.
 - A prominent hemangiopericytomatous vascular pattern may also be present.
 - Scattered small lymphocytes often sprinkled throughout the neoplastic component
 - Ulceration, hemorrhage, and necrosis not prominent features
 - Focal rhabdomyoblastic differentiation identified in a minority of cases (11%) characterized by:
 - Large cells with bright, eosinophilic cytoplasm, prominent nuclei, and focal cross-striations
- No evidence to suggest origin from a nerve
- Immunohistochemistry:
 - S100 protein positive in all tumors, at least focally:
 - Diffuse (57%), patchy (36%), or restricted to isolated tumor cells (7%)

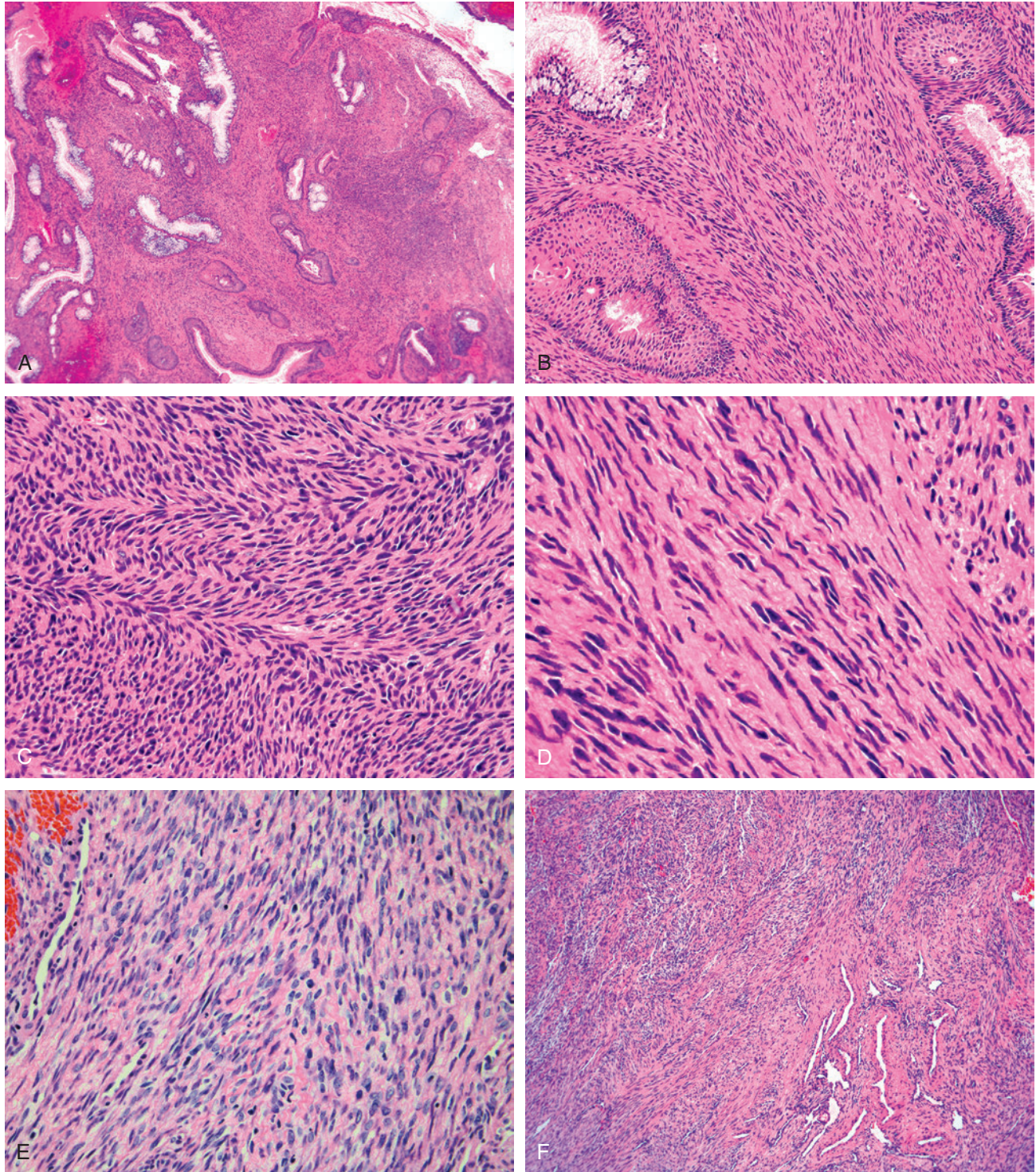


Fig. 3-108. Low-grade sinonasal sarcoma with neural and myogenic differentiation (LGSSNMF).

A, Polypoid lesion showing a submucosal spindle cell proliferation, characteristically with associated benign epithelial glandular proliferation. **B**, Higher magnification of the combined spindle cell proliferation with fascicular pattern of growth and benign glands. **C**, Cellular spindle cell proliferation showing “herringbone” pattern of growth. **D**, Spindle cells wavy to buckled appearance suggestive of neurogenic differentiation. **E**, In spite of increased cellularity the nuclei are uniform in appearance, lacking significant pleomorphism and increased mitotic activity; a scanty amount of intercellular collagen is present. **F**, Hemangiopericytomatous vascular pattern may also be present (*lower right*).

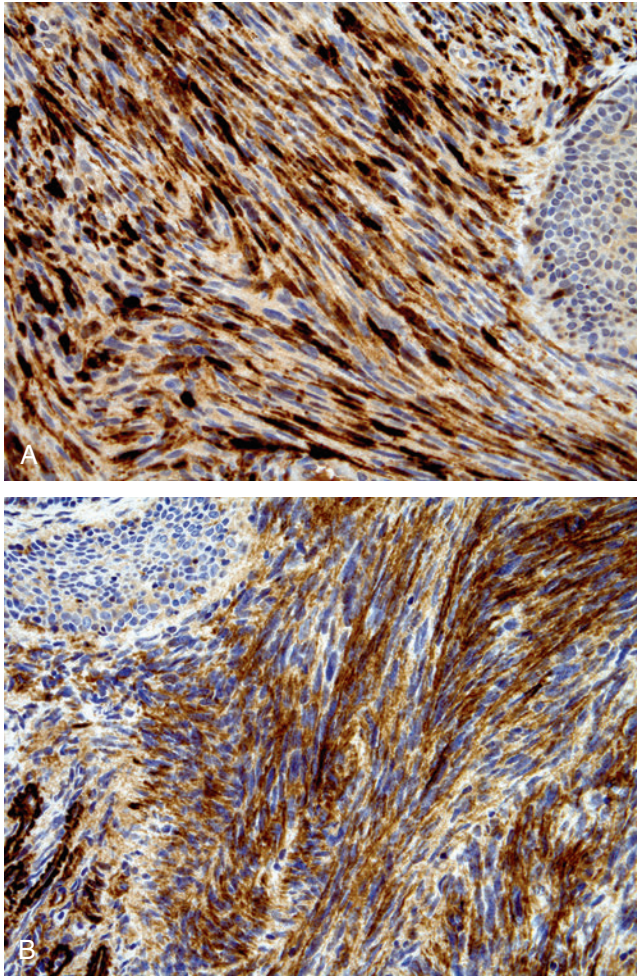


Fig. 3-109. Low-grade sinonasal sarcoma with neural and myogenic differentiation (LGSSNMF).

Immunoreactivity includes (A) S100 protein and (B) muscle-specific actin. S100 protein is at least focally present in all cases and in a majority of cases is diffuse and strong. Concomitant expression of actins (SMA or MSA) is seen in a majority of cases and often is diffuse.

- Concomitant expression of either actins (SMA or MSA) seen in 96% of the cases:
 - Diffuse (52%), patchy (39%), isolated tumor cells (9%)
- Diffuse MSA positive in 43%
- Additional reactivity may include:
 - CD34 (focal more often than diffuse)
 - Focal desmin
 - Weak EMA
 - Keratin (AE1/AE3) very focal
 - No reactivity for myogenin, estrogen receptor (ER), and progesterone receptor (PR)
- Electron microscopy
 - Moderate amount of intermediate filaments and rough endoplasmic reticulum

- Occasional subplasmalemmal filaments with dense bodies
- Intracellular collagen fibrils readily identified
- No desmosomes, pinocytotic vesicles, basal lamina, or interdigitating processes were seen.
- Cytogenetics and molecular genetics:
 - RT-PCR for SYT-SSX1 and SYT-SSX2 negative in 18 cases evaluated
 - t(2;4)(q37.1;q31.3) chromosomal translocation in two cases:
 - Distinctive cytogenetic signature not being reported in any of the neoplasms considered in the differential diagnosis (see below) supports the notion that LGSSNMF is a separate biological entity likely characterized by a specific fusion gene.
 - Recurrent chromosomal translocation t(2;4)(q35;q31.1) resulting in a PAX3-MAML3 fusion protein reported:
 - Potent transcriptional activator of PAX3 response elements
 - LGSSNMF characterized by aberrant expression of genes involved in neuroectodermal and myogenic differentiation closely simulating developmental roles of PAX3

Differential Diagnosis

- Fibrosarcoma
- Malignant peripheral nerve sheath tumor
- Synovial sarcoma, monophasic
- Malignant triton tumor
- Teratocarcinosarcoma
- Solitary fibrous tumor
- Sinonasal glomangiopericytoma
- Cellular schwannoma
- Schneiderian papilloma
- Respiratory epithelial adenomatoid hamartoma

Treatment and Prognosis

- Surgery is the treatment of choice with/or without radiotherapy and included:
 - Surgical excision
 - Craniofacial resection in three cases for recurrent disease, including orbital exenteration in one case
- Clinical follow-up ranged from less than 1 year to 28 years (mean, 8.3 years):
 - Local recurrences reported in 44% of cases
 - Disease recurred locally from less than 1 year to a maximum of 9 years after treatment
 - Fourteen patients alive and two died from other causes
 - No known regional or distant metastases, and no patients died of disease

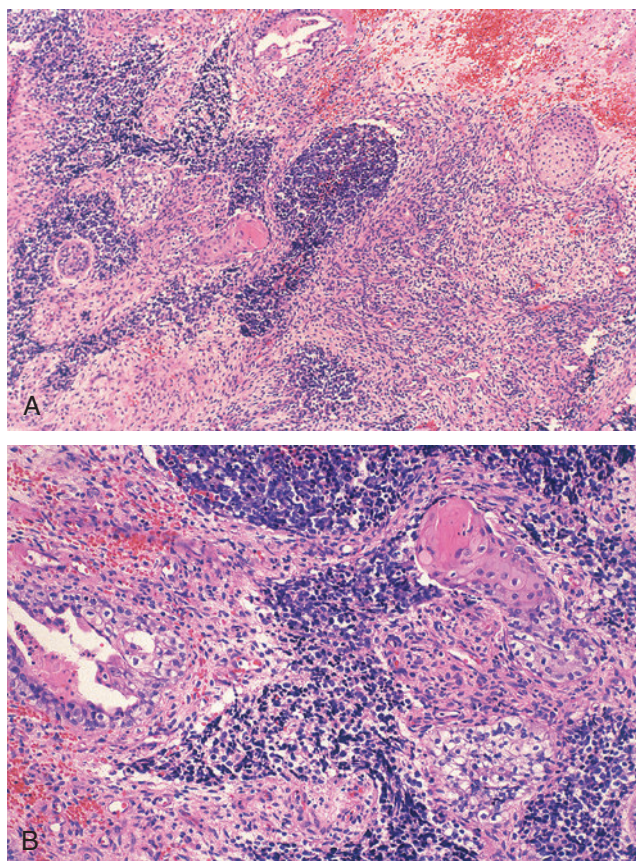


Fig. 3-110.

Sinonasal teratocarcinosarcoma characterized by variable admixture of epithelial (squamous nests), small round cell (neuroectodermal) infiltrate, and a variably cellular stroma composed of a spindle-shaped cells.

Sinonasal Teratocarcinosarcoma (Figs. 3-110 through 3-113)

Definition: High-grade malignant sinonasal tract neoplasm with combined histologic features of carcinosarcoma and teratoma.

Synonyms: Malignant teratoma; teratocarcinoma; teratoid carcinosarcoma

Clinical

- Uncommon tumor
- More common in men than in women; occurs over a wide age range with a median age of 60 years
- Generally presents as a rapidly growing neoplasm with symptoms primarily including nasal obstruction and epistaxis
- Most common site of involvement is the nasal cavity; other sites of involvement include the ethmoid and maxillary sinuses

- Radiology:
 - Nasal cavity mass or clouding/opacification of a sinus
 - Associated bone destruction may be seen
- No known cause

Pathology

Gross

- Friable to firm, red-brown mass

Histology

- All neoplasms are characterized by a combination of epithelial and mesenchymal tissue components and teratoid elements with heterogeneous or variegated architectural growth patterns.
- Epithelial components include:
 - Glandular or ductal structures lined by benign-appearing partly ciliated columnar epithelium
 - Nonkeratinizing immature (fetal-appearing) squamous epithelium with clear cytoplasm:
 - Important and characteristic histologic finding for the diagnosis
 - Supportive evidence of the teratoid nature of this neoplasm given its description in teratomas of other organ systems
 - Squamous epithelium without clear cells
 - Areas of squamous carcinoma and adenocarcinoma
 - Poorly differentiated malignant epithelial elements
 - Transitions among the above epithelial components can be seen.
- Mesenchymal components include:
 - Benign- and malignant-appearing fibroblasts or myofibroblasts
 - Rhabdomyosarcoma
 - Benign cartilage with an immature or “fetal” appearance and chondrosarcoma
 - Osteoid and/or osteosarcoma
- Teratoid components include:
 - “Fetal-appearing” clear cell squamous epithelium
 - Neuroepithelial component with neuroblastoma-like areas, neural rosettes, neurofibrillary matrix, and organoid structures
- No areas of seminoma, germinoma, choriocarcinoma, or embryonal carcinoma are present.
- Histochemistry:
 - Abundant glycogen as demonstrated by diastase-sensitive, PAS-positive material seen in clear cells
 - Mucin and PAS-positive material seen within the lumen and/or cytoplasm of the glandular component
- Immunohistochemistry: dependent on the cytologic components and includes:
 - Epithelial components: reactivity with cytokeratins, epithelial membrane antigen

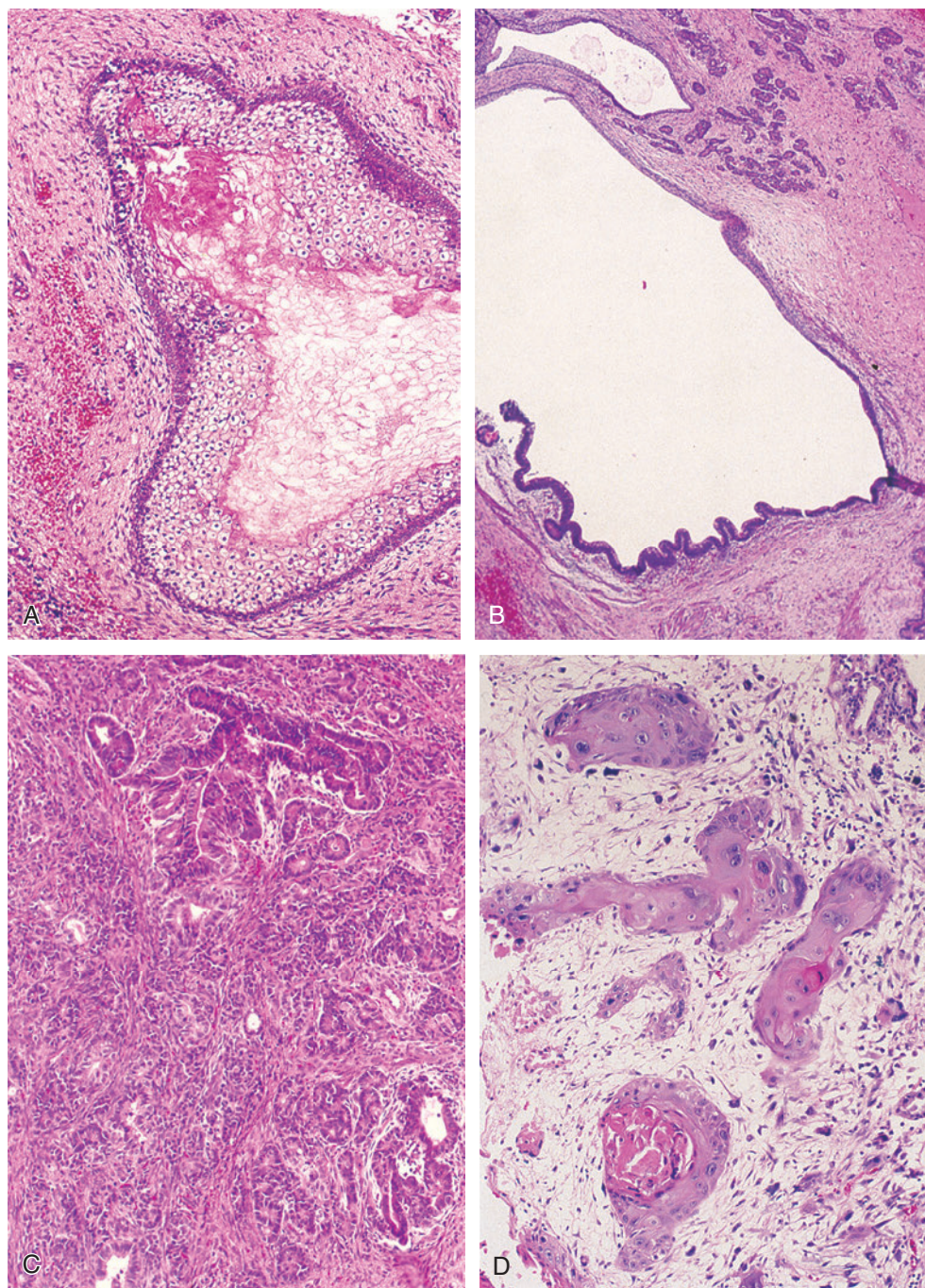


Fig. 3-111. Sinonasal teratocarcinosarcoma.

The epithelial component may include (A) nonkeratinizing clear cell squamous epithelium (fetal type) and (B) dilated glandular space lined by an epithelium demonstrating a transition from a bland-appearing cuboidal and columnar epithelium (benign) to a cellular columnar epithelium with hyperchromatic, stratified nuclei (malignant). C, Adenocarcinoma associated with a malignant fibroblastic stromal component. D, Squamous cell carcinoma admixed with a malignant pleomorphic mesenchymal component.

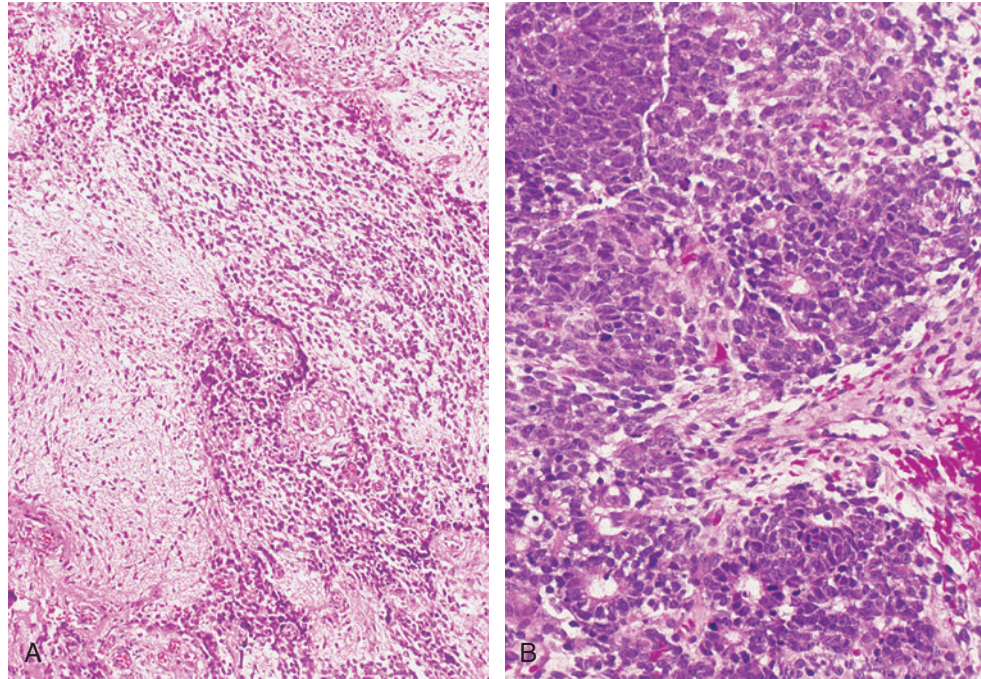


Fig. 3-112. Sinonasal teratocarcinosarcoma.

A, Neurofibrillary matrix associated with an immature and undifferentiated small round cell infiltrate. **B**, Neural rosettes associated with a neurosarcomatous cellular infiltrate.

- Mesenchymal components: vimentin, desmin, actins, myoglobin, myf-4, S100 protein, BER-EP4
- Neuroepithelial/primitive cell components: CD99, S100 protein, chromogranin, CD57 (Leu-7), neuron specific enolase, glial fibrillary acidic protein (GFAP)
- No immunoreactivity for alpha-fetoprotein and human chorionic gonadotropin (HCG)

Differential Diagnosis

- Squamous carcinoma and variants thereof (e.g., adenosquamous carcinoma)
- Adenocarcinoma
- Olfactory neuroblastoma
- Sinonasal undifferentiated carcinoma
- Carcinoma ex-pleomorphic adenoma and carcinosarcoma
- Malignant mesenchymoma
- Ewing sarcoma family of tumors
- Rhabdomyosarcoma
- Craniopharyngioma
- Germ cell tumors including yolk sac tumor (endodermal sinus tumor) and choriocarcinoma:
 - May rarely occur as primary neoplasm in the upper aerodigestive tract (UADT)
 - Yolk sac tumors of the UADT tend to occur in children:
 - Associated with elevated serum alpha-fetoprotein

- Choriocarcinoma of the UADT tend to occur in adults:
 - Associated with elevated serum HCG
- Histology similar to occurrence in more usual (gonadal) sites
- Treatment and prognosis:
 - For yolk sac tumor:
 - If possible, complete surgical resection
 - Combination radiation and chemotherapy (platinum-based)
 - Distant visceral and nodal metastases occur.
 - For choriocarcinoma:
 - Chemotherapy for germ cell malignant tumors
 - Uncertain outcome

Treatment and Prognosis

- Aggressive therapy, including radical surgical extirpation and irradiation
- Highly malignant neoplasm with an average survival of <2 years
- Recurrence of tumor is common with extensive local invasion
- Tendency for extensive local invasion including soft tissues, bone, orbit, and central nervous system
- Metastatic disease occurs primarily to cervical lymph nodes.

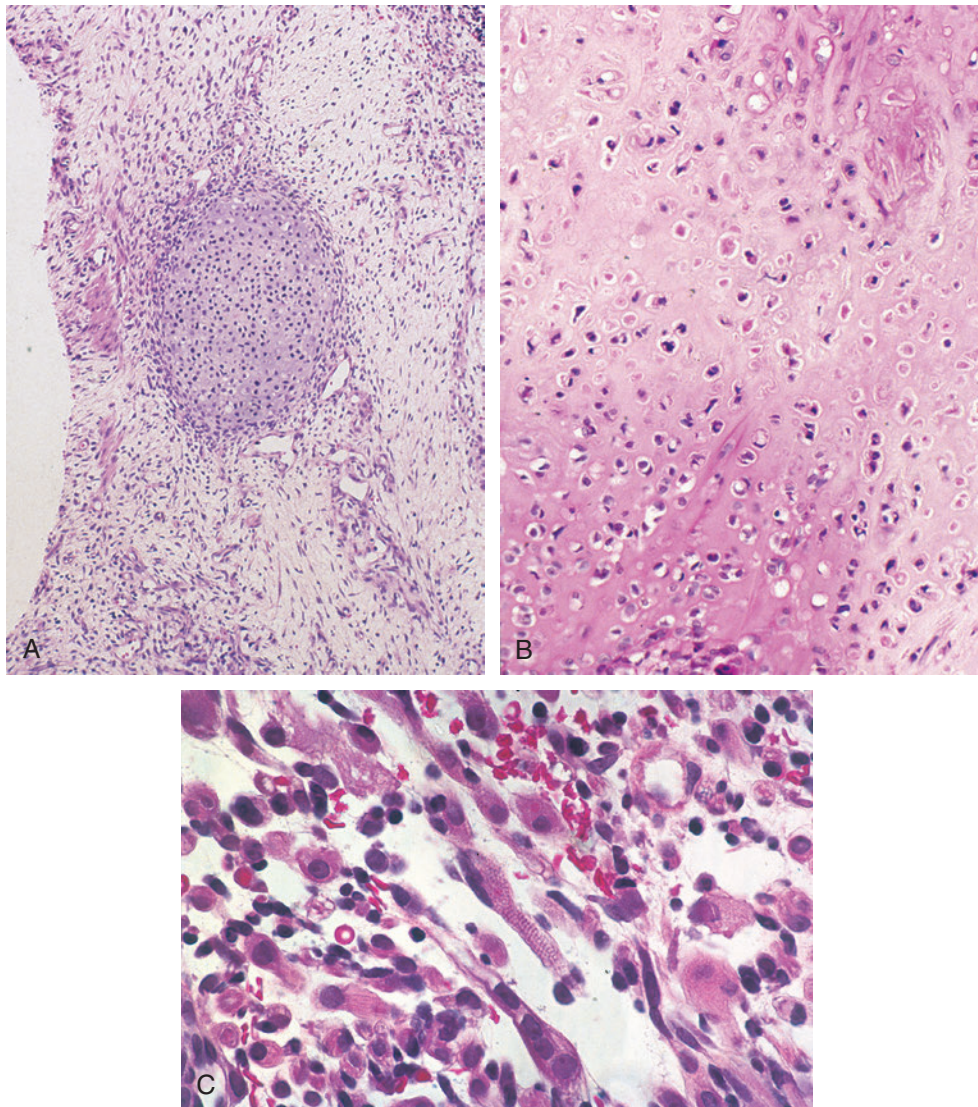


Fig. 3-113. Sinonasal teratocarcinosarcoma.

Aside from a spindle cell (benign and/or malignant) stromal proliferation, the mesenchymal components of sinonasal teratocarcinosarcoma may include (A) immature cartilaginous nest; (B) chondrosarcoma; and (C) rhabdomyosarcoma including strap cells and identifiable cross striations.

SECONDARY TUMORS

(Fig. 3-114)

Definition: Tumors involving the sinonasal tract that originate from separate (noncontiguous) primary sites excluding hematolymphoid malignancies (i.e., lymphomas and leukemias).

Clinical

- Rare occurrence
- More common in men than in women; occurs over a wide age range
- Symptoms similar to primary sinonasal tumors:
 - Nasal obstruction, epistaxis, headache, pain, visual disturbances, facial swelling, cranial nerve deficits
- Metastatic tumors to the sinonasal tract may represent the initial manifestation of disease from an otherwise clinically occult primary tumor (e.g., renal cell carcinoma); more often, metastasis to the upper aerodigestive tract is part of widely metastatic disease.
- May be solitary or multifocal lesions
- Most common to maxillary sinus but also may involve multiple sinuses and the sphenoid sinus

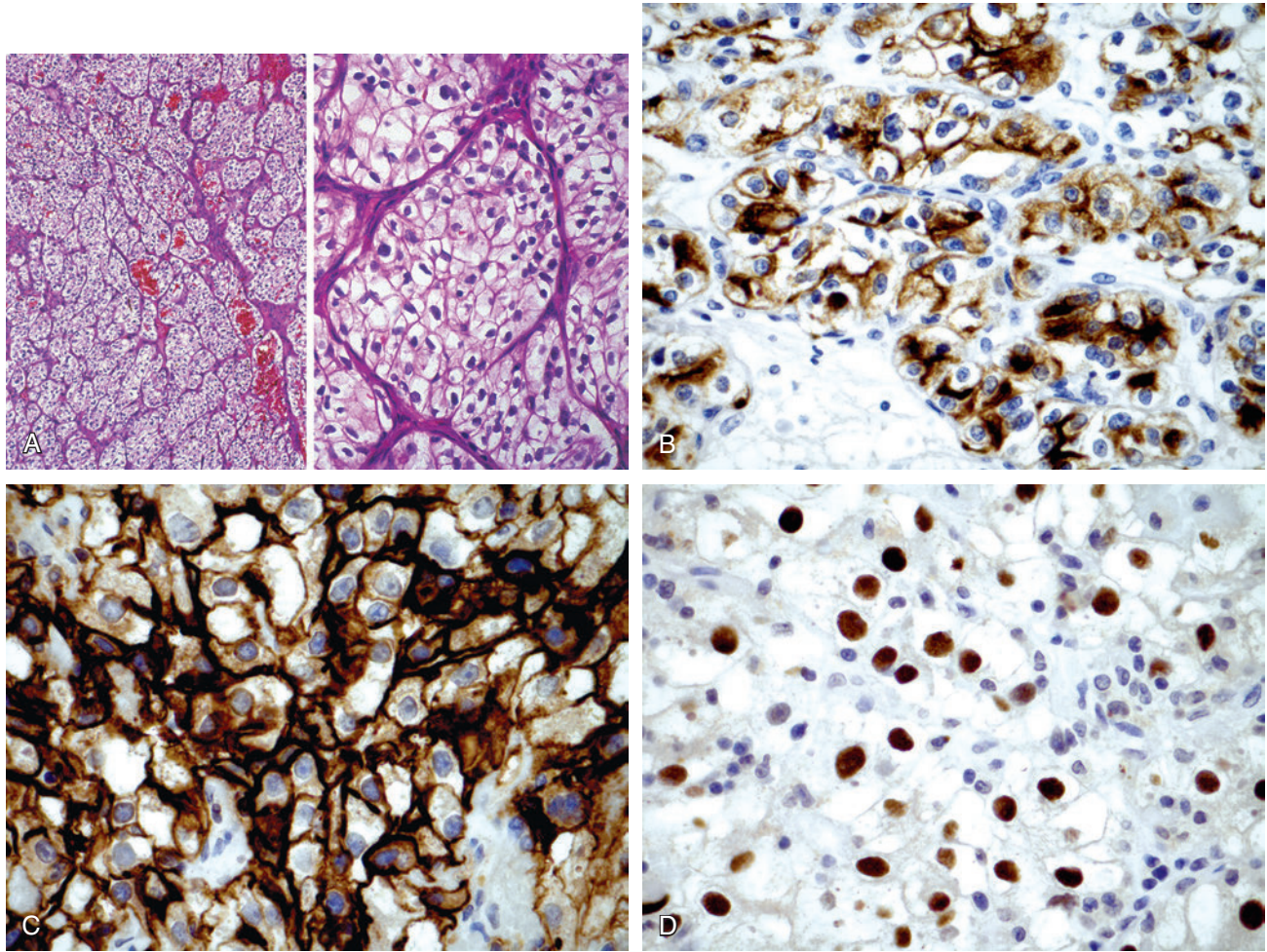


Fig. 3-114. Metastatic renal cell carcinoma to the maxillary sinus.

A, The histology of this tumor including the presence of cell nests separated by fibrovascular stroma composed of cells with clear cytoplasm and distinct cell membranes with intraluminal red blood cells is unusual for a primary sinonasal tract tumor and should engender the consideration of a metastasis to this site from a separate (distant) primary tumor. This consideration was relayed to the clinicians, and in the patient work-up an occult primary renal tumor was found. The histology of the renal tumor and the sinonasal tumor were identical, and the diagnosis of a primary renal cell carcinoma metastatic to the sinonasal tract was made. Immunohistochemical findings of the sinonasal tract tumor (prior to the discovery of the primary renal tumor) included reactivity for **(B)** renal cell carcinoma (RCC) marker and **(C)** CD10 and **(D)** PAX8 (nuclear) supporting the diagnosis of metastatic renal cell carcinoma.

TABLE 3-13 Secondary Tumors to the Sinonasal Tract

Primary Tumor	Frequency	Immunohistochemistry*
Kidney	40%	CD10, RCC, PAX8 positive
Lung	9%	Napsin A, TTF-1 positive
Breast	8%	Mammaglobin, BRST-2 positive
Thyroid	8%	Thyroglobulin, TTF-1, PAX8 positive
Prostate	7%	Prostein, PSA, PSAP positive
Miscellaneous	28%	

*Markers in conjunction with light microscopy confirm diagnosis. CAIX, Carbonic anhydrase IX; PSA, prostate specific antigen; PSAP, prostatic acid phosphatase; RCC, renal cell carcinoma marker; TTF-1, thyroid transcription factor 1.

- Although virtually every conceivable malignancy may metastasize to the upper aerodigestive tract, the most common primary tumor metastatic to this region is renal cell carcinoma (Table 3-13).
- Differential diagnosis for metastatic renal cell carcinoma to the sinonasal tract includes:
 - Sinonasal renal cell-like adenocarcinoma (SRCLA):
 - Represents a rare sinonasal neoplasm, which is a histologic mimic of renal cell carcinoma (RCC) in patients without evidence of a primary RCC
 - More common in woman than in men (3:1); occurs over a wide age range from 22 to 69 years (mean 46 years)

- Histology:
 - Uniformly composed of clear cells forming solid or glandular patterns
 - Tumor cells are cuboidal to polyhedral; spindle-shaped cells may be present.
 - Bland cytomorphology lacking significant nuclear pleomorphism increased mitotic activity or necrosis; moderate nuclear pleomorphism may be present.
 - No perineural or lymph-vascular invasion
 - No evidence of squamous differentiation
- Histochemical staining:
 - Absence of epithelial mucin
- Immunohistochemistry staining:
 - Positive for CK7 (4/4), CK20 (focal 1/4), S100 (1/4), CD10 (1/2)
 - Negative for vimentin, RCC marker thyroglobulin, actin, calponin
- Treatment primarily with surgery with or without adjuvant radiotherapy (RT)
- All patients are disease free at 2, 4, 5, and 8 years after diagnosis.
- Difficulties in categorizing a given neoplasm within known primary tumors for a given site should prompt consideration for the possibility of metastatic disease originating from a distant site.
- Immunohistochemical staining is often required to confirm the diagnosis of a metastasis to the sinonasal tract (see Table 3-13).

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Non-Neoplastic Lesions of the Pharynx

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE PHARYNX (Box 9-1)

BOX 9-1 Classification of Non-Neoplastic Lesions of the Pharynx, Including Naso-, Oro-, and Hypopharynx

Nasopharyngeal Cysts

- Rathke pouch cyst
- Tornwaldt cyst
- Dermoid cyst
- Retention cysts
- Others

Hamartomas, Choristomas, and Teratomatous Lesions

- Nasopharyngeal hamartoma
- Heterotopic CNS tissue
- Nasopharyngeal dermoid
- Lymphangiomatous polyp
- Salivary gland anlage tumor

Infectious and Related Diseases and Lesions

- Viral (HPV, EBV, HIV, CMV, HSV), including infectious mononucleosis, HIV-associated lymphoid hyperplasia of Waldeyer ring; others
- Fungal
- Bacterial including gonorrhea, syphilis, bacillary angiomatosis, others
- Protozoal
- Sarcoidosis
- Others

Reactive, Inflammatory, and Tumor-like Lesions

- Tangier disease
- Others

NASOPHARYNGEAL CYSTS

- Nasopharyngeal cysts are divided into congenital cysts and acquired cysts:
 - Congenital cysts of the nasopharynx include:
 - Rathke pouch cyst
 - Tornwaldt cyst
 - Dermoid cyst
 - Acquired cysts of the nasopharynx include:
 - Midline and lateral retention cysts

Rathke Pouch (Cleft) Cyst (Figs. 9-1 through 9-3)

Definition: Congenital cystic dilatation of Rathke cleft due to failure to obliterate the lumen between the anterior lobe of the pituitary and the pars intermedia.

Embryology and Anatomy

- Rathke pouch is an ectodermally derived outpocketing arising from the roof of the primitive oral cavity lying superior to the buccopharyngeal membrane that develops around the third week of gestation and grows toward the brain.
- Rathke pouch ultimately forms the anterior lobe of the pituitary gland.
- By the fifth week of gestation, this pouch has elongated and become constricted at its attachment to the oral epithelium and comes into contact with the infundibulum, which ultimately develops into the posterior lobe of the pituitary gland.
- The posterior part of Rathke pouch develops into the pars intermedia:
 - Lumen between the anterior lobe and the pars intermedia gradually obliterates; however, if the lumen does not close, a cleft is formed (Rathke cleft) that may become cystic, developing a Rathke cyst.

Clinical

- Rathke pouch cyst represents approximately 2% of all lesions of the sella turcica.
- Typically, Rathke pouch cyst is an asymptomatic, congenital lesion that is incidentally found in routine autopsies.
- Symptomatic cysts occur but are uncommon:
 - Symptomatic cysts are more common in women than in men and occur over a wide age range but are most common in the fourth decade of life.
 - Symptoms include headaches, visual disturbances, nausea, vomiting, pituitary-related abnormalities, including galactorrhea, amenorrhea, diabetes insipidus, acromegaly, and meningeal irritation.
 - Sudden onset of severe headache or sudden increase in headache severity may occur and has been associated with hemorrhage into the cyst, a

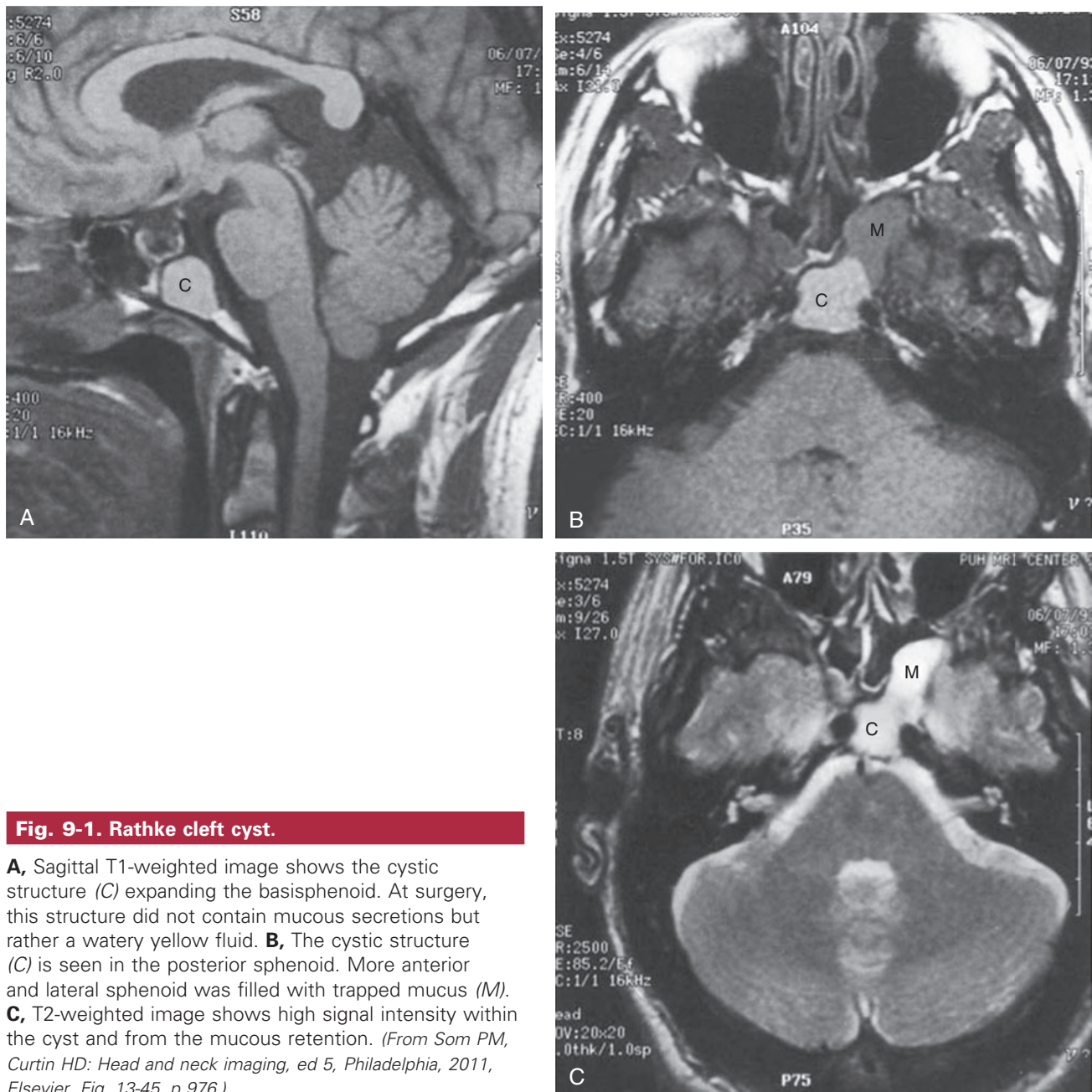


Fig. 9-1. Rathke cleft cyst.

A, Sagittal T1-weighted image shows the cystic structure (C) expanding the basisphenoid. At surgery, this structure did not contain mucous secretions but rather a watery yellow fluid. **B**, The cystic structure (C) is seen in the posterior sphenoid. More anterior and lateral sphenoid was filled with trapped mucus (M). **C**, T2-weighted image shows high signal intensity within the cyst and from the mucous retention. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 13-45, p 976.)

presentation that mimics the clinical syndrome of pituitary tumor apoplexy, leading to the designation of Rathke cleft cyst apoplexy.

- Increased serum prolactin has been reported in Rathke pouch cysts.
- Rare association with Klinefelter syndrome has been reported.
- Hybrid lesions, including Rathke cleft cyst and pituitary adenoma, have been reported.
- Radiology:
 - Well-circumscribed, round, or lobulated intrasellar mass:

- Wall of cyst is generally thin.
- Cyst content usually similar to cerebrospinal fluid
- More complex cysts show increased density with septa partitioning the cystic portion.
- Most lesions have intrasellar and suprasellar components although lesions confined to the sella turcica can be found, as well as suprasellar lesions and intrasphenoidal lesions may occur.
- Usually lacks associated calcifications:
 - Absence of calcifications assists in differentiating a Rathke pouch cyst from a

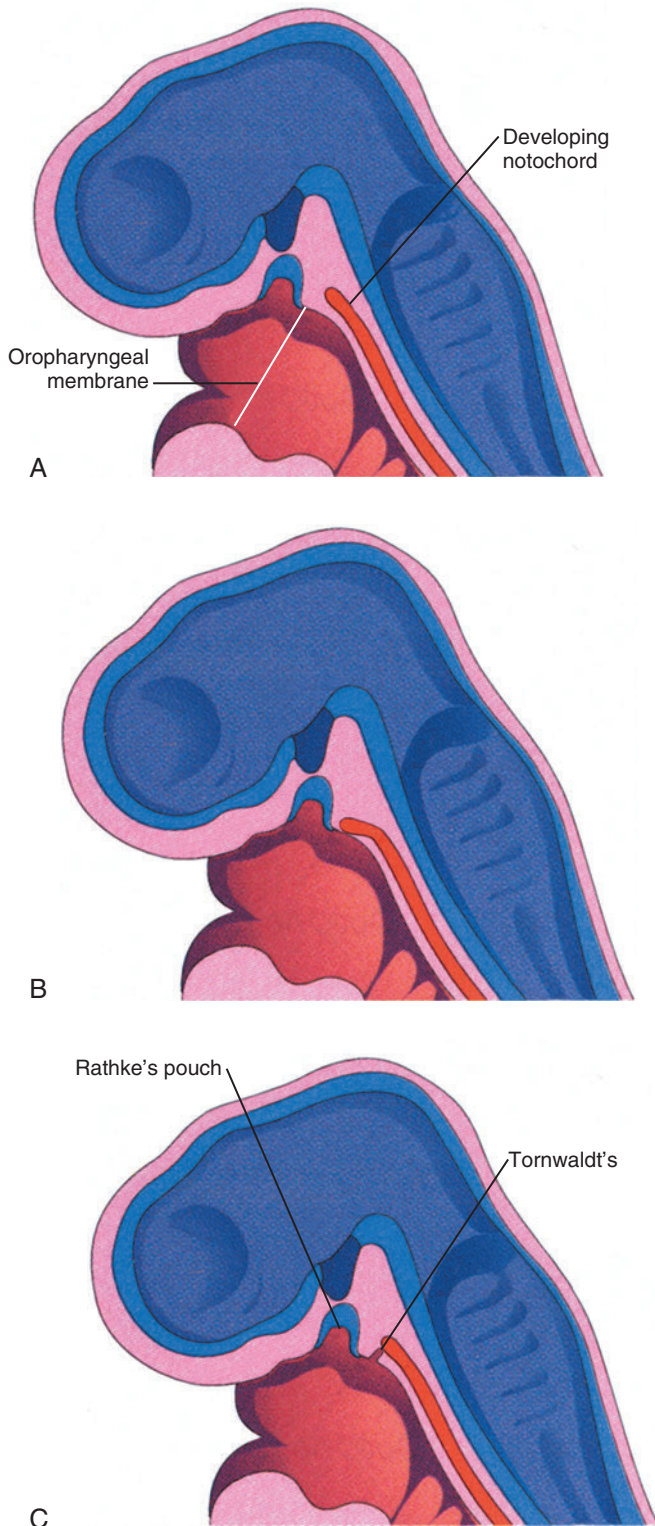


Fig. 9-2. Embryologic development of Rathke pouch cyst and Tornwaldt cyst.

A, Sagittal drawing of the developing pharynx. The level of the oropharyngeal membrane is shown. This membrane separates the ectodermally derived mucosa from the endodermally derived mucosa. The location of the developing notochord is shown in the mesoderm that will eventually become the clivus. **B**, Sagittal drawing shows the normal ventral migration of the notochord to touch the pharyngeal mucosa. **C**, Sagittal drawing shows Tornwaldt sinus or pit that develops if the notochord attaches to the pharyngeal mucosa and drags it dorsally as the notochord migrated back to its normal location. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-66, p 1791.)

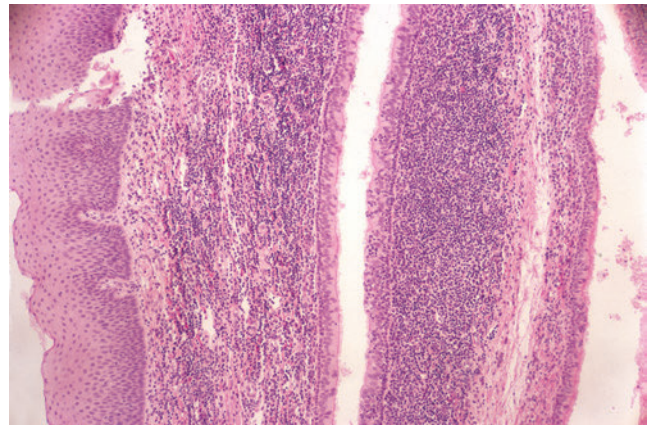


Fig. 9-3. Rathke pouch cyst.

Pharyngeal submucosal cyst lined by a ciliated respiratory epithelium.

Pathology

Histology

- Cysts are lined by cuboidal to columnar epithelium with or without cilia; goblet cells can be found and foci of squamous epithelium may be present.
- Mineralization (calcifications), cholesterol granulomas, and xanthomatous cells can be found.
- Immunohistochemistry:
 - Epithelial cells are reactive for cytokeratins and epithelial membrane antigen (EMA) with variable reactivity for S100 protein, chromogranin, glial fibrillary acidic protein, and pituitary peptide markers.

Differential Diagnosis

- Rathke pouch cyst, which is localized to the area of the sella turcica, contrasts to Tornwaldt cyst located in the posterior pharynx.

- craniopharyngioma; craniopharyngiomas are characterized by the presence of calcifications.
- Rare examples of Rathke pouch cyst may be associated with mineralization.

Treatment and Prognosis

- Drainage of the cyst with partial removal of the cyst wall (for diagnosis) via a transsphenoidal approach is the preferred treatment.
- Endoscopic endonasal resection used as a safe and effective approach in treatment
- 5% recurrence rate has been reported.

Tornwaldt Cyst

(see Figs. 9-2 and 9-4)

Definition: Developmental anomaly of the posterior superior nasopharynx, in which there is persistence of the pharyngeal-to-notochord contact, creating a potential space into where there is in-growth of pharyngeal tissue.

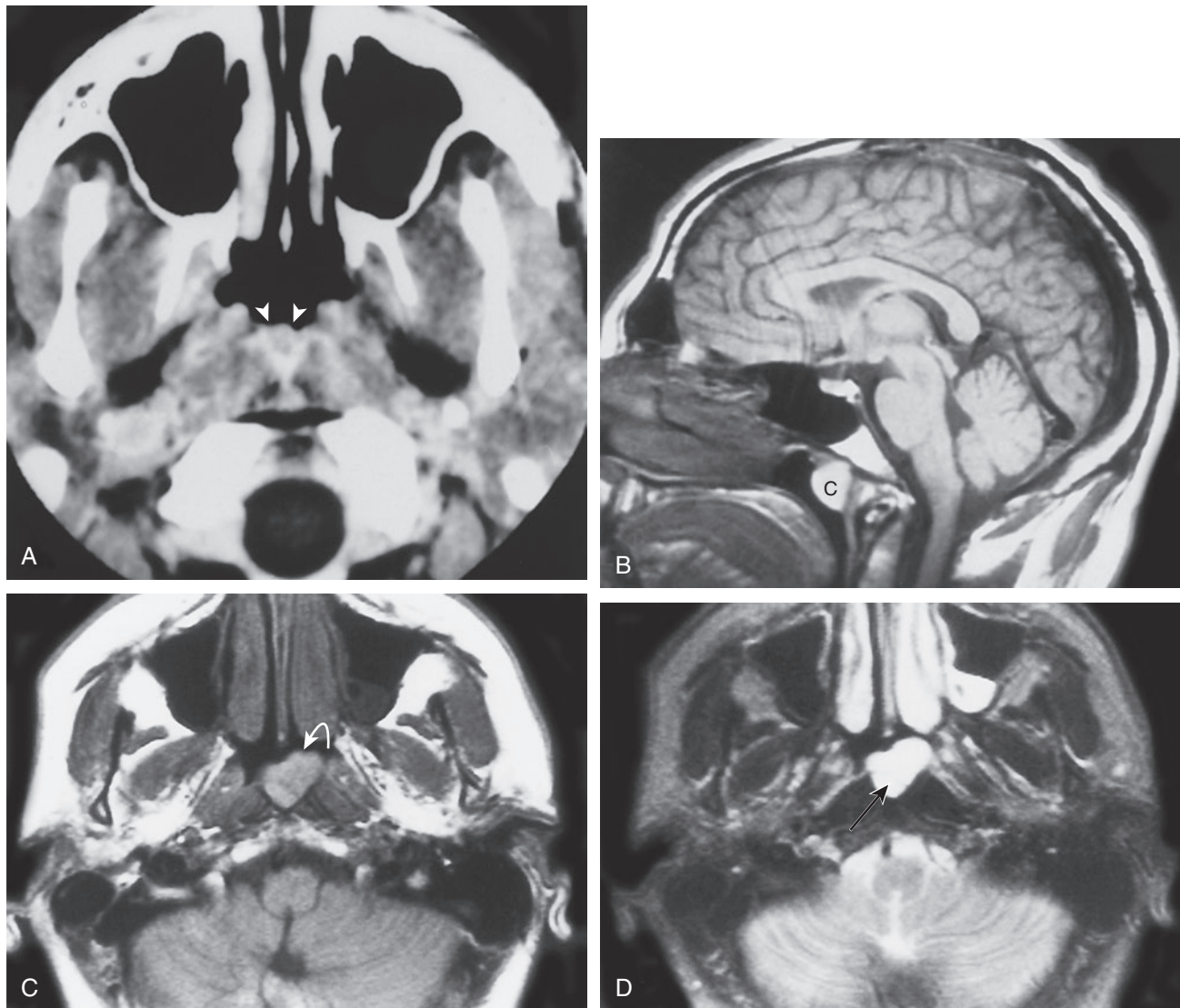


Fig. 9-4. Tornwaldt cyst.

A, CT scan through the upper nasopharynx demonstrates a midline Tornwaldt cyst (*arrowheads*). Note that its density is similar to that of the surrounding muscle. The high density of this cyst is probably related to its high protein concentration. **B**, Sagittal T1-weighted MR scan through the upper nasopharynx demonstrates a high signal intensity Tornwaldt cyst (*c*). The high intensity is a result of the high protein concentration within the cyst. This shortens the T1 relaxation time sufficiently to produce an increase in intensity on T1-weighted images. **C**, Axial T1-weighted noncontrast MR image shows a well-delineated lesion (*arrow*) with increased signal intensity located within the nasopharynx. This was a Tornwaldt cyst. **D**, There is increased signal within the lesion on the T2-weighted sequence, which is consistent with the cystic nature of the mass. Note the internal septation present within the lesion (*arrow*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-68, p 1792.)

Synonyms: Pharyngeal bursa; Tornwaldt bursa; when infected this is referred to as Tornwaldt disease or syndrome; also spelled Thornwald cyst.

Embryology and Anatomy

- Pharyngeal bursa is a sac-like depression on the posterosuperior nasopharyngeal wall that forms around the sixth week of gestation when the cephalic portion of the notochord comes into close contact with the foregut:
 - Contact between the pharynx and the notochord is usually transient but may persist in adults, in whom the pharyngeal respiratory epithelium may grow, creating a potential space that may be walled off, creating the Tornwaldt cyst.

Clinical

- Tornwaldt cyst is uncommon.
- No gender predilection
- These cysts may occur at any age, although most are diagnosed in the second to fourth decades of life.
- They may be asymptomatic, but when infected, symptoms include drainage into the nasopharynx of purulent material; in addition, symptoms may include headaches, otalgia, and fullness of the ear, halitosis, and neck soreness or stiffness.
- Cysts are located in the midline of the posterior nasopharyngeal wall but may be found slightly off midline:
 - Usually extends upward and backward toward the occipital bone
 - Tornwaldt cyst lies caudal to the location of Rathke cleft cyst.
- Endoscopic appearance of these lesions is that of a submucosal, firm, and smooth mass; adjacent mucosa may be erythematous.
- Radiology:
 - Appear as a mass high on the posterior nasopharyngeal wall; air may be seen in the tract extending from the midline posterior nasopharynx toward the occipital tubercle.
 - On CT scan, the cyst may contain fluid of similar density as cerebrospinal fluid and does not enhance after contrast; calcifications may be identified.

Pathology

Histology

- Cysts are submucosal; the lining includes a ciliated respiratory epithelium; squamous metaplasia is present in the setting of an infected cyst.

Differential Diagnosis

- Rathke pouch cyst, which is localized to the area of the sella turcica, contrasts to Tornwaldt cyst located in the posterior pharynx.

Treatment and Prognosis

- Surgical excision is the preferred treatment; incomplete excision will result in recurrence.
- Antibiotic therapy is used preoperatively for patients with infected cysts.

Other Nasopharyngeal Cysts

- Acquired retention cysts of the nasopharynx of seromucinous gland origin, as well as lymphoid crypt origin, can occur in midline or lateral locations.

PHARYNGEAL HAMARTOMAS, CHORISTOMAS, AND TERATOMATOUS LESIONS

Definitions

Hamartoma: Non-neoplastic developmental anomaly caused by excessive growth of normal cells and/or tissue indigenous to its site of occurrence. Hamartomatous lesions may occur in all head and neck sites but tend to predilect to the nasal cavity, paranasal sinuses, and the nasopharynx.

Choristoma (heterotropia, ectopia, aberrant rest): Non-neoplastic developmental anomaly of essentially normal tissue but with the tissue elements being foreign to its anatomic location

Nasopharyngeal Hamartoma

Clinical

- Uncommon lesion
- Reports of nasopharyngeal hamartomas are often included with nasal hamartomas, so a true incidence of hamartomas exclusively limited to the nasopharynx cannot be determined.
- No gender predilection; occur in adults and in children
- In adults, the clinical presentation may include nasal obstruction, difficulty breathing, post-nasal drainage, and epistaxis.
- In pediatric patients, the clinical presentation may include noisy breathing, stridor, feeding difficulties, and transient cyanosis.

Pathology

Gross

- Polypoid to cauliflowerlike, circumscribed, and lobulated masses partially or completely filling the nasopharynx and measuring from 1 to 4 cm in greatest dimension.

Histology

- May be composed of epithelial and/or mesenchymal components:
 - Epithelial hamartoma:
 - Minor salivary gland elements (seromucous glands, ducts, acini)
 - Epithelium (squamous and columnar cells)
 - Mesenchymal components:
 - Blood vessels, lymphoid tissue, fibrous stroma
- Metaplastic components such as bone may be present.

NOTE: The epithelial hamartomas may be histologically identical to the respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma of the sinonasal tract (see Section 1 for more complete discussion).

Differential Diagnosis

- Teratoma
- Epithelial neoplasms:
 - Adenocarcinoma
 - Papilloma, carcinoma
- Mesenchymal neoplasms:
 - Hemangioma, angiosarcoma, others

Treatment and Prognosis

- Simple excision is curative.

Pharyngeal/Nasopharyngeal Central Nervous System Heterotopias

Definition: Presence of central nervous system (CNS) tissue as a mass lesion in the nasopharynx without connection to the cranial cavity.

Clinical

- Rare lesion that may occur in association with congenital anomalies

Pathology

Histology

- Histology of these lesions is similar to heterotopic CNS tissue of the nasal cavity, but in contrast to the nasal lesions, those of the nasopharynx may include the presence of ependymal elements as well as intracytoplasmic melanin.

Treatment and Prognosis

- Simple excision is curative.

Nasopharyngeal Dermoid

(Fig. 9-5)

Definition: Developmental (congenital) anomaly predominantly composed of ectodermal and mesodermal tissue but lacking endodermal-derived tissues.

NOTE:

- Absence of endodermal-derived structures and presence of limited heterogeneity of tissue types argue against inclusion as a teratoma.
- The fact that these lesions contain skin, a tissue type not normally found in the nasopharynx, suggests that these lesions may be better classified as a choristoma than a hamartoma, and possibly of first branchial arch origin; some authors argue that these lesions are best classified as a subset of benign teratoma.

Synonym: Hairy polyp

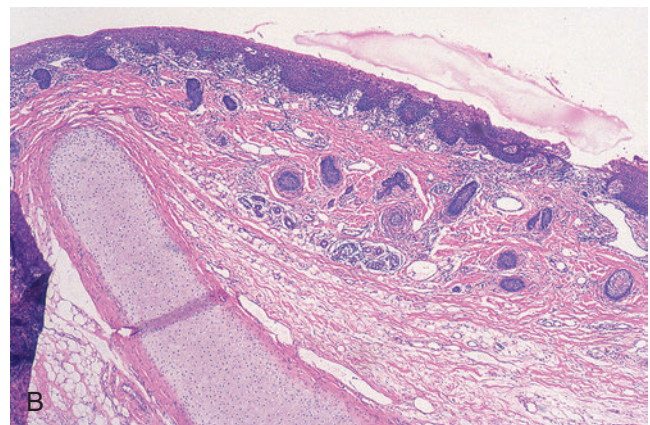


Fig. 9-5. Nasopharyngeal dermoid (hairy polyp).

A, Polypoid solid lesion with identifiable hairs on the surface. **B,** Histology includes a combination of ectodermal and mesodermal tissues including skin (keratinizing squamous epithelium), cutaneous adnexal structures, including hair follicles and sebaceous glands, and cartilage.

Clinical

- Predilection for female infants with majority of the cases occurring in the infantile period
- Symptoms include difficulties in breathing, swallowing, or sucking.
- May arise in other areas of the pharynx including oropharynx, as well as in association with the eustachian tube and the middle ear

Pathology**Gross**

- Polypoid, predominantly solid but partially cystic lesions; may be pedunculated or sessile

Histology

- Combination of various ectodermal and mesodermal tissues, including:
 - Skin (keratinizing squamous epithelium) and cutaneous adnexa
 - Cartilage, bone, muscle (striated or smooth), fibrous tissue, mature adipose tissue, and vascular tissue
 - Lymphoid aggregates may be identified.
- Polypoid lesions covered by skin with identification of hair follicles and sebaceous glands within the submucosa and identification of elastic cartilage:
 - These histologic findings identified in a lesion of the ear have suggested to some authors that these lesions are of branchial cleft origin, representing congenital accessory auricles akin to accessory tragus.

Differential Diagnosis

- Teratoma:
 - Absence of endodermally derived tissue and absence of the wide variety of tissue types usually seen in teratoma will allow for distinguishing these lesions.

Treatment and Prognosis

- Simple surgical excision is curative.

Lymphangiomatous Polyp of the Tonsil (Figs. 9-6 and 9-7)

Definition: Non-neoplastic developmental lesion composed of tissue elements native to the nasopharynx and categorized as a hamartoma.

Synonym: Lymphoid polyp

Clinical

- Uncommon lesion
- No gender predilection; occur over a wide age range from the first decade to the seventh decade with a mean age of occurrence at 25 years

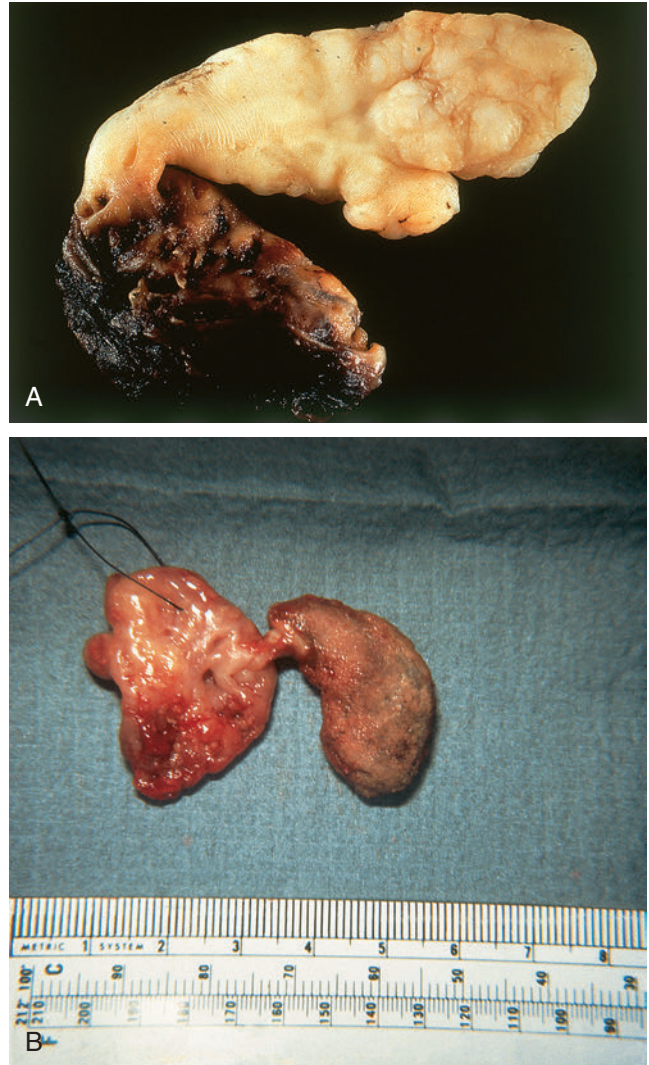


Fig. 9-6. Tonsillar lymphangiomatous polyp.

Pedunculated polyps with solid (A) and partially cystic (B) appearance.

- Clinical presentation includes dysphagia, sore throat, and the sensation of a mass lesion in the throat:
 - Symptoms may be present from a few weeks to years.
- Majority are of palatine tonsil origin but occasionally may originate from the nasopharynx or from the nasopharyngeal tonsil (i.e., adenoids):
 - Unilateral lesions without side predilection
- Clinical examination, many of these lesions are felt to be neoplasms

Pathology**Gross**

- The majority are polypoid or pedunculated with a smooth external surface, spongy to firm consistency that on cut section have a white, tan, or yellow

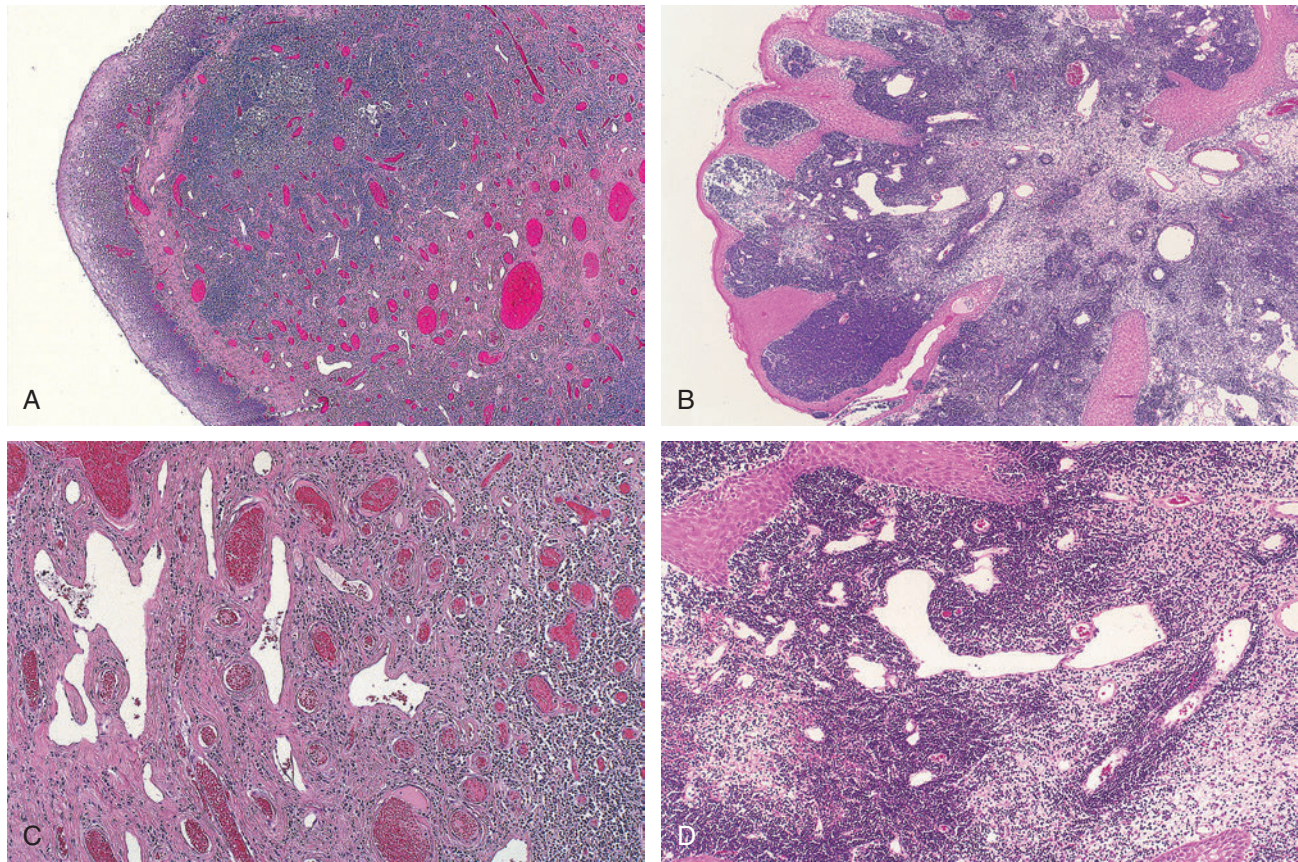


Fig. 9-7. Tonsillar lymphangiomatous polyp.

Polypoid lesions in which the surface squamous epithelium is rounded (**A**) or bosselated (**B**) with a submucosal proliferation of dilated lymphatic vascular channels and lymphoid cell infiltrate with clear demarcation from the surface epithelium (**A**) intimate association with the surface epithelium (**B**); **C** and **D**, Lymph-vascular channels (which are endothelial cell-lined) vary in size and shape and are variably associated with a fibrous connective tissue component and lymphocytic cell infiltrate.

appearance measuring from 0.5 to 3.8 cm in greatest dimension.

- Some lesions are sessile.

Histology

- Covered by squamous or respiratory epithelium composed of a submucosal proliferation of dilated lymphatic vascular channels and varying amounts of fibrous connective tissue.
- Vascular components are thin-walled and usually contain proteinaceous fluid and mature lymphocytes.
- In addition, mature adipose tissue may be present, and prominent fibrosis may dominate in any given lesion.
- Some lesions may be exclusively or predominantly papillary with a lymphoid and edematous stroma.
- Additional findings that can be identified include epithelial hyperplasia, hyperkeratosis, and dyskeratosis without epithelial dysplasia and nested epitheliotropism; the latter includes the presence of mature lymphocytes packed into rounded intramucosal spaces.
- Special stains are not required for the diagnosis.
- Immunohistochemistry:
 - Vascular endothelial markers, including Factor VIII-related antigen, CD31 and CD34, as well as podoplanin (D2-40), present in the endothelial and subendothelial cells of the vascular channels.
 - Smooth muscle actin reactivity can be found within the vascular walls.
 - Lymphoid component shows reactivity for B-cell (CD20) and T-cell (CD3) markers.

Differential Diagnosis

- Nasopharyngeal angiofibroma:
 - Occurs in adolescent males
 - Typically presents with epistaxis due to its rich blood supply that often attains large sizes with extensive growth and even bone erosion
 - Histologically have a cellular stroma composed of stellate fibroblasts and staghorn-shaped, thin-walled vascular structures, the latter typically lacking or with an attenuated smooth muscle component
 - Fibroblastic cells are immunoreactive for β -catenin
 - In contrast to nasopharyngeal angiofibromas, the lymphangiomatous polyps may occur in women and tend to have a relatively paucicellular fibrous stroma with a prominent lymphoid component.
- Fibroepithelial polyps
- Papillomas
- Epithelial neoplasms characterized by the presence of an exophytic surface epithelial proliferation of multilayered bland epithelial cells and lacking an associated lymphoid component
- Majority of squamous papillomas lack surface keratin, although occasionally prominent (hyper) keratosis may be identified
- Rare examples of Schneiderian-type papillomas may occur in the pharynx (oro- and nasopharynx), but the histology of the lesions contrast so distinctly

from the lymphangiomatous polyps, making differentiation straightforward.

- Lymphangioma:
 - Neoplasm of endothelial-lined lymphatic spaces that are histologically characterized by the presence of widely dilated and irregularly appearing vascular channels, features not usually associated with lymphangiomatous polyps

Treatment and Prognosis

- Simple surgical excision usually in the form of a unilateral tonsillectomy is curative.

Salivary Gland Anlage Tumor (SGAT) (Fig. 9-8)

Definition: Benign tumor with mixed epithelial and mesenchymal elements recapitulating early stages in the embryology of salivary glands between the fourth and eighth weeks of development.

Synonym: Congenital pleomorphic adenoma

Clinical

- Rare lesion with fewer than 20 cases reported in the literature
- Male predilection; usually presents in immediate neonatal period or in early infancy (by age of 6 weeks)
- Symptoms include respiratory distress, nasal airway obstruction, and/or feeding difficulties.

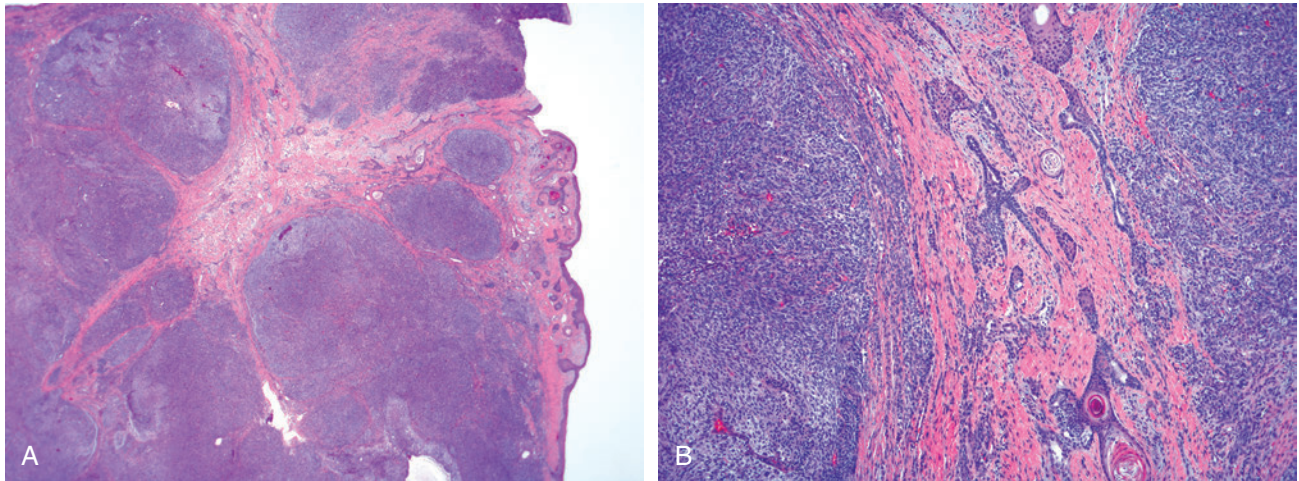
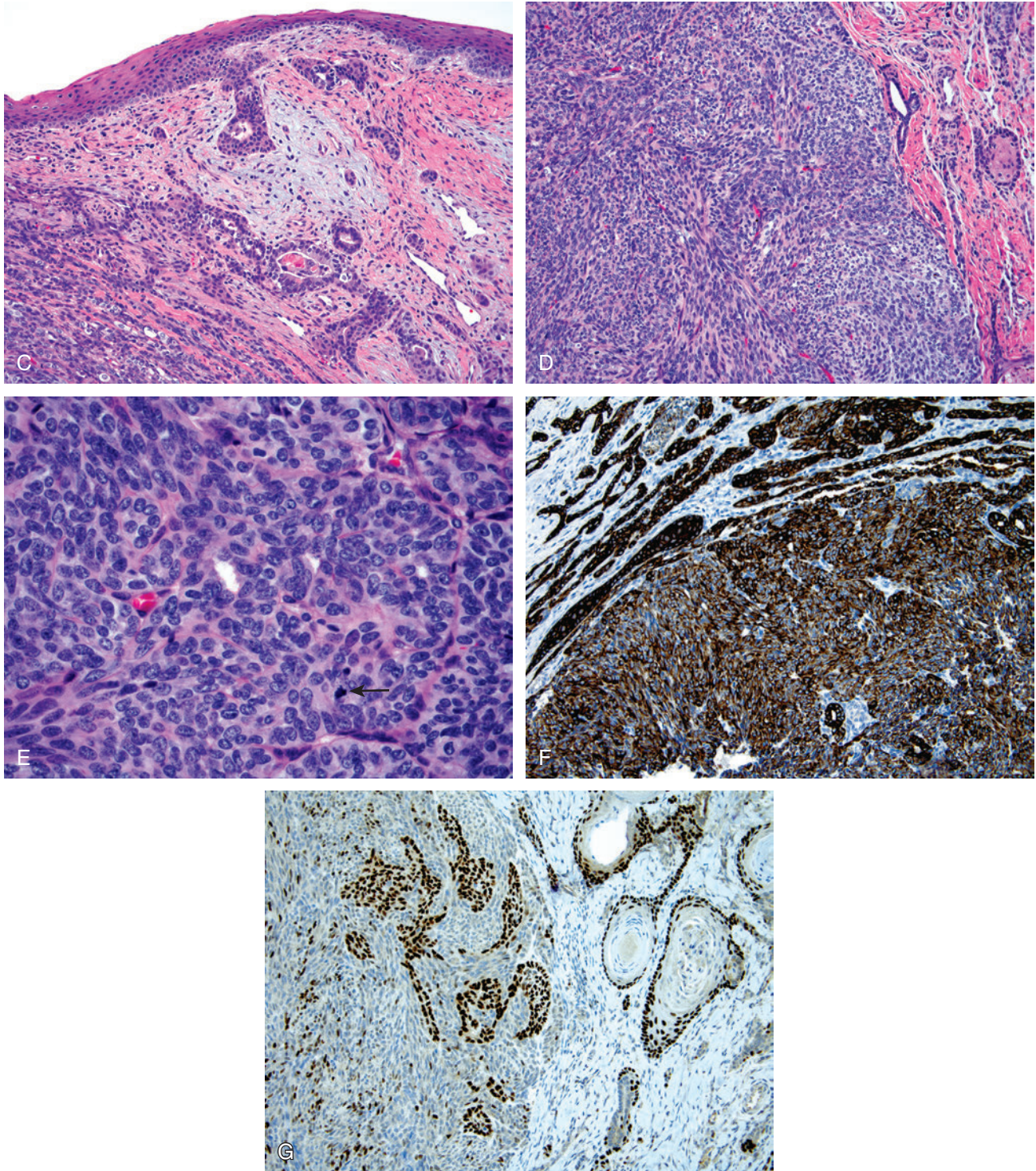


Fig. 9-8. Salivary gland anlage tumor (SGAT).

A, At low magnification, SGAT is characterized by multiple submucosal solid nodules separated by less cellular stroma and network of delicate linear and branching small duct-like structures and nests of solid or cystic squamous epithelium with variable (internodular) fibromyxoid stroma. **B**, Duct-like structures and squamous nests (with and without keratinization) are more prominently seen toward periphery of (and in between) the cellular stromal nodules.

Continued

**Fig. 9-8, cont'd**

C, Focally, duct-like structures may be connected to surface epithelium. **D**, Cellular nodule composed of fusiform cells forming short fascicles or trabecular growth pattern. **E**, Stromal cells are composed of ovoid to spindle-shaped nuclei with uniform dispersed nuclear chromatin and eosinophilic cytoplasm with indistinct cell borders; a mitotic figure is present (*arrow*). **F**, Cytokeratin (AE1/AE3) immunoreactivity is present in the epithelial components (squamous nests and duct-like structures) and mesenchymal component. **G**, Variable p63 reactivity is present in the epithelial components (squamous nests and duct-like structures) and mesenchymal component.

- Often located at or near midline in the nasopharynx:
 - Uniform midline presentation is a feature in common with other developmental anomalies in the head and neck region, including:
 - Dermoid sinus, nasal glioma, and thyroglossal duct cyst
- Imaging by CT and MRI helpful in determination of size of the mass and relationship to surrounding anatomic structures.

Pathology

NOTE: There is uniformity in the gross and microscopic features from case to case.

Gross

- Pedunculated polyp measuring from 1.5 to 4 cm
- May be ulcerated with hemorrhage and necrosis

Histology

- Surface lined by a nonkeratinizing squamous mucosa
- At low magnification, multiple submucosal solid nodules separated by less cellular stroma and network of delicate linear and branching small duct-like or glandular structures and nests of solid or cystic squamous epithelium set in a variably fibromyxoid stroma:
 - Duct-like structures and squamous nests (with or without keratinization) more prominent toward periphery of the more cellular stromal nodules but may be present within more central aspects of the cellular stromal nodules
 - Duct-like structures may be connected to surface epithelium in areas.

- Epithelial units within internodular stroma blend into cellular nodules.
- Cellular nodules are composed predominantly of fusiform cells forming short fascicles or trabecular structure:
 - Stromal cells characterized by ovoid to spindle-shaped nuclei with uniform dispersed nuclear chromatin and eosinophilic cytoplasm with indistinct cell borders
 - Mitotic figures may be present.
- Extensive hemorrhagic necrosis may be present:
 - Likely the result of torsion
- Rarely, bone formation may be present.
- Immunohistochemistry:
 - Epithelial components:
 - Reactive for cytokeratins (pancytokeratins, CK7), p63
 - EMA restricted to tubular structures
 - Mesenchymal components:
 - Reactive for vimentin, cytokeratins (AE1/AE3, CAM 5.2, CK7, OSCAR), p63, and muscle-specific actin
 - Nonreactive for S100 protein and GFAP
 - Variable proliferation rate (by Ki67 staining) from tumor to tumor and even within the same tumor from as low as 1% to as high as 20% to 30%
 - Consistent diffuse and widespread reactivity for salivary gland amylase

Treatment and Prognosis

- Simple excision (polypectomy) is curative.
- No reported recurrences

INFECTIOUS DISEASES OF THE NASOPHARYNX AND OROPHARYNX

- Infections of the pharynx include bacterial, viral, fungal, mycobacterial, protozoal, and other infectious agents.
- Breadth of infectious diseases of these sites is extensive, and this section focuses on select infectious diseases of these anatomic sites.

TONSILLITIS

Definition: Primary (bacterial) infection of the palatine tonsils.

Synonyms: Chronic tonsillitis, hyperplastic tonsils; tonsils with benign lymphoid hyperplasia; chronic fibrosing tonsillitis

Clinical

- Tonsillitis is one of the more common diseases of the head and neck.
- No gender predilection
- Patients with acute exudative tonsillitis are typically young and include children, teenagers, and young adults.
- Symptoms include rapid onset of fever and localized pain to the tonsillar region (odynophagia) and malaise; associated referred pain to the ear (otalgia) and dysphagia may be present.
- Involvement of the adjacent pharyngeal wall as well as the adenoids is not infrequently seen.
- Incubation periods tend to be short (i.e., days) and associated lymphadenopathy is common.

- Etiologic agent in this setting is typically a bacterial infection:
 - Most often group A β -hemolytic streptococci, *Haemophilus influenzae*, *Staphylococcus aureus*
 - Less common etiologic agents include *Corynebacterium diphtheriae* (diphtheria) and *Bordetella pertussis* (whooping cough)
 - Viruses may cause tonsillitis, including adenoviruses and Epstein-Barr virus (EBV).
- On examination the tonsils (and/or adenoids) are enlarged, hyperemic, and covered by a yellow exudate.

Pathology

Histology

- An acute inflammatory infiltrate of the tonsils is hardly ever seen in surgical pathology material.
- More typically the tonsils, as well as adenoids, show the presence of benign lymphoid hyperplasia characterized by enlarged and irregularly shaped germinal centers that include the presence of tingible body macrophages and with identifiable mantle lymphocytes.
- Often there is polarity (i.e., increased cellularity) of the mantle cell lymphocytes toward the site of the antigenic stimulation; the latter usually is from the mucosa surface such that there is a mantle lymphocyte expansion on the side of the germinal center that is oriented toward the surface.
- In association with the benign lymphoid hyperplasia there often is interfollicular expansion with increased mature plasma cells. In the presence of a viral infection a prominent immunoblastic proliferation may be seen.
- Viral inclusions may be identified:
 - EBV infection may result in the clinical and histologic features of infectious mononucleosis (see below).
- Fibrosis may or may not be present.
- Depending on the time frame, the histology associated with peritonsillar abscess may include the presence of pools of neutrophils (which is the histologic definition of an abscess) or chronic inflammatory cells or both.
- Actinomycotic organisms in the form of “sulfur granules” are saprophytes and normally found in the tonsillar crypts; therefore the presence of these microorganisms in the tonsillar crypts is not an indication of an infection:
 - To consider a diagnosis of an actinomycotic infection, the microorganism must be identified within the tonsillar parenchyma (see Section 4, Neck).
 - Similarly, the presence of neutrophils within the tonsillar crypt is not an indication of acute tonsillitis; neutrophils must be present in the

parenchyma to consider the diagnosis of acute tonsillitis (or adenoiditis).

- Surface epithelium is usually intact and unremarkable but may be eroded (particularly in resolving acute tonsillitis) or may rarely show papillary hyperplasia that histologically includes the presence of surface papillary projections formed by hyperplastic lymphoid tissue.

Differential Diagnosis

- Usually the diagnosis of tonsillitis is straightforward.
- HIV-infection of the tonsils (and adenoids)
- Other specific infectious diseases
- Neoplasm (e.g., lymphoma)

Treatment and Prognosis

- Treatment for bacterial infection involves administration of antibiotics:
 - Penicillin is primary antibiotic used in treatment.
 - Broad-spectrum cephalosporins (e.g., cefuroxime axetil) can be used for primary treatment and can be effective for persistent infection.
 - Patients allergic to penicillin can be treated with azithromycin.
- The issue relative to surgery is controversial:
 - Some patients have repeated (recurrent) attacks of tonsillitis, and these patients may be antibiotic-resistant, resulting in the recurrent attacks. For these (and perhaps other) patients surgical management may be required.
 - Patients who experience at least three episodes of tonsillitis in 3 consecutive years, five episodes in 2 years, or seven episodes in 1 year may benefit from surgery.
- Complications of surgery include postoperative bleeding, which can occur in up to 3% of patients:
 - Primary postoperative bleeding occurs within the first 24 hours after surgery and usually is related to the surgical procedure.
 - Secondary or delayed postoperative bleeding occurs more than 24 hours after surgery and usually is related to loosening of the sutures of infection.

PERITONSILLAR ABSCESS

Definition: Collection of purulent material behind the posterior capsule of the tonsil.

Synonym: Quincke

Clinical

- No gender predilection; primarily occurs in adolescents and adults
- Approximately one third of patients have a prior history (one or more episodes) of tonsillitis.

- Development of abscess occurs over time with gradually increasing pharyngeal (throat) discomfort occurring over days with subsequent dysphagia, odynophagia, ipsilateral otalgia, “hot potato” voice, trismus, and fever.
- Etiologic agents most often include α - and β -hemolytic streptococci and anaerobic bacteria (mainly *Bacteroides* spp. and *Fusobacterium nucleatum*).
 - Due to the prior utilization of antibiotics, culture-negative peritonsillar abscess may occur in up to 40% of cases.
- On examination the tonsils are enlarged and bulging with deviation of the uvula and soft palate:
 - Often bilateral
 - Abscess typically located in the superior pole of the tonsils
 - Cervical adenopathy may be present.
- Radiology:
 - CT scan useful in localizing the abscess and confirming the diagnosis

Pathology

Histology

- Large (confluent) pools of neutrophils and/or chronic inflammatory cells in peritonsillar soft tissues

Differential Diagnosis

- Peritonsillitis:
 - Presence of acute and chronic inflammation with granulation tissue
 - In contrast to peritonsillar abscess, there is no pooling of inflammatory cells.

Treatment and Prognosis

- Conservative management including analgesics, antibiotics, fluids, incision, and drainage:
 - Incision and drainage are needed for:
 - Diagnosis and in excluding the possibility of a neoplastic process
 - Gathering material for culture and antibiotic sensitivity
- Tonsillectomy selectively used
- Conservative management is effective therapy with low recurrence rates (5% to 15%).
- Complications if unrecognized and/or untreated or inappropriately managed may include:
 - Extension of abscess into parapharyngeal space potentially into the wall of the carotid artery
 - Extension of abscess superiorly to the base of skull and/or into the cranial cavity
 - Extension inferiorly to the hypopharynx (piriform sinus) with obstruction of and possible rupture into the airway
 - Extension into the mediastinum via the carotid sheath or retropharyngeal space

VIRAL DISEASES

- Numerous viral diseases may potentially infect sites in the nasopharynx and oropharynx.
- This section is limited to the more common types of viral infections that may be seen in these locations.

Human Papillomavirus (HPV)-Related Diseases

- HPV represents a large group of small, double-stranded circular DNA viruses.
- HPV is strongly epitheliotropic.
- HPV is a sexually transmitted disease.
- Non-neoplastic diseases associated with HPV include (but may not be limited to):
 - Verrucae (verruca vulgaris [wart], condyloma acuminatum)
 - Focal epithelial hyperplasia (Heck disease)
- HPV is also associated with epithelial neoplasms, including benign and malignant neoplasms:
 - Squamous papilloma:
 - Associated with low-risk viruses, including types 6, 11
 - Oropharyngeal carcinomas (for more complete discussion see next chapter):
 - Associated with high-risk viruses, including type 16, 18
 - Active role of HPV may be as a promoter in the multistep process of carcinogenesis in squamous cells of the upper aerodigestive tract:
 - Two viral oncoproteins of high-risk HPV, E6 and E7, promote tumor progression by inactivation of p53 and retinoblastoma tumor suppressor gene products, respectively.
 - These viral oncoproteins are capable of disrupting the cell-cycle regulatory pathways in the genetic progression to SCC.
 - Dysfunction of the retinoblastoma gene product results in abnormal cell proliferation and the development of malignant tumors.
 - Types of oropharyngeal carcinomas associated with HPV:
 - Nonkeratinizing carcinoma
 - Variants of squamous cell carcinoma, including:
 - ◻ Basaloid squamous cell carcinoma
 - ◻ Verrucous carcinoma
 - ◻ Papillary squamous cell carcinoma
 - ◻ Spindle cell squamous carcinoma
 - ◻ Adenosquamous carcinoma
 - Small cell neuroendocrine carcinoma
- Oropharyngeal carcinomas, including base of tongue and tonsil strongly associated with HPV infection
- Histologically, a feature associated with HPV infection are koilocytes characterized by the presence of cells with condensed, pyknotic (“raisin-shaped”)

nuclei with perinuclear clear areas referred to as halos; binucleate and multinucleate cells may be present.

- Immunohistochemistry:
 - Immunomarkers are available for identification of HPV, including p16.
- Cytogenetics and molecular genetics:
 - Detection of HPV by using labeled probes to detect HPV RNA and DNA, as well as in situ polymerase chain reaction, has increased the detection of HPV.
 - HPV-16 is strongly associated with oropharyngeal carcinomas, and integration has been shown to be tightly coupled to the neoplastic process.

Cytomegalovirus and Herpesvirus

- See Section 2, Oral Cavity.

Epstein-Barr Virus–Related Diseases

- Epstein-Barr virus (EBV) is an enveloped icosahedral herpesvirus with double-stranded linear DNA.
- EBV is strongly tropic for B-lymphocytes and also is tropic for T-lymphocytes.
- Detection can be achieved by in situ hybridization for Epstein-Barr–encoded RNA (EBER).
- Non-neoplastic diseases associated with EBV include (but are not limited to):
 - Infectious mononucleosis
 - T/NK-cell chronic active EBV infection (CAEBV)
 - Post-transplantation lymphoproliferative disease (PTLD):
 - EBV is an important pathogen in recipients of solid organ transplants (SOT).
 - EBV disease and its associated PTLD are more frequently seen when primary EBV infection occurs after transplant, a common scenario in pediatric SOT recipients.
 - Oral hairy leukoplakia: see Section 2, Oral Cavity
 - Possible role for EBV has been suggested in chronic inflammatory/autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, as well as in multiple sclerosis (MS):
 - Infectious mononucleosis has been shown to increase the risk of developing MS later in life.
 - EBV seroprevalence rates are higher in MS as compared with controls, in adult as well as in pediatric MS patients.
 - EBV antibody titers and EBV-specific T-cells are increased in MS patients as compared with healthy individuals.
 - CNS B-cells of MS patients have been reported to harbor EBV.
- There is increasing evidence that viruses may play a role in MS pathogenesis, acting as environmental triggers, but it is not known if any single virus is causal, or rather several viruses can act as triggers in disease development, including EBV and human herpesvirus 6 (HHV-6).
- EBV is also associated with neoplastic proliferations, including:
 - Epithelial malignancies:
 - Nasopharyngeal carcinoma, nonkeratinizing differentiated and undifferentiated types
 - Lymphoepithelial-like carcinoma (e.g., salivary gland, others)
 - Gastric carcinoma
 - Hematolymphoid malignancies:
 - Nasal-type NK/T-cell lymphoma
 - Burkitt lymphoma:
 - Occurs in approximately 30% to 40% of sporadic cases
 - Hodgkin lymphoma
 - Central nervous system lymphoma
 - Lymphomatoid granulomatosis
 - Aggressive NK-cell leukemia/lymphoma
 - T-cell lymphoproliferative disorders of childhood:
 - Hydroa vacciniforme-like lymphoma
 - Systemic EBV-positive T-cell lymphoproliferative disease
 - EBV-positive diffuse large B-cell lymphomas of the elderly
 - Diffuse large B-cell lymphoma associated with chronic inflammation
 - Pyothorax-associated lymphoma
 - Angioimmunoblastic T-cell lymphoma
 - AIDS-related lymphomas
 - Primary effusion lymphoma:
 - Type of diffuse large B-cell lymphoma occurring in HIV-infected patients consistently associated with HHV8 and commonly coinfecting by EBV
 - Sarcomas:
 - Leiomyosarcoma

Infectious Mononucleosis (IM) (Fig. 9-9)

Definition: IM is a systemic, benign, self-limiting infectious lymphoproliferative disease primarily caused by but not limited to Epstein-Barr virus (EBV) infection.

Pathogenesis

- EBV penetrates the nasopharyngeal epithelium and lymphoid tissues infecting B-lymphocytes.
- EBV enters B-lymphocytes through the CD21 molecule (attaches to C3d complement receptor) on the

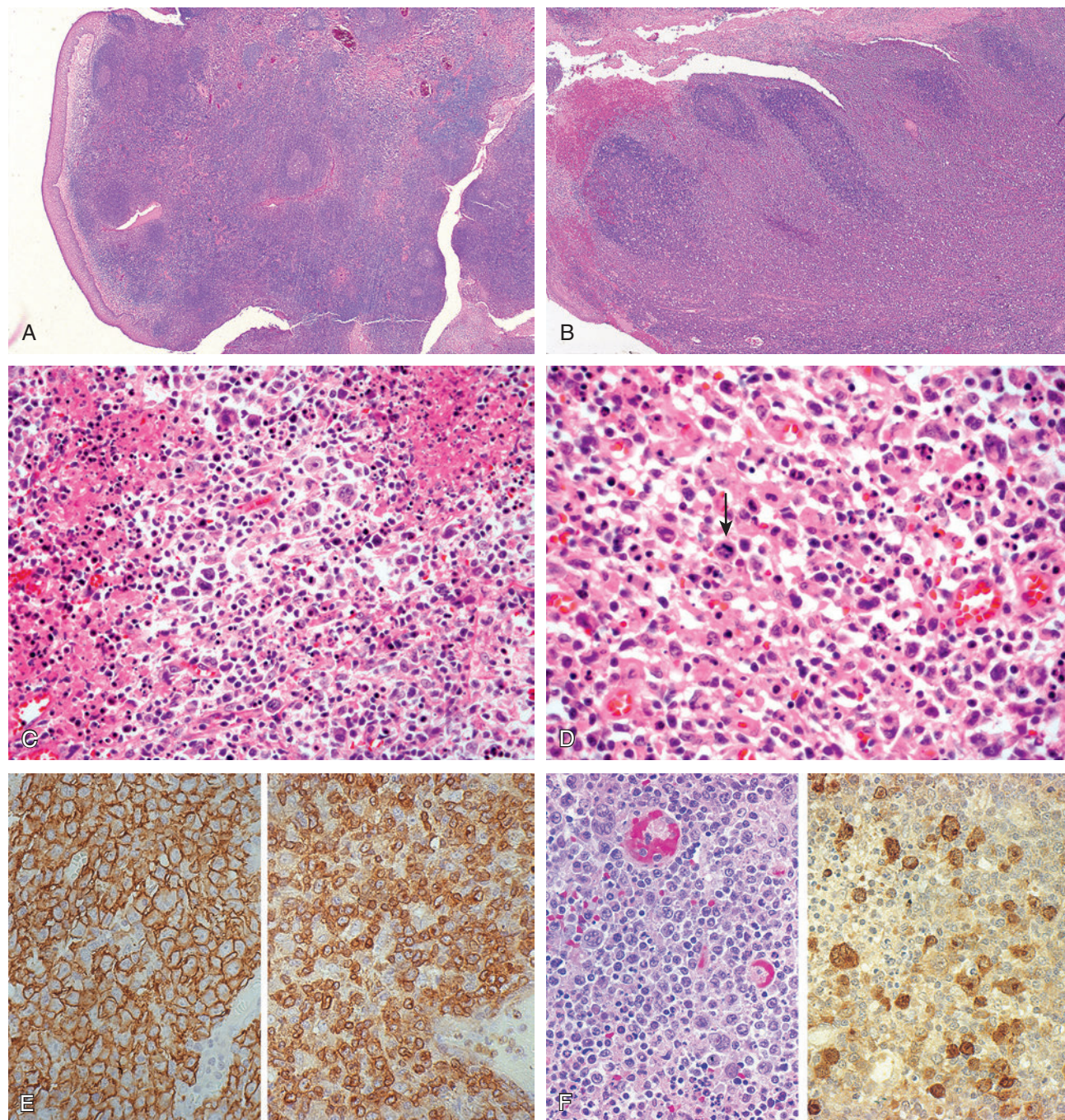


Fig. 9-9. Infectious mononucleosis.

A and **B**, Excised tonsil showing distortion and partial effacement of tonsillar architecture with preservation of germinal centers with interfollicular (cellular) expansion. **C** and **D**, Interfollicular areas include a proliferation of immunoblasts, plasma cells, Reed-Sternberg-like cells, and lymphocytes showing marked nuclear atypia with prominent nucleoli, increased mitotic activity (*arrow*) that may include atypical forms and necrosis (confluent foci and individual cell). Out of context with the clinical history and laboratory findings these histologic features suggest a possible diagnosis of malignant lymphoma. **E**, Immunoreactivity is present for *left* B-cell markers (CD20) and *right* T-cell markers (CD3). **F**, Split field showing the atypical lymphoid proliferation (*left*) with immunoreactivity for EBV latent membrane protein (*right*).

Continued

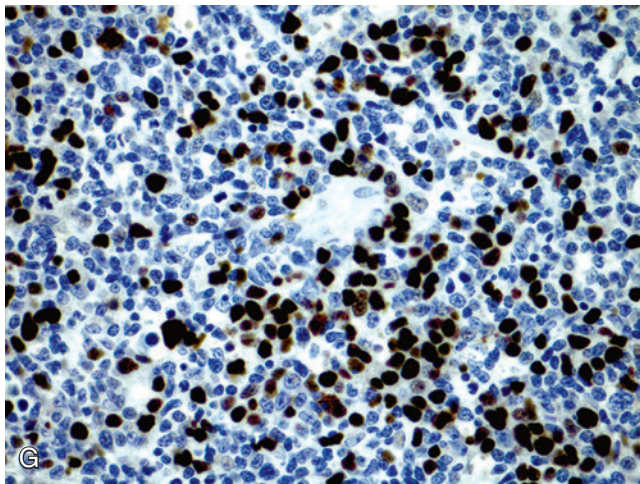


Fig. 9-9, cont'd

G, In situ hybridization for Epstein-Barr encoded RNA (EBER) is positive.

surface of B cells or nasopharyngeal epithelial cells and enters these cells.

- EBV infects B-cells and elicits humoral and cellular immune responses, inducing the formation of new antigens, including:
 - Viral capsid antigen (VCA)
 - Membrane antigen (MA)
 - Early antigen (EA), including two subtypes:
 - Diffuse (EA-D)
 - Restricted (EA-R)
 - Epstein-Barr nuclear antigen (EBNA)
 - Lymphocyte-detected membrane antigen (LYDMA)
- Earliest phase of disease characterized by infection of B-cells that proliferate, develop neo-antigens, circulate, stimulate immune response, and synthesize immunoglobulin.
- VCA, EA, and EBNA are the viral protein most important for serodiagnosis in immunocompetent patients.

Clinical

- No gender predilection; may occur in all age groups but primarily affects adolescents and young adults
- EBV is estimated to cause from 80% to 95% of the cases of infectious mononucleosis.
- Clinical presentation of EBV-associated IM includes:
 - Acute pharyngotonsillitis with patients experiencing sore throat, fever, and malaise
 - Lymphadenopathy and hepatosplenomegaly with chemical evidence of hepatitis may represent the systemic manifestations of the disease.
 - Pharyngotonsillitis is often severe and may be exudative; lymphadenopathy commonly affects

posterior cervical lymph nodes, but anterior and posterior nodes may be involved.

- A prodromal period of from 2 to 5 days consists of malaise and fatigue and frequently occurs prior to the onset of the full syndrome.
- Diagnosis of infectious mononucleosis is established in a patient with typical clinical presentations and appropriate laboratory findings (see below); tissue confirmation of the diagnosis is usually not required and it is in the atypical case where the patient presents with adenotonsillar and/or lymph node enlargement without fever, sore throat, or splenomegaly that a biopsy may be needed to establish a diagnosis and rule out a malignant process.
- Laboratory findings in IM include:
 - Absolute lymphocytosis with more than 50% lymphocytes in a total leukocyte population of more than 5000/mm³
 - Prominent atypical lymphocytes (Downey cells), which are often more than 10% of the total leukocyte count (the atypical lymphocytes in the peripheral blood are thought to represent mostly activated T-lymphocyte populations in response to B-cell infection)
 - Mild to moderate elevations of liver enzymes, including aspartate and alanine aminotransferase
 - Diagnosis can be confirmed by the demonstration of serum antibodies to horse red cells (positive Mono-Spot test) or sheep erythrocytes (positive Paul-Bunnell heterophile antibody test)
 - Of the many patients in the United States with typical clinical features of IM, 70% or more have a positive heterophile antibody test identifying EBV as the cause.
 - Of the 30% without heterophile antibody, about 50% are IgM-VCA positive, also verifying EBV infection.
 - Patients who consistently prove to be heterophile antibody or Mono-Spot negative, serodiagnosis is invaluable and includes:
 - An appreciable serum response to EBV viral capsid antigen (VCA) with IgM and IgG antibodies at the time of clinical presentation
 - At presentation or shortly thereafter, many infected patients will develop antibodies to early antigen complex (EA).
 - During the early phase of primary infection, antibodies to EBV nuclear antigens (EBNA) are usually not demonstrable.
 - IgM antibodies to VCA disappear within 2 to 3 months following infection; antibodies to EA disappear within 2 to 6 months following infection; IgG antibodies to VCA and anti-EBNA antibodies persist for life and are indicative of a chronic carrier state.

- In immunocompromised patients, serologic tests are of limited value:
 - Direct detection methods considered more reliable:
 - EBV viral load by PCR better tests in immunocompromised patients
- Other microorganisms associated with mononucleosis-like syndromes include:
 - Cytomegalovirus (CMV), *Toxoplasma gondii*, rubella, hepatitis A virus, and adenoviruses
 - In patients with IM exhibiting the typical clinical presentation and hematologic findings but who are heterophile antibody negative:
 - Patients may still have EBV antibody-positive but heterophile-negative IM.
 - CMV is the most common cause of heterophile-negative IM.
 - Non-EBV infectious agents causing infectious mononucleosis are not associated with a positive heterophile antibody test and Mono-Spot test.

Pathology

Gross

- Moderate to severe pharyngitis may be seen characterized by marked swollen and enlarged tonsils covered by dirty gray exudates.
- Tender lymphadenopathy, particularly of the posterior cervical lymph nodes, occurs.

Histology

- At low magnification, there is distortion and/or partial effacement of the nodal/tonsillar architecture with reactive follicular hyperplasia characterized by enlarged and irregularly shaped germinal centers.
- There is expansion of the interfollicular areas with polymorphous proliferation of small lymphocytes, transformed lymphocytes, immunoblasts, plasma cells, and Reed-Sternberg-like cells:
 - Lymphocytic and immunoblastic proliferation often displays marked cytologic atypia with one or more prominent nucleoli, increased mitotic activity, and phagocytosis.
 - Presence of immunoblasts may result in a mottled appearance to the affected site.
 - Immunoblasts may cluster or occasionally form sheets effacing portions of the tissue simulating a malignant lymphoma.
 - Immunoblasts may occasionally be binucleate, simulating the appearance of the Reed-Sternberg cells of Hodgkin lymphoma.
- Necrosis may be seen and is usually focally characterized by individual cell necrosis, although larger confluent zones of necrosis (geographic-type necrosis) may be present.
- A vascular proliferation with prominent endothelial cells is always present. In nodal involvement at least

some subcapsular sinuses are patent and contain a polymorphous lymphoid infiltrate similar to the interfollicular infiltrate.

- Atypical lymphoid proliferation may infiltrate:
 - Walls of the blood vessels
 - Outside the confines of the tonsil into adjacent soft tissues
- Histochemistry:
 - Histochemical stains for microorganisms are negative.
- Immunohistochemistry:
 - B-cell and T-cell reactivity:
 - Large cells show heterogeneous staining for CD20 and CD3.
 - Polytypical immunoglobulin staining of large cells
 - Immunoblasts may stain with CD30
 - Absence of CD15 immunoreactivity
 - Immunoreactivity can be seen for EBV latent membrane protein.
 - In situ hybridization for Epstein-Barr–encoded RNA (EBER) is positive in a proportion of cells including small and large cells.
- Cytogenetics and molecular genetics:
 - Clonal B cells are often absent; small clonal or oligoclonal B-cell populations may be found.
 - PCR analysis for detection of virus:
 - Determination of EBV viral load
 - Represents a more reliable and sensitive means for detecting the presence of virus than serodiagnosis

Differential Diagnosis

- Nonspecific reactive tonsillitis/lymphadenopathy
- Non-Hodgkin malignant lymphomas:
 - Especially of large cell or immunoblastic lymphoma (B-cell lineage) and anaplastic CD30+ large cell lymphoma
 - Markedly atypical interfollicular cellular proliferation in IM that may infiltrate blood vessels and/or outside the tonsil into adjacent soft tissues can easily be misinterpreted as a non-Hodgkin lymphoma
 - Attention to the clinical history, especially the relatively typical demographics associated with IM, should at least alert the pathologist to the possibility of this diagnosis.
 - Confirmatory laboratory analysis and absence of immunohistochemical and/or molecular biologic confirmation of a neoplastic process assist in avoiding the potential trap of misdiagnosing IM for a lymphoma.
- Hodgkin disease:
 - Primary Hodgkin lymphoma of the tonsils and/or mucosal sites of the upper aerodigestive tract

is exceedingly rare; when Hodgkin disease involves these sites, it usually does so secondarily following primary nodal disease.

- HIV-associated changes (see below)

Treatment and Prognosis

- Favorable clinical course often with resolution of symptoms over a period of several months
- Therapy is supportive, including rest and fluid intake.
- Rarely, serious and potentially fatal complications may develop and include airway obstruction and splenic rupture, the latter secondary to splenic involvement with massive splenomegaly.
- Most serious complications arise in individuals with X-linked lymphoproliferative disease (XLP):
 - XLP caused by mutations in *SH2D1A* and *XIAP* (*BIRC4*); may also occur in rare instances with no identified underlying genetic cause
 - Occurs in males with mutations in the signaling lymphocyte activation molecule-associated protein that regulates T and NK cells
 - Mutation mapped to chromosome Xq24-25 coding for cell surface receptor on T- and NK-cells but not B-cells
 - These patients are immunosuppressed and possess a rare, familial, fatal form of combined immunodeficiency.
 - Three most commonly recognized phenotypes of *SH2D1A*-related XLP are:
 - Hemophagocytic lymphohistiocytosis (HLH) associated with Epstein-Barr virus (EBV) infection:
 - Treatment similar to that of other life-threatening genetic hemophagocytic disorders and includes immunosuppressive agents such as steroids and etoposide; rituximab therapy may also be considered
 - Dysgammaglobulinemia:
 - Is typically hypogammaglobulinemia of one or more immunoglobulin subclasses
 - Treated by intravenous immunoglobulin (IVIG) therapy
 - Lymphoproliferative disorders (malignant lymphoma):
 - Malignant lymphomas are typically high-grade B-cell lymphomas, non-Hodgkin type, often extranodal, and in particular involving the intestine.
 - Treated with standard chemotherapy appropriate to the tumor
 - Regardless of clinical phenotype, the only curative treatment is allogeneic hematopoietic cell transplantation, which should be considered in most patients as early as possible.

Human Immunodeficiency Virus (HIV) Infection and Acquired Immunodeficiency Syndrome (AIDS)

- Clinical syndrome of acquired immune deficiency syndrome (AIDS) is characterized by opportunistic infection(s) and/or neoplasia with associated immunodeficiency.
- AIDS-related pathology may be seen in every organ system as a result of infection by the human immunodeficiency virus (HIV-1), the causative agent for AIDS.
- Head and neck represent a microcosm of the entire body with respect to the manifestations of AIDS.
- Virtually every conceivable pathologic process associated with HIV infection and AIDS can be found within the head and neck, including a wide variety of opportunistic infections, reactive lymphoproliferative processes, and hematolymphoid and non-lymphoid neoplasms:
 - These pathologic changes may be the initial manifestations of HIV infection or AIDS or they may represent a component of systemic disease.
- A variety of HIV- and AIDS-related pathologic lesions occur in the head and neck region ([Box 9-2](#)).

Pathogenesis

- Infection with HIV-1 initiates a series of events within the host immune system that ultimately leads to the destruction of cellular immunity, resulting in AIDS characterized by profound depletion of CD4⁺ lymphocytes rendering the host susceptible to the opportunistic infections and tumors that are the hallmark of AIDS.
- HIV-1 is:
 - A human retrovirus of the lentivirus genus
 - Membrane-bound, double-stranded RNA characterized by the presence of a unique enzyme, reverse transcriptase, at its core
 - Reverse transcriptase allows the viral RNA to be transcribed “backwards” into DNA and then inserted into the host genome
 - Major structural core proteins include:
 - p24 capsid protein
 - p18 matrix protein
- HIV-1 preferentially infects CD4⁺ (helper) T-cell lymphocytes and other cells of the immune system that bear the CD4 receptor and one of two chemokine receptors (CCR-5 and CXCR-4) on their surface:
 - These cells include CD4⁺ lymphocytes, dendritic cells, and macrophages.

BOX 9-2 HIV- and AIDS-Related Pathology of the Head and Neck**I. Opportunistic Infections***Viral*

- Cytomegalovirus
- Herpetic
- Others

Bacteria

- Mycobacteria (*Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*)
- Others

Fungal

- *Cryptococcus neoformans*
- Aspergillus
- Others

Protozoal

- *Toxoplasma gondii*
- *Pneumocystis jiroveci* (formerly *carinii*)
- Cryptosporidium
- Microsporidiosis

II. Benign Lesions

- Lymphadenopathy
- Extranodal lymphoid proliferation (adenotonsillar disease)
- HIV salivary gland disease
- Bacillary angiomatosis

III. Nonhematolymphoid Malignancies

- Kaposi sarcoma
- Malignant lymphomas
- Carcinomas
- Other

- Transmission of HIV-1 occurs through blood, sexual (body fluids), and maternofetal routes.
- HIV-2:
 - Following discovery of HIV-1, patients in West Africa with AIDS-like symptoms were identified whose serum antibodies reacted not with HIV-1 but with a distantly related lentivirus that was designated HIV-2.
 - HIV-2 is approximately 40% to 50% similar to HIV-1 in overall nucleotide sequence homology but with major differences in genomic organization, including an absence of the *vpu* gene present in HIV-1 and the addition of the *vpx* gene absent in HIV-1.
 - Antigenically HIV-2 and HIV-1 are distinct.
 - Like HIV-1, HIV-2 selectively infects CD4⁺ cells.
 - HIV-2 has the potential to cause profound immunodeficiency and an AIDS syndrome indistinguishable from that caused by HIV-1 but:
 - It appears to be less virulent than HIV-1.
 - It causes disease in a smaller fraction of individuals and over a more protracted period.

- Transmissibility of HIV-2 is less than that of HIV-1, and therefore the prevalence of HIV-2 is declining.

Epidemiology

- The overwhelming majority of early cases of HIV infection and AIDS in the United States and Europe were reported in men who have sex with men (homosexual and bisexual); although this remains the major risk group, intravenous drug users and women are the two groups with the highest increase in rates of AIDS in the United States:
 - Nearly 20% of new HIV infections are attributable to injecting drug use.
 - The main risk factor for women who acquire HIV during sex is the risk behavior of their male partners.
- Sub-Saharan Africa represents the epicenter of the global HIV/AIDS pandemic:
 - Most HIV transmissions in Africa (and Asia) are heterosexually transmitted.
 - Because infected females are usually at peak reproductive ages, the incidence of vertical transmission is also high.
- Recipients of contaminated blood and blood products (patients with hemophilia) were at much higher risk of acquiring the infection prior to the use of screening of blood products for HIV in 1984; this mode of transmission continues to be a threat in areas of the world where the blood supply is not screened.
- By January 2010 approximately 75 million people had become infected with HIV since the beginning of the epidemic in 1981; of those 75 million, more than 40 million people have died of AIDS.
- According to estimates by the Joint United Nations Program on HIV/AIDS:
 - 33.4 million people were living with HIV by December 2008.
 - 2.7 million people became newly infected in 2008, half of whom were young, between the ages of 15 and 24 years.
 - Continuing rise in the population living with HIV infection reflects a combination of continued high rates of HIV infection and beneficial impact of antiretroviral therapy (ART), resulting in fewer deaths.

Spectrum of Disease

- HIV-1 causes a spectrum of disease.
- With initial infection there are a constellation of findings that are caused directly by infection with HIV-1 and the patient's immune response.
- Transient, symptomatic illness is associated with high titer viremia and a vigorous response to the invading virus.

- In the United States, 40% to 90% percent of infected patients manifest this syndrome.
- Clinical manifestations of the primary infection are nonspecific:
 - A flu-like viral syndrome characterized by fever, fatigue, pharyngitis, lymphadenopathy including tonsillar and adenoidal enlargement, and a maculopapular rash
 - Due to the abundance of lymphoid tissue in the head and neck, including lymph nodes and extranodal lymphoid tissues (e.g., Waldeyer tonsillar ring and parotid gland), this anatomic region is especially likely to manifest these findings.
- During primary HIV infection there is a peak in viral load, which then decreases and levels out at what is known as the “set point”; this viral set point is prognostically significant:
 - Individuals with a low viral set point are more likely to progress slowly to AIDS (more than 10 years).
 - Individuals with a high viral set point are likely to progress rapidly to AIDS (less than 5 years).
- During primary infection the immune system responds vigorously to the virus:
- Patient is not immunodeficient.
- Patient is HIV-1 infected but does not have AIDS.
- As disease proceeds, especially if untreated, the virus begins to destroy the cellular arm of the patient’s immune system.
- As CD4⁺ cells of the immune system are destroyed, the patient loses the ability to fight off the myriad pathogens that are ubiquitous in our world.
- AIDS is the immunodeficiency that results from HIV-1 infection.
 - Infections seen in AIDS include pathogenic microorganisms as well as opportunistic infections.
- Diagnosis of HIV-1 infection is conceptually simple. Like most infections, it begins when the pathogen invades the host.
- Diagnosis of AIDS is much less clear cut:
 - AIDS is a diagnosis of criteria.
 - In the United States the diagnosis is made by fulfilling criteria developed by the CDC:
 - CDC classification system ([Table 9-1](#)) is based on three clinical categories (A, B, and C) and three CD4-T-cell count categories (1, 2, and 3).
 - HIV-1 viral load, which has become a critical tool in diagnosing and managing patients with HIV-1 infection, is not included in the CDC criteria.
- Early diagnosis is critical, owing to effective initiation of antiretroviral therapy that may, if administered in the earliest phase of infection, have a major positive impact on prognosis and long-term survival.
- Indicators of HIV disease and AIDS are listed in [Box 9-3](#):
 - Clinical staging and case definition of HIV for resource-constrained settings were developed by WHO in 1990 and revised in 2007.

TABLE 9-1 Clinical Categories: CDC Classification System for HIV-Infected Adults or Adolescents

CD4 ⁺ T-Cell Categories	A Asymptomatic, Acute, or PGL	B* Symptomatic, B-Conditions	C AIDS-Indicator Conditions
1 = ≥500/ml or 29%	A1	B1	C1
2 = 200-499/ml or 14% to 28%	A2	B2	C2
3 = <200/ml or immunologic AIDS	A3	B3	C3

PGL, Progressive generalized lymphadenopathy.

Persons under subcategories A3, B3, C1, C2, and C3 are reportable as AIDS cases in the United States and territories (effective 01 January 1993).

*Category symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meets at least one of the following criteria:

They are attributed to HIV infection or indicate a defect in cell-mediated immunity.

They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

Bacillary angiomatosis
 Oropharyngeal candidiasis (thrush)
 Vulvovaginal candidiasis, persistent or resistant
 Pelvic inflammatory disease (PID)
 Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
 Hairy leukoplakia, oral
 Herpes zoster (shingles), involving two or more episodes or at least one dermatome
 Idiopathic thrombocytopenic purpura
 Constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting >1 month
 Peripheral neuropathy

BOX 9-3 Indicators of HIV Disease and AIDS**Clinical Stage 1**

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for >1 month
- Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (hemoglobin <8 g/dl)
- Neutropenia (neutrophils <500 cells/ μ l)
- Chronic thrombocytopenia (platelets <50,000 cells/ μ l)

Clinical Stage 4

- HIV wasting syndrome, as defined by the CDC (see [Table 9-1](#))
- *Pneumocystis* pneumonia
- Recurrent, severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal *Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

- Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and it does not require a CD4 cell count.
- The staging system is used in many countries to determine eligibility for antiretroviral therapy, particularly in settings in which CD4 testing is not available.
- Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (see [Box 9-3](#)).
- These stages are defined by specific clinical conditions or symptoms.
- For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged 15 years or older.
- The WHO Case Definition for HIV Infection and AIDS is listed in [Box 9-4](#).
 - Cases diagnosed with advanced HIV infection (including AIDS) not previously reported should be reported according to a standard case definition.

BOX 9-4 WHO Case Definition for HIV Infection**Adults and Children 18 Months or Older**

- HIV infection is diagnosed based on:
 - Positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or on different operating characteristics.
- and/or
 - Positive virologic test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virologic test obtained from a separate determination

Children Younger Than 18 months

- HIV infection is diagnosed based on:
 - Positive virologic test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive HIV p24 antigen) confirmed by a second virologic test obtained from a separate determination taken more than 4 weeks after birth
 - Positive HIV antibody testing is not recommended for definitive or confirmatory diagnosis of HIV infection in children until 18 months of age.

BOX 9-5 Criteria for Diagnosis of Advanced HIV (Including AIDS*)

- Clinical criteria for diagnosis of advanced HIV in adults and children with confirmed HIV infection:
 - Presumptive or definitive diagnosis of any stage 3 or stage 4 condition[†] and/or
- Immunologic criteria for diagnosing advanced HIV in adults and children 5 years or older with confirmed HIV infection:
 - CD4 count less than 350 per mm³ of blood in an HIV-infected adult or child and/or
- Immunologic criteria for diagnosing advanced HIV in a child younger than 5 years of age with confirmed HIV infection:
 - %CD4⁺ <30 among those younger than 12 months
 - %CD4⁺ <25 among those aged 12 to 35 months
 - %CD4⁺ <20 among those aged 36 to 59 months

*AIDS in adults and children is defined as: clinical diagnosis (presumptive or definitive) of any stage 4 condition (defined in Annex 1) with confirmed HIV infection: OR immunologic diagnosis in adults and children with confirmed HIV infection and >5 years of age; first-ever documented CD4 count less than 200 per mm³ or %CD4⁺ <15: OR among children with confirmed HIV infection aged 12 to 35 months first ever documented %CD4 <20: OR among children with confirmed HIV infection and less than 12 months of age first ever documented %CD4 <25.

[†]Annex 1 provides criteria for presumptive or definitive diagnosis of all conditions.

- Advanced HIV infection is diagnosed based on clinical and/or immunologic (CD4) criteria among people with confirmed HIV infection (Box 9-5).
- AIDS case reporting for surveillance is no longer required if HIV infection or advanced HIV infection is reported.

HIV Infection of Extranodal Lymphoid Tissues of Waldeyer Tonsillar Ring (Figs. 9-10 and 9-11)

Definition: Primary HIV infection of the extranodal tissues of Waldeyer ring occurring in association with known systemic disease or representing the initial manifestation of HIV infection in otherwise asymptomatic patients not known to be HIV infected.

Clinical

- More common in men than women, and occurs most frequently in the third to fifth decades of life (median age, fourth decade):
 - May occur in pediatric ages
- HIV infection may first present clinically as enlargement of the lymphoid tissues of Waldeyer's ring, including the tonsils and adenoids.
- Clinical presentations vary and include nasal congestion, airway obstruction, sore throat (pharyngitis),

otitis media unresponsive to antibiotic therapy, otalgia, facial weakness, fever, and a nasopharyngeal or tonsillar mass.

- Clinical spectrum of HIV infection includes three phases: early or acute, chronic, and crisis or final.
- Morphologic changes parallel the course of HIV infection (see below).
- In early stages of disease:
 - Florid follicular hyperplasia of lymphoid tissues results in enlargement of the affected sites, causing lymphadenopathy as well as enlargement of the tonsils and/or adenoids.
 - Tonsillar enlargement may cause airway obstruction and/or otitis media and raise the clinical concern for neoplastic involvement of these sites.
 - Similar to the lymphoid tissue changes that occur with the progression of disease, the identification of the HIV also changes over time:
 - In nodal tissues, the follicular dendritic cells of the germinal centers have been shown to be reservoirs of HIV RNA.
 - Follicular dendritic cells entrap but do not actively produce HIV, allowing for presentation of the virus to competent immune cells of B-cell lineage.
 - With progression of disease and continued immune suppression, the germinal centers involute and then disappear.
- Clinically, the tonsils and adenoids are enlarged, usually bilaterally, but unilateral enlargement may occur:
 - Enlargement of the tonsils or adenoids may raise the concern of a hematolymphoid or epithelial neoplasm prompting surgical removal of the enlarged organ.
- Concurrent (unilateral) cervical adenopathy may be present.
- Large ulcers leading to complete destruction of the tonsil may also be present.
- Patients may or may not be known to be infected with HIV and/or suffering from AIDS:
 - Risk factors for the patients who were known or suspected to be HIV positive include men who have sex with men (homosexual and bisexual), blood transfusion recipients, and/or intravenous drug abuse.
 - Patients not known to be HIV infected often present without any of the clinical stigmata of HIV infection.
- Serologic evaluation is confirmatory for HIV infection.

Pathology

Histology

- Histomorphologic changes seen in affected lymph nodes and peripheral lymphoid tissues represent a

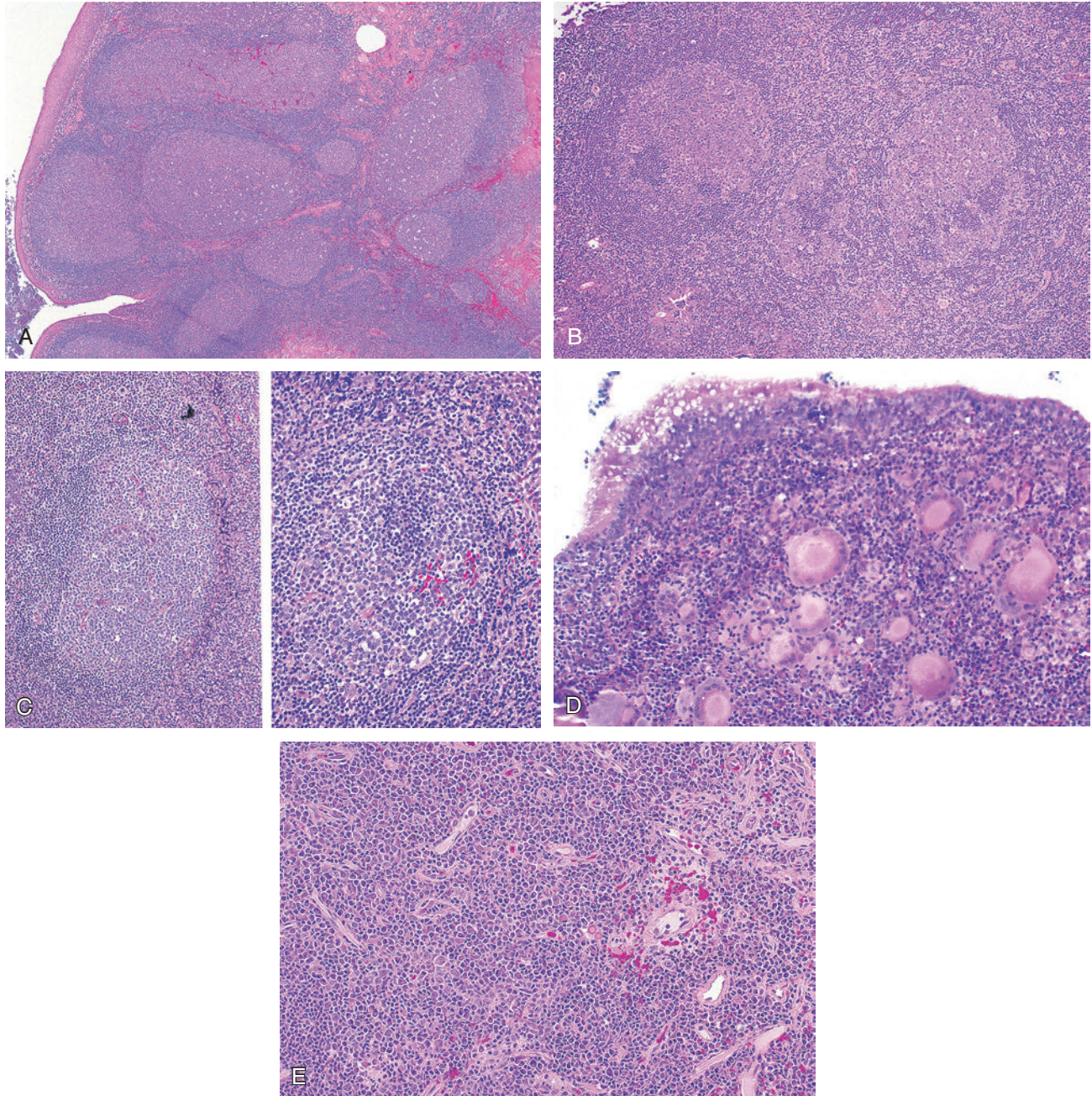


Fig. 9-10. Human immunodeficiency virus (HIV) infection of Waldeyer's tonsillar tissues.

A, Early histologic manifestations of HIV infection include the presence of florid follicular hyperplasia (FFH) characterized by enlarged and irregularly shaped germinal centers with loss or attenuation of mantle lymphocytes; some germinal centers approximate the surface epithelium. **B**, Three lymphoid follicles in varying stages, including the two larger ones showing attenuated to partially absent mantle cell lymphocytes, and the smaller germinal center (*center*) infiltrated by small lymphocytes referred to as follicle lysis resulting in creating a "moth-eaten" appearance. **C**, Higher magnification shows (*left*) follicular hyperplasia with absent mantle cell lymphocytes and (*right*) follicle lysis characterized by "infiltrating" small lymphocytes and absence of clearly defined mantle zones. **D**, Multinucleated giant cells are characteristically localized near or within the surface epithelium and/or near or within crypt epithelium (*not shown*). **E**, Histologic features in patients with more advanced stages of disease include the effacement of lymphoid tissue architecture, loss of the normal lymphoid cell population with replacement by a benign plasma cell infiltrate, and the presence of increased vascularity.

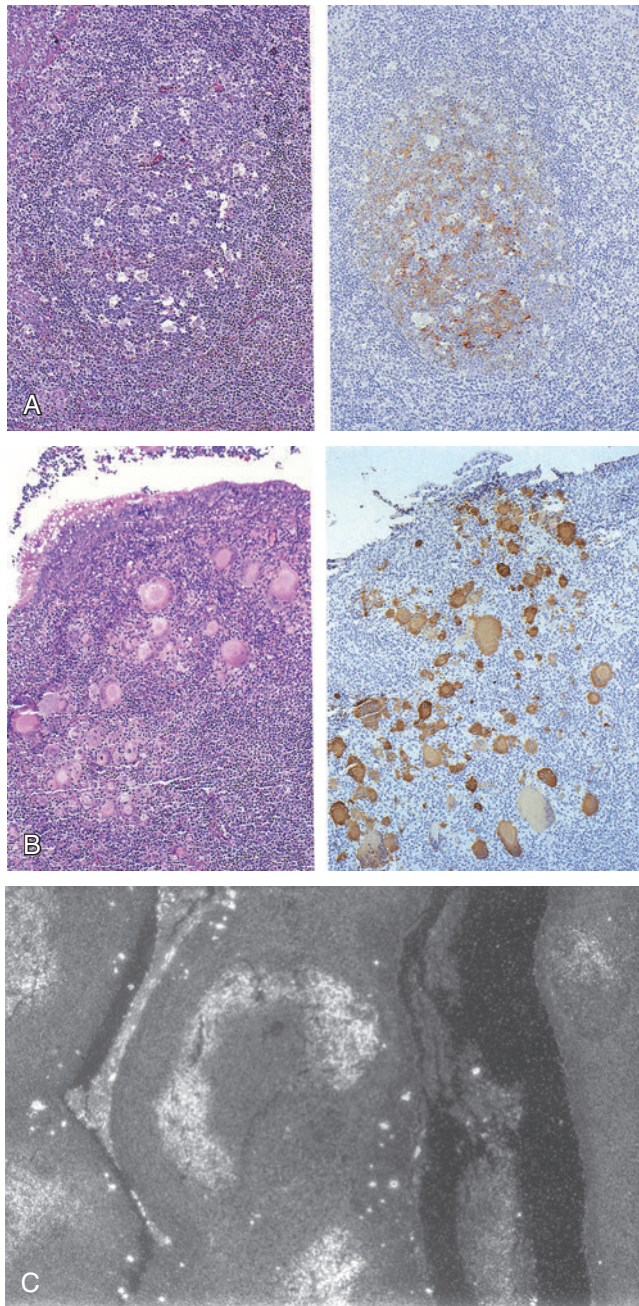


Fig. 9-11. Immunohistochemistry and in situ hybridization (ISH) in HIV infection.

Confirmation of HIV infection by immunohistochemical reactivity with HIV p24 core antigen. **A**, (left) HIV-infected tonsillar tissue showing follicle lysis; (right) HIV p24 immunoreactivity within follicular dendritic cells. **B**, (left) HIV-infected tonsillar tissue showing multinucleated giant cells that are (right) HIV p24 immunoreactive. **C**, In situ hybridization for HIV-1 RNA using antisense riboprobe, darkfield microscopy, showing signal in enlarged and irregularly shaped germinal centers, as well as in scattered interfollicular cells and multinucleated giant cells, the latter approximating the epithelial layer.

continuum that varies according to the duration and progression of disease.

- Histomorphologic changes in HIV-induced tonsillar and adenoidal enlargement vary with the progression of disease.

Acute and/or Chronic Stage

- May include florid follicular hyperplasia with and without follicular fragmentation, and follicle lysis with areas of follicular involution
- Additional findings included the presence of monocytoïd B-cell hyperplasia, paracortical and interfollicular zone expansion with immunoblasts and plasma cells, interfollicular clusters of high endothelial venules, intrafollicular hemorrhage, and the presence of multinucleated giant cells (MGC).
- MGC characteristically cluster adjacent to or within the adenoidal surface epithelium or the tonsillar crypt epithelium.

Advanced Stage

- Features correlate with the lymphoid obliteration seen in the terminal stages of HIV infection or AIDS:
- Effacement of nodal architecture, loss of the normal lymphoid cell population with replacement by a benign plasma cell infiltrate, and the presence of increased vascularity.
- MGC characteristically seen in the early and chronic stages of disease are not identified in the more advanced stages of HIV infection.
- Histochemistry:
 - Special stains for microorganisms (other than HIV) are negative.
- Immunohistochemistry:
 - Reactivity for the HIV core antigen p24 (gag protein), an indicator of active HIV infection consistently identified in the early and chronic stages of disease:
 - Anti-HIV p24 reactivity is seen within the follicular dendritic cell (FDC) network of the germinal centers, in scattered interfollicular lymphocytes, in the multinucleated giant cells, and within intraepithelial cells of crypt epithelium.
 - HIV p24-positive intraepithelial cells are S100 protein (a dendritic cell marker) positive, and their morphologic appearance correlates with the appearance of dendritic cells (DC).
 - Reactivity with B-cell (CD20) and T-cell markers or subsets (CD45RO, CD3, OPD4) is seen within the germinal centers and in the interfollicular regions, as well as in scattered intraepithelial cells.

- In more advanced stages of disease, characterized by loss of germinal centers and the presence of a predominant plasma cell infiltrate:
 - Show a relative absence of lymphoid cell markers (CD20, CD3, or OPD4)
 - Plasma cell infiltrate shows reactivity with kappa and lambda light chains indicative of a benign proliferation.
- Surface and crypt epithelia are cytokeratin reactive.
- Immunoreactivity with Epstein-Barr virus–latent membrane protein (EBV-LMP), herpes simplex virus (HSV), or cytomegalovirus (CMV) is not present
- Cytogenetics and molecular genetics:
 - Evidence of HIV RNA by in situ hybridization is seen in the follicular dendritic cell network, in the multinucleated giant cells, and in mature lymphocytes localized to the germinal centers, interfollicular zones, and within the surface and/or crypt epithelia.
 - Strongest signal is present in the multinucleated giant cells.

Differential Diagnosis

- Other infectious diseases
- Infectious-related proliferative processes (e.g., infectious mononucleosis)
- Malignant lymphoma

Treatment and Prognosis

- Early initiation of antiretroviral therapy has reduced HIV-associated morbidity and has significantly prolonged life and disease-free interval.
- Antiretroviral therapy can reliably reduce viral loads to levels below 50 copies/ml when circulating virus is susceptible to available drugs:
 - When viral loads are reduced to low levels, further immune decline is usually prevented and immune function is usually improved.
 - Most patients with effective virologic suppression demonstrate improvement in CD4 count but a few patients will not show benefit for unknown reasons.
- As HIV infection of Waldeyer tonsillar ring may be the initial manifestation of HIV infection, recognition of its pathologic features is essential to initiation of antiretroviral therapy.

AIDS-Related Opportunistic Infectious Diseases of the Pharynx

- A number of opportunistic infections occurring in association with the immune-compromised state

caused by HIV or secondary to AIDS can be found to infect the upper aerodigestive tract, including viruses, fungi, and protozoa.

Viruses

- Infestation of head and neck sites in HIV-positive and AIDS patients is common.
- Among the more common viruses that infect head and neck sites in this setting are cytomegalovirus and herpesvirus (simplex and zoster).

Cytomegalovirus (CMV) (Fig. 9-12)

- CMV is a large, double-stranded DNA virus and a member of the herpesvirus family.
- In fully immunocompetent individuals, CMV rarely causes clinically evident disease.
- When immune mechanisms are deficient, especially those mediated by CD4 positive and CD8 positive lymphocytes, latent virus replicates and causes pathologic injury.
- CMV is the most common opportunistic pathogen recognized at autopsy in AIDS patients.
- In general, CMV infection involving the head and neck is not common; when it occurs in the head and neck, CMV infection is seen as an ulcerative mucocutaneous lesion.

Pathology

Gross

- Single or multiple, oval, tan-white, ulcerated lesions with a hyperemic rim with or without associated exudates

Histology

- Mucosal ulceration, necrosis, and cytopathic effects
- Cytopathic findings include:
 - Nucleomegaly
 - Characteristic intranuclear and/or intracytoplasmic inclusions typically in nonepithelial cells, including endothelial cells and fibroblasts rather than in squamous cells:
 - Intranuclear basophilic Cowdry type B inclusion (so-called owl's eye inclusions)
 - Ill-defined amphophilic cytoplasmic inclusions
- Immunohistochemistry:
 - Positive CMV immunoreactivity and/or in situ hybridization

Treatment

- Antiviral therapy (valganciclovir and ganciclovir) may prove effective.
- In AIDS patients, CMV infection generally resolves when CD4 counts exceed 100/mm³ but is a grave prognostic sign if counts do not recover to those levels.

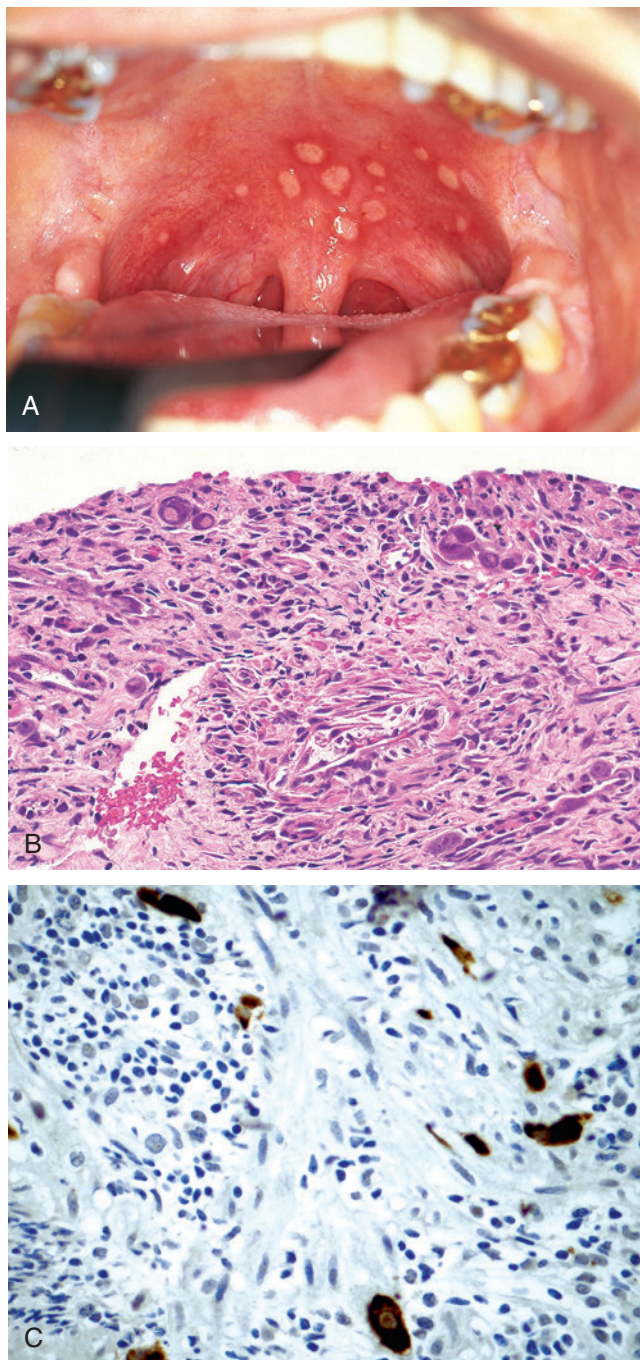


Fig. 9-12. Cytomegalovirus (CMV) pharyngitis.

A, Multiple, discrete, oval mucosal lesions are seen. **B**, Histologic findings include the presence of mesenchymal cells showing cytomegaly with characteristic intranuclear and intracytoplasmic inclusions (top of image). **C**, In situ hybridization for CMV confirms the diagnosis showing intranuclear and intracytoplasmic positivity.

Herpes Simplex Virus (HSV) (Figs. 9-13 and 9-14)

- Herpes simplex viruses are large, enveloped, double-stranded DNA viruses and members of the family Herpesviridae.
- Two distinct subtypes of herpes simplex virus are identified:
 - Type 1 referred to as the “oral” type
 - Type 2 referred to as the “genital” type:
 - Virus type is not necessarily a reliable indicator of anatomic site affected, especially with changing sexual habits.
 - Distinction between HSV-1 and HSV-2 not relevant
- Because of its tendency to infect cells of ectodermal origin (skin or mucous membranes) herpes simplex virus (HSV) is a frequent cause of mucocutaneous disease in the HIV-positive patient.
- Head and neck manifestations are those of an ulcerated lesion with involvement of intraoral, nasal cavity, lip, external ear, pharynx, and tonsil; in addition, enlargement and tenderness of cervical and submental lymph nodes may be seen.
- Infection of the pharynx may appear as vesicular lesions that bleed easily and may be covered with a black crust or as shallow tonsillar ulcers covered with gray exudates.
- Herpes zoster may occur as varicella (chickenpox) or as dermatomal zoster (shingles); the latter, while not specific for HIV infection, appears to be related to HIV infection and may represent an early marker for the immunosuppression associated with HIV infection.
- Herpes zoster can localize to any dermatome, is neurotropic, and can cause unremitting pain.
- Head and neck manifestations include involvement of the eighth nerve or geniculate ganglion (Ramsay Hunt syndrome), producing severe ear pain, hearing loss, vertigo, and facial nerve paralysis.

Pathology

Gross

- Single or multiple, oval, tan-white, ulcerated lesions with a hyperemic rim with or without associated exudates

Histology

- In mucosal sites, there is focal ulceration, intraepithelial vesicles, acantholysis, neutrophilic infiltrate, necrosis, balloon degeneration of epithelial cells, and intranuclear inclusions within the degenerating epithelial cells:
 - Diagnostic cytopathic features include nuclear molding, multinucleated giant cells, and eosinophilic inclusions.



Fig. 9-13. Herpes simplex virus infection.

Mucocutaneous herpes simplex virus infection with involvement of the (A) external lip and (B) labial mucous membrane (herpetic stomatitis). C, Herpes zoster infection or dermatologic zoster (shingles).

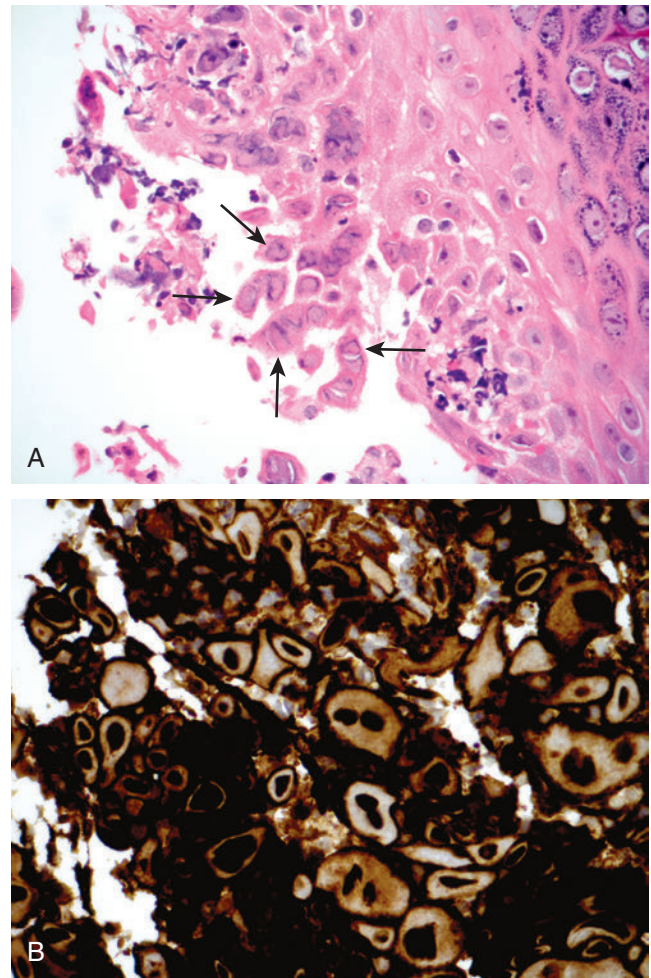


Fig. 9-14. Herpes simplex virus infection.

A, Histologic findings in herpes simplex virus (HSV) includes balloon degeneration of epithelial cells with intranuclear inclusions within degenerating epithelial cells (arrows). B, In situ hybridization for HSV confirms the diagnosis showing intranuclear positivity.

- The edge of the ulcer and sloughed squamous cells are the best sites for identification of characteristic cytopathic changes.
- Herpes zoster virus:
 - Intranuclear inclusions indistinguishable from those seen in herpes simplex are identified.
- Immunohistochemistry:
 - Positive HSV immunoreactivity and/or in situ hybridization
- DNA amplification by PCR has significantly improved sensitivity for confirmation of HSV.

Treatment

- Acyclovir antiviral chemotherapy is the first-line treatment for the management of herpes simplex virus 1 (HSV-1) and 2 (HSV-2) diseases.

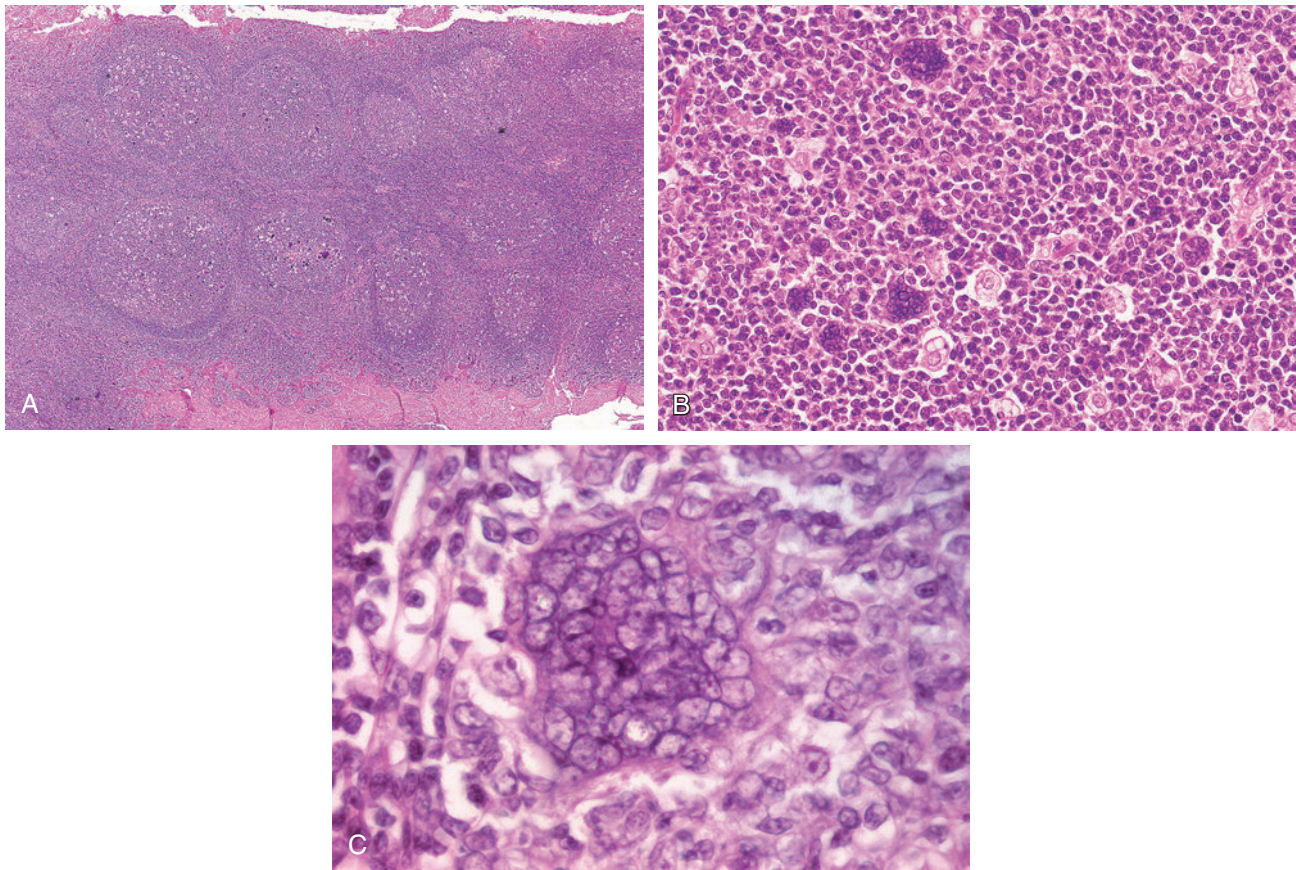


Fig. 9-15. Measles tonsillitis.

Reactive follicular epithelial hyperplasia with interfollicular multinucleated (Warthin-Finkeldey type) giant cells.

Other Viruses

- Other viral diseases of the pharynx (i.e., tonsils) in immune-competent individuals includes measles (Fig. 9-15):
 - Acute childhood illness caused by RNA paramyxovirus
 - Also referred to as rubeola
 - Highly contagious and transmitted by oral and respiratory secretions
 - Patients are typically immunocompetent.
 - Availability of live measles virus vaccine has made this disease less common in the United States.
 - Following a prodromal period, a generalized rash develops beginning on the face and spreading to the trunk and extremities:
 - Rash usually resolves within 10 days.
 - Immunosuppressed patients may not develop characteristic rash.
 - Tonsillar involvement results in reactive follicular hyperplasia with interfollicular Warthin-Finkeldey-type giant cells characterized by multiple nuclei arranged in grape-like clusters.

FUNGI

- See Section 2, Oral Cavity, for more complete discussion.
- Many fungi including *Candida* species may secondarily infect HIV-positive patients and are implicated in causing disease in the HIV-infected patient.
- In the head and neck the single most important fungal pathogen is the *Candida* species.
- Oral candidiasis (thrush) frequently occurs in AIDS patients, and its presence is a strong indication for the subsequent development of AIDS.
- Identification of the microorganism can be accomplished by culture on Sabouraud agar.
- *Candida* is seen in association with oral hairy leukoplakia, where it is identified on the surface of the lesion; this form of *Candida* infection is unrelated to AIDS.
- Candidiasis limited to the oral cavity and/or pharynx is treated with topical nystatin or oral ketoconazole and its derivatives; however, if oral or pharyngeal infection represents part of systemic involvement, amphotericin B is the preferred drug.

- Oropharyngeal histoplasmosis is closely associated with immunosuppression status, especially in patients presenting AIDS, and oropharyngeal histoplasmosis may represent the initial manifestation of disseminated histoplasmosis.

BACTERIA AND SPIROCHETES

- AIDS patients may experience an increased incidence of otolaryngic gonorrhea and syphilis.

Gonorrhea

Definition: Localized and systemic disease caused by *Neisseria gonorrhoeae*, a pyogenic gram-negative diplococcus.

Clinical

- Otolaryngologic manifestations include gonococcal pharyngitis, which generally is asymptomatic but may present with sore throat, tonsillar hypertrophy, or cervical adenopathy.
- Microorganism infects mucosal and glandular structures.

Pathology

Histology

- Acute inflammation may be present but is not common
- Intracellular diplococci may be seen by methylene blue or Brown and Brenn staining within the submucosa (intracellularly in leukocytes) and occasionally in cellular debris in tonsillar crypts.
- Gram stain smears from the pharynx are unreliable due to the presence of other organisms, so samples must be cultured on appropriate media (chocolate agar) for identification.

Treatment and Prognosis

- Ceftriaxone is the preferred drug for routine treatment of gonorrhea.
- Recommendation includes to treat all patients with gonorrhea with an oral regimen active against *C. trachomatis*, usually azithromycin:
 - Dual therapy may enhance efficacy of treatment for pharyngeal gonorrhea and using more than one drug may retard selection of antimicrobial resistance in *N. gonorrhoeae*.
 - Such treatment is warranted, even in persons who test negative for *C. trachomatis*.

Syphilis (Fig. 9-16)

Definition: Systemic venereal disease caused by *Treponema pallidum*, a member of the family Spirochaeta-

ceae, which includes *T. pertenue* (yaws) and *T. carateum* (pinta).

Clinical

- Clinical stages of syphilis are primary, secondary, tertiary, and congenital, any of which can affect virtually every site in the head and neck, causing an array of clinical manifestations.
- Protean clinical manifestations include involvement of the head and neck resulting in:
 - Tonsillar involvement manifesting as a painless solitary chancre, which appears at the site of inoculation in the primary stage:
 - Chancres may clinically mimic a neoplasm.
 - Skin lesions and lymphadenopathy (seen in 90% of the patients in the secondary or disseminated stage):
 - Characteristic chancre develops at the site of infection.
 - Oral involvement may include the lips, tongue, palate, gingiva, and tonsils.
 - Pharyngotonsillitis may be a presenting symptom in secondary syphilis, and mucosal involvement produces so-called mucous patches, which are highly contagious.
- Other head and neck symptoms in the secondary stage may include rhinitis, laryngitis, pharyngitis, cranial nerve deficits, sensorineural deafness, labyrinthitis, and glossitis.
- Tertiary stage typically involves the central nervous system (neurosyphilis) and aorta (cardiovascular syphilis); however, localized, nonprogressive lesions may develop in mucosal otolaryngologic sites termed benign tertiary syphilis or gummas:
 - Gummatous reaction represents a pronounced immunologic reaction of the host.
- Laboratory evaluation includes two types of serologic tests for syphilis:
 - Nontreponemal (nonspecific) antibody tests:
 - Detect antibodies to lipoprotein material and cardiolipin released from cells damaged by treponemes
 - Screen for disease and monitor course of disease
 - Include venereal disease research laboratory test (VDRL), rapid plasma reagin (RPR), unheated serum reagin (USR), and toluidine red unheated serum (TRUST)
 - Treponemal (specific) antibody tests:
 - Detect the presence of antibodies to treponemal antigens and used to confirm positive nontreponemal screening test or to confirm infection in face of negative nontreponemal test in late or latent disease stages, which can occur in up to 30% of patients with tertiary syphilis
 - Include fluorescent treponemal antibody absorption test (FTA-ABS)

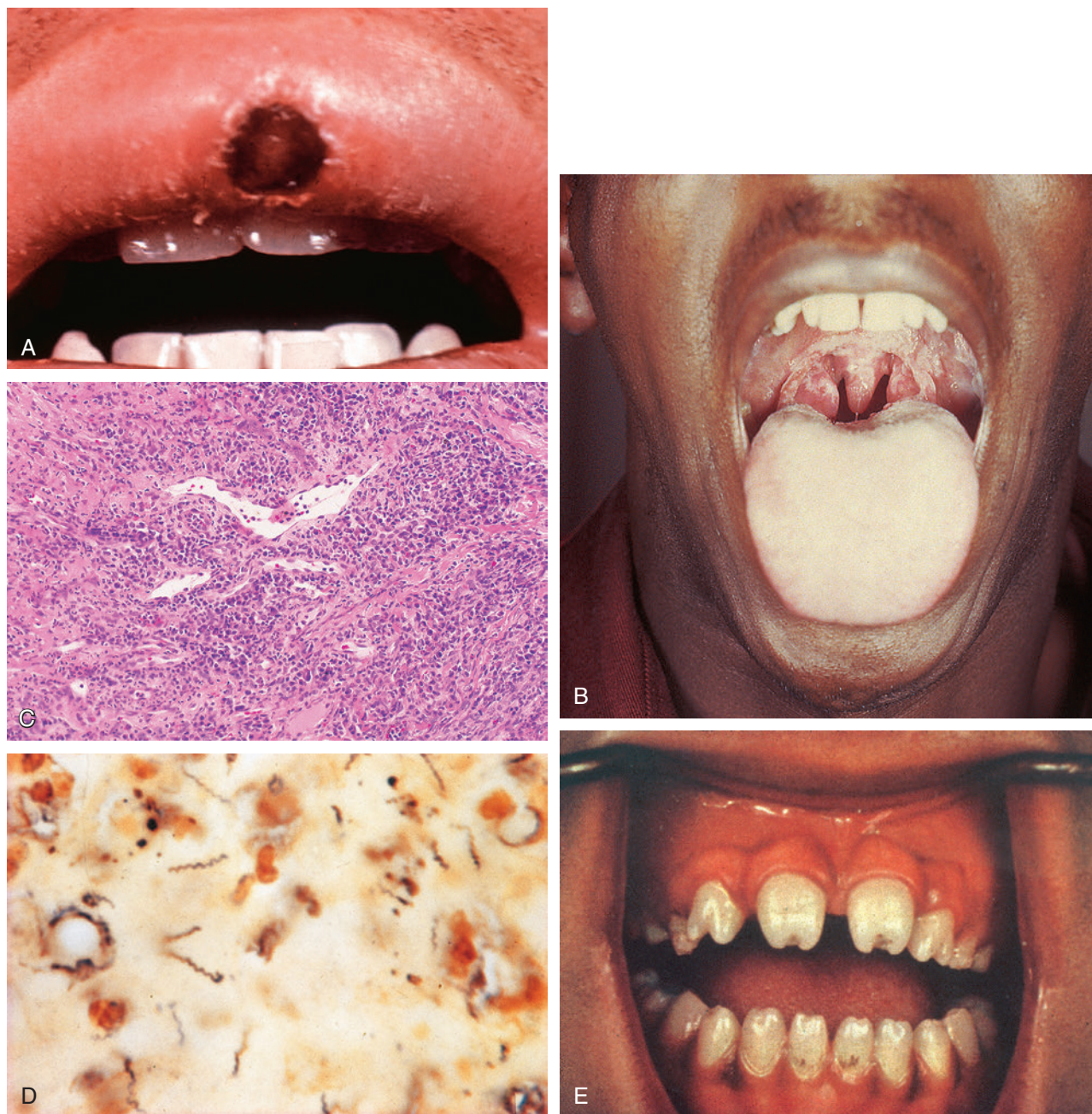


Fig. 9-16. Syphilis.

A, Chancre of the lip. **B**, Syphilitic pharyngotonsillitis appearing as diffuse white exudate overlying the soft palate, uvula, and tonsils. **C**, Histologic findings include an inflammatory infiltrate predominantly composed of plasma cells, as well as scattered histiocytes, lymphocytes, and neutrophils with a tendency to cluster around small blood vessels. **D**, Microorganisms can be demonstrated by Warthin-Starry staining appearing as elongated, thin rod-like, or corkscrew-shaped structures. **E**, Hutchinson's incisors seen in congenital syphilis in which the teeth are small with abnormal notching.

- Microhemagglutination–T. *palladium* test (MHA-TP):
 - MHA-TP is preferred owing to its relative simplicity.
- Enzyme immunoassay (EIA) increasingly used for screening

Pathology

Histology

- An inflammatory infiltrate can be seen that is predominantly composed of plasma cells with scattered histiocytes, lymphocytes, and polymorphonuclear leukocytes:
 - Inflammatory infiltrate has a tendency to involve small blood vessels that display endothelial cell proliferation (“plasma cell endarteritis”).
 - Concentric layers are produced that markedly narrow affected vessel’s lumen, resulting in obliterative endarteritis.
 - Obliterative endarteritis coupled with the inflammatory infiltrate produced by the spirochetes represents the histologic hallmarks of the disease.
- Histochemistry:
 - Microorganisms can be demonstrated in the chancre by Warthin-Starry staining and appear as elongated, thin, rod-like structures.
- Diagnosis of treponematoses:
 - Darkfield microscopy
 - Fluorescence microscopy
 - Immunohistochemistry

Differential Diagnosis

- Nonspecific inflammatory reactions

Treatment and Prognosis

- Treatment of choice remains penicillin:
 - Penicillin G and other β -lactam antibiotics:
 - Single intramuscular injection
 - For those persons allergic to penicillin, doxycycline and tetracycline are effective alternatives.

Additional Notes

- Congenital syphilis:
 - Develops via transplacental infection
 - Primarily occurs with mucocutaneous and osseous manifestations including in decreasing percentage: frontal boss > short maxilla > high palatal arch > saddle nose > mulberry molars > Hutchinson incisors > sternoclavicular thickening > interstitial keratitis > rhagades > VIII nerve deafness

Bacillary Angiomatosis (BA) (Fig. 9-17)

Definition: Pseudoneoplastic capillary proliferative lesion almost exclusively occurring in immunocompro-

mised patients (as a complication of HIV infection), usually presents as a cutaneous vascular lesion and is caused by an opportunistic bacterial infection belonging to *Bartonella* species (formerly *Rochalimaea*).

Synonyms: Epithelioid angiomatosis; epithelioid hemangioma-like vascular proliferation

Pathogenesis

- *Bartonella* is a genus of small gram-negative bacilli that includes a number of species pathogenic for humans, including:
 - *Bartonella henselae*
 - *Bartonella quintana*
 - *Bartonella bacilliformis*
 - *Bartonella elizabethae*
- Bacillary angiomatosis is caused by *B. henselae* or *B. quintana*.

Clinical

- No gender predilection; occurs over a wide age range
- Most commonly presents as a cutaneous lesion commonly associated with systemic symptoms, including fever, chills, weight loss, and night sweats
- Clinically, lesions are similar in appearance to lobular capillary hemangioma (pyogenic granuloma) and Kaposi sarcoma characterized by the presence of multiple erythematous papules with or without crusting.
- May involve other organs sites, including:
 - Lymph nodes
 - Spleen and liver
 - Mucosal sites of the upper respiratory tract
 - Conjunctiva
- May occur in association with Kaposi sarcoma
- May occur in immune-competent individuals

Pathology

Gross

- Varies widely from cutaneous erythematous papules to mushroom-shaped papules and nodules to deep-seated rounded lesions without change in skin color
- Exceptionally, may appear as a mucosal-based, erythematous nodular proliferation

Histology

- Regardless of its clinical presentation, the histologic features are the same and include a well-circumscribed lobular capillary proliferation with overall features similar to those seen in lobular capillary hemangioma.
- Small capillaries are arranged around ectatic vessels, which are lined by prominent-appearing endothelial cells.
- Cytologic atypia, mitotic figures, and necrosis are not usually present but occasionally may be seen.

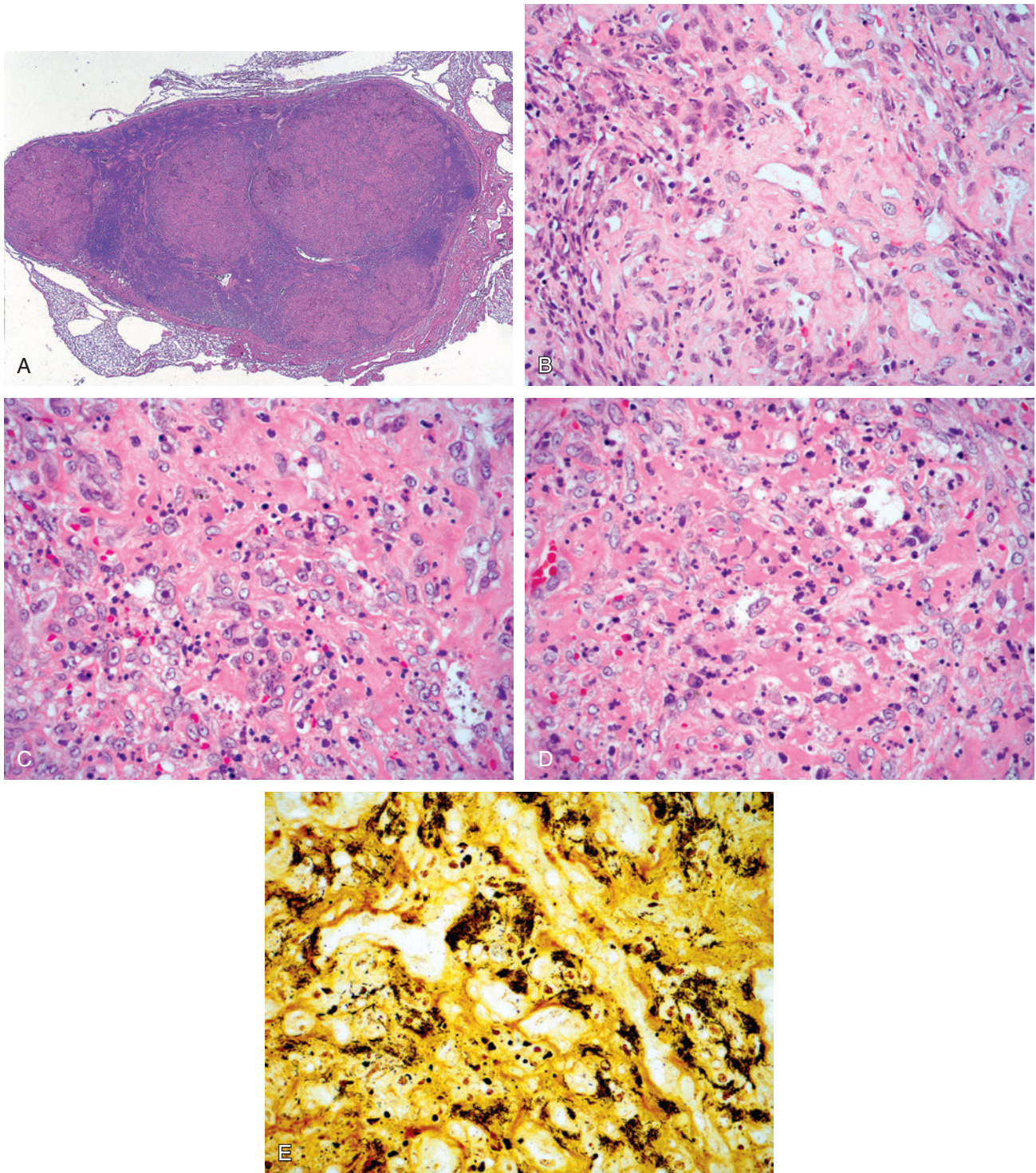


Fig. 9-17. Bacillary angiomatosis (BA).

A, Lymph node replaced by well-circumscribed lobular proliferation. **B**, Proliferation of small capillaries lined by prominent-appearing endothelial cells; an associated fibrotic stroma is present. **C** and **D**, Solid area obscuring the vascular proliferation including atypical, enlarged vesicular nuclei with prominent nucleoli; note the presence of neutrophils and/or neutrophilic debris representing an important histologic feature in BA. **E**, Warthin-Starry staining shows slender-appearing rod-shaped bacilli representing *Bartonella* species (formerly *Rochalimaea*), either *B. henselae* or *B. quintana*. Bacilli form the darker staining clumps.

- Solid areas may be present and may obscure the vascular proliferation.
- A variable edematous, mucinous, or fibrotic stroma is seen separating the lobular proliferation.
- An important histologic feature is the presence of neutrophils and neutrophilic debris adjacent to the capillary proliferation; associated with the neutrophils are granular clumps.
- Typically lacks spindled cells, interconnecting vascular channels, or hyaline globules.
- Overlying epithelium may be ulcerated, thinned, or show pseudoepitheliomatous hyperplasia.
- Histochemical stains:
 - Warthin-Starry staining shows individual slender rod-shaped bacilli, which form the darker staining granular clumps.
- Immunohistochemistry:
 - Endothelial cells are positive for CD31, CD34, Factor VIII-related antigen
 - HHV-8 negative
- PCR used to identify the presence of microorganisms confirming the diagnosis:
 - Routine cultures considered inadequate for isolating bacilli.

Differential Diagnosis

- Lobular capillary hemangioma
- Epithelioid hemangioma
- Angiosarcoma
- Kaposi sarcoma:
 - HHV-8 positive

NOTE: The presence of granular material, neutrophils, and neutrophilic debris and the absence of cytologic atypia, ramifying and interconnecting vascular channels, necrosis, mitotic activity, and hyaline globules, assist in differentiating BA from these other vascular lesions.

- Verruga peruana, another vascular proliferation process caused by an infectious agent (*Bartonella bacilliformis*), is endemic to Peru:
 - Presence of characteristic inclusions referred to as Rocha-Lima inclusions allows for differentiation
 - Rocha-Lima inclusions that consist of conglomerates of intracytoplasmic granules that are colored red by Romanowsky-Giemsa stains may be seen within the endothelial cells.
 - Finding of Rocha-Lima inclusions on light-microscopic studies and/or the demonstration of *Bartonella* organisms in the lesions can establish the diagnosis in a given lesion.

Treatment and Prognosis

- Treatment for BA is directed at the causative microorganism:
 - Erythromycin is the preferred drug and is effective, often resulting in the resolution of the lesions.

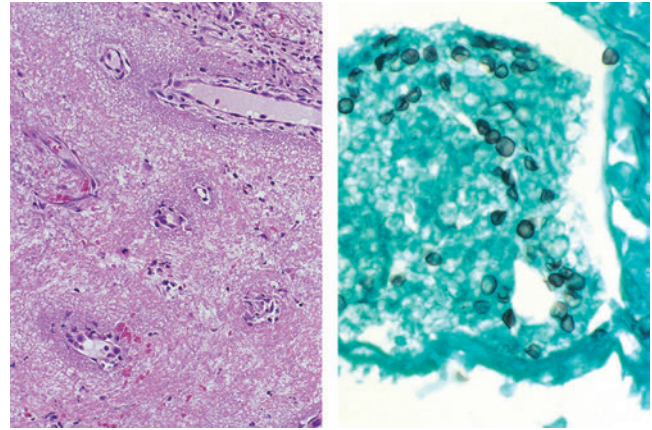


Fig. 9-18. *Pneumocystis jiroveci* (formerly *carinii*).

Left, foamy exudate within which the (right) characteristic microorganisms are identified by Gomori methenamine silver (GMS) stain.

- Tetracyclines are the first alternative in patients who cannot tolerate erythromycin.
- Combination of doxycycline plus rifampin may be used in immunocompromised patients with severe disease
- If left untreated, BA is progressive and potentially life threatening.

PROTOZOA (Fig. 9-18)

- *Pneumocystis jiroveci* (formerly *carinii*) is an opportunistic organism that is usually associated with pneumonia in the immunodeficient host and is the most common life-threatening infection in AIDS patients.
- Unusual for pneumocystis to cause clinical manifestations outside of the pulmonary system
- In the head and neck, pneumocystis infection has been identified involving the external auditory canal and the middle ear (see Section 7).
- Clinical manifestations differ according to the site of infection and include ear pain, hypomobility of the tympanic membrane, and otitis media, as well as conductive and sensorineural hearing losses.
- Presumed mode of dissemination from the lung to extrapulmonary sites is via vascular channels; typically, the pulmonary manifestations of pneumocystis infection precede those of extrapulmonary involvement; however, on occasion the initial diagnosis of AIDS has been made following identification of its associated pathology in extrapulmonary locations.

Pathology

Gross

- May appear as a polypoid mass arising from the external or middle ear

Histology

- Findings are similar to those seen in the lung and include a submucosal foamy exudate within which the organism can be identified by Gomori methenamine silver (GMS) stain.
- Overlying epithelium is often ulcerated.

Treatment

- Treatment of otologic pneumocystosis should be directed at systemic pneumocystosis even in the face of subclinical pulmonary manifestations.

TANGIER DISEASE (Fig. 9-19)

Definition: Severe high-density lipoprotein (HDL) deficiency syndrome characterized by the accumulation of cholesterol in tissue macrophages (xanthomatous cells) in various body sites and prevalent atherosclerosis.

Clinical

- Initially observed on Tangier Island in the Chesapeake Bay area of the United States
- Rare autosomal-recessive disorder caused by mutation in the ATP binding cassette transporter 1 (*ABCA1*) gene:
 - *ABCA1* gene mediates the secretion of excess cholesterol from cells into the HDL metabolic pathway.
 - HDLs play a central role in transporting cholesterol from peripheral tissues to the liver for elimination from the body.
 - Impairment of HDL-mediated cholesterol transport favors cholesterol deposition in the

arterial wall and promotes development of arteriosclerosis.

- No gender predilection; occurs in all age groups
- Clinical manifestations relate to deposition of cholesteryl esters in nonadipose tissues chiefly in:
 - Peripheral nerves leading to neuropathy
 - Reticulo-endothelial organs, such as tonsils, liver, spleen, lymph nodes, and the cornea, causing their enlargement and discoloration
- Tonsillar involvement results in symptoms of pharyngotonsillitis.
- An association with early cardiovascular disease can be variable.
- A unique phenotype of Tangier disease from a novel splice site mutation in the *ABCA1* gene has been reported that is associated with a central nervous system presentation resembling multiple sclerosis and the presence of premature atherosclerosis.
- Laboratory findings:
 - Deficiency of HDLs, low levels of apoproteins, low levels of high-density lipoprotein cholesterol (HDL-C), low to normal low-density lipoprotein levels, and normal to increased plasma triglyceride levels

Pathology

Gross

- Tonsils are enlarged and yellow.

Histology

- Multifocal deposition of clear (xanthomatous) cells throughout the involved tissue

Differential Diagnosis

- Lipid storage diseases
- Nonspecific tonsillitis

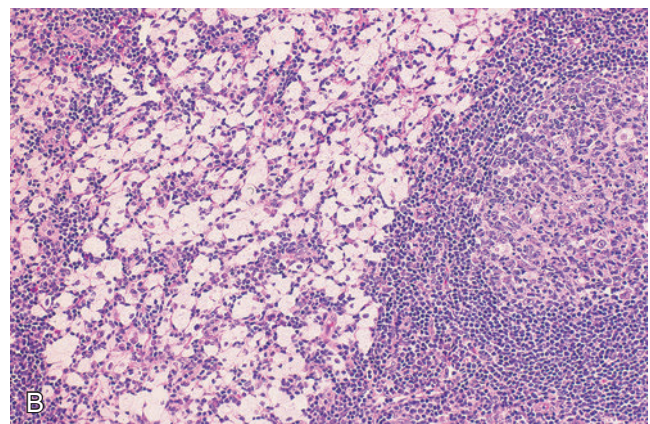


Fig. 9-19. Tangier disease.

A, Tonsillectomy specimen showing enlarged and slightly yellow-appearing tonsils. **B**, Deposition of xanthomatous cells in the tonsillar parenchyma.

Treatment and Prognosis

- Management is essentially symptomatic.
- To date, there is no specific treatment for Tangier disease:
 - Drugs known to increase HDL levels have been shown to be ineffective in Tangier patients.
 - Possible and more realistic therapeutic strategy designed to obtain selective increase of mature HDL concentration to restore cholesterol efflux
 - Recently designed drugs such as the cholesteryl ester transfer protein (CETP) inhibitors

dalcetrapib and anacetrapib and reconstituted forms of HDL could be considered until the development of gene therapy.

- Prognosis is good; however, coronary artery disease is common in patients over the age of 40 years of age.

FURTHER READING

References may be accessed online at [ExpertConsult.com](#).

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Neoplasms of the Pharynx

CLASSIFICATION OF PHARYNGEAL NEOPLASMS

(Box 10-1)

General Considerations

- Similar to tumors of other upper aerodigestive tract sites, the most common tumors of the pharynx are of epithelial origin:
 - The most common benign neoplasm is a (squamous) papilloma.
 - The most common malignant neoplasm is squamous cell carcinoma or variant thereof.
- Unique carcinoma types identified in pharyngeal sites are the viral-associated head and neck squamous cell carcinomas, including:
 - Epstein-Barr virus (EBV)-associated squamous cell carcinoma typically localized to the nasopharynx
 - Human papillomavirus (HPV)-associated squamous cell carcinoma typically localized to the oropharynx (i.e., tonsil and base of tongue)
- Incidence of viral-associated head and neck squamous cell carcinoma, in particular the HPV-associated carcinoma, is increasing while the incidence of nonviral-associated HNSCC-related to tobacco and alcohol has stabilized and even is decreasing.

BOX 10-1 Classification of Neoplasms of the Pharynx, Including Nasopharynx, Oropharynx, and Hypopharynx

Benign

Epithelial

- Squamous papilloma
- Minor salivary gland tumors

Mesenchymal/Neuroectodermal

- Angiofibroma
- Craniopharyngioma
- Vascular neoplasms (e.g., hemangioma, lymphangioma)
- Peripheral nerve sheath tumors
- Paraganglioma
- Lipomas
- Rhabdomyomas
- Fibrous histiocytic tumors
- Leiomyomas
- Osseous and cartilaginous tumors
- Others

Malignant

Epithelial/Neuroendocrine

- Squamous cell carcinoma including:
 - Conventional-type and variants (e.g., verrucous carcinoma, papillary [exophytic] squamous cell carcinoma, spindle cell squamous carcinoma, basaloid squamous cell carcinoma, adenosquamous carcinoma, others)

- Viral-related head and neck squamous cell carcinomas
 - HPV-associated squamous cell carcinoma
 - EBV-associated squamous cell carcinoma
- Neuroendocrine carcinomas
- Minor salivary gland tumors
- Low-grade nasopharyngeal papillary adenocarcinoma
- Others

Hematolymphoid Malignant Neoplasms

- Non-Hodgkin lymphomas
- Hodgkin lymphoma
- Plasma cell neoplasms
- Others

Melanocytic/Mesenchymal/Neuroectodermal

- Mucosal malignant melanoma
- Rhabdomyosarcoma
- Synovial sarcoma
- Chordoma
- Reticulum dendritic cell sarcoma
- Leiomyosarcoma
- Liposarcoma
- Malignant peripheral nerve sheath tumors
- Vascular neoplasms (e.g., angiosarcoma, others)
- Teratocarcinosarcoma

Secondary Neoplasms

BENIGN NEOPLASMS

SQUAMOUS PAPILLOMA

(Fig. 10-1)

Definition: Benign, exophytic epithelial neoplasm composed of branching fronds of squamous epithelium with fibrovascular cores.

Synonym: Squamous cell papilloma

Clinical

- Most common benign neoplasm of the upper aerodigestive tract mucosa but involvement of the nasopharynx and oropharynx is uncommon

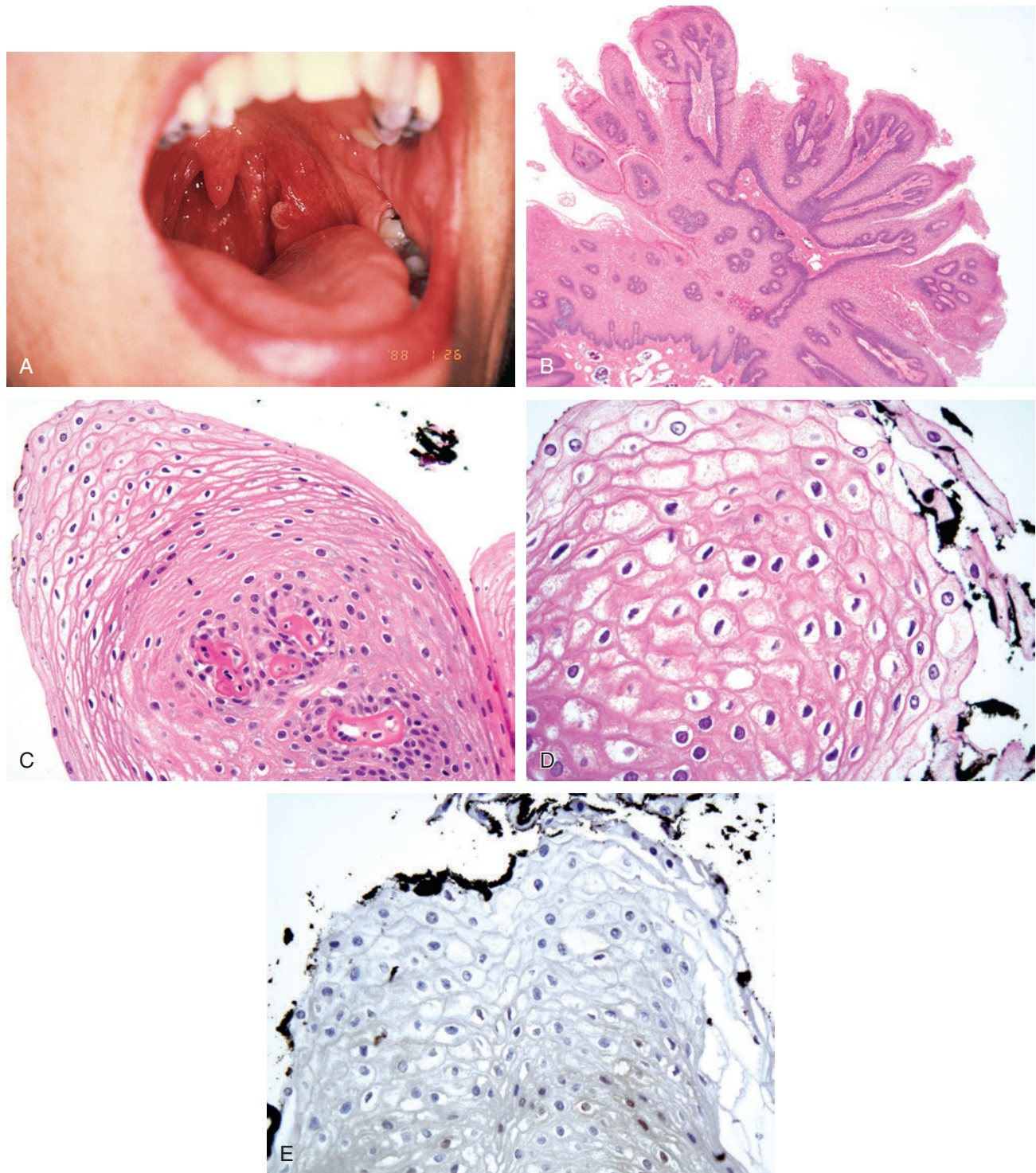


Fig. 10-1. Squamous papilloma of the pharynx.

A, Squamous papilloma of the tonsil appearing as an exophytic warty-looking lesion. **B**, Exophytic epithelial proliferation with fingerlike projections and fibrovascular cores. **C**, Papillary frond composed of a benign squamous epithelial proliferation devoid of surface keratosis. **D**, High magnification of cells with viral-associated changes (koilocytes) characterized by hyperchromatic, raisinoid-appearing nuclei with irregular nuclear contours; such papillomas are most often associated with low-risk HPV viruses including types 6, 11. **E**, By and large, squamous papillomas of the upper aerodigestive tract including those of the oropharynx are p16 negative.

- No gender predilection; most commonly seen in the third to fifth decades of life
- Any site can be affected but most frequently identified involving the tonsil and uvula
- Symptoms relate to a painless mass.
- Majority are solitary but occasionally may be multiple
- Viral (human papillomavirus [HPV]) cause:
 - No definitive association between HPV and the pharyngeal papillomas

Pathology

Gross

- Exophytic, pink to tan-white lesion with a warty or cauliflower-like appearance; variation in size from a few millimeters up to 3.0 cm in greatest dimension

Histology

- Multiple finger-like projections with prominent fibrovascular cores covered by hyperplastic squamous epithelium; typically there is an absence of keratosis:
 - Squamous cell component generally is free of any dysplastic change.
 - Variable amount of hyper-, para-, and orthokeratosis may be seen.
 - On rare occasions, an “inverted” growth may be seen.

Special Stains

- p16 immunohistochemical staining is negative.

Differential Diagnosis

- Verrucous carcinoma
- Exophytic squamous cell carcinoma

Treatment and Prognosis

- Conservative but complete surgical excision
- Recurrences occur infrequently and relate to inadequate excision.
- Malignant transformation not known to occur.

BENIGN MINOR SALIVARY GLAND NEOPLASMS

- Benign salivary gland neoplasms of the nasopharynx and oropharynx are uncommon but do occur.
- Virtually any benign or malignant salivary gland neoplasm may occur in the pharynx but:
 - Most common type is a pleomorphic adenoma
 - Less often, monomorphic adenomas including basal cell adenoma, myoepithelioma, and oncocytoma occur.

- The more common malignant minor salivary gland neoplasms of the pharynx include mucoepidermoid carcinoma and adenoid cystic carcinoma.
- For a more complete discussion see Section 2, Oral Cavity, and Section 6, Salivary Glands.
- Minor salivary gland neoplasms of the pharynx may appear as polypoid or exophytic growths, usually covered by an intact mucosa, and vary in size from 1 to 7 cm.
- Similar to minor salivary gland neoplasms of other upper aerodigestive tract, those of the pharynx, whether benign or malignant, are unencapsulated, but in contrast to malignant minor salivary gland tumors, benign minor salivary gland neoplasms are relatively circumscribed without invasive growth:
 - Often the initial diagnostic modality includes incisional biopsy, in which the neoplasm appears fragmented and often the fragments are entirely composed of the lesion without surrounding tissues; given the overlapping light microscopic findings (growth pattern, cell types) and immunoreactivity shared by the more common types of benign and malignant minor salivary gland neoplasms, in this setting:
 - Without unequivocal evidence of invasive growth, differentiation between a benign from malignant minor salivary gland neoplasm cannot be achieved.
 - S100 protein evaluating for the presence or absence of perineural invasion is useful as arguably the sole immunostain in this scenario; the absence of perineural invasion by light microscopy and S100 protein staining does not exclude a diagnosis of carcinoma.
 - Using the designation “minor salivary gland neoplasm, not further specified” is appropriate with the recommendation for conservative but complete resection to include tumor-free margins.
 - Following complete excision with availability of surrounding tissues to evaluate for the presence or absence of invasive growth, a definitive diagnosis should be achievable.
 - Involvement of surface epithelium does not constitute invasion.
- Surgical excision is the preferred treatment for all types of benign minor salivary gland tumors.
- Surgery is usually curative, with local recurrence being seen in less than 10% of patients:
 - Recurrent tumors are generally due to incomplete (initial) excision.

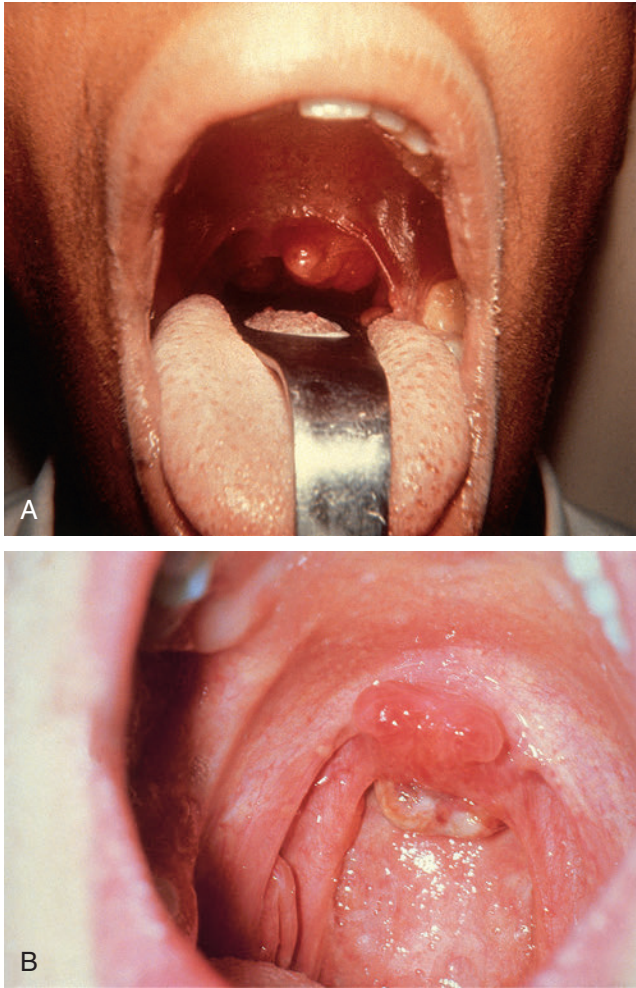


Fig. 10-2. Angiofibroma.

Clinical appearance of nasopharyngeal angiofibroma may include **(A)** lobulated, red-pink (vascular-appearing) mass or **(B)** tan-white (fibrous-appearing) mass. Both lesions originated from the posterolateral wall of the nasal cavity near the sphenopalatine foramen extending into the nasopharynx and oropharynx.

(NASOPHARYNGEAL) ANGIOFIBROMA

(Figs. 10-2 through 10-4)

Definition: Benign neoplasm composed of an admixture of mature vascular and fibrous tissue with locally destructive properties.

Synonyms: Juvenile angiofibroma; angiofibroma

NOTE: Evidence suggests that this tumor does not originate from the nasopharynx but rather from a fibro-vascular nidus in the posterolateral wall of the nasal cavity near the sphenopalatine foramen secondarily

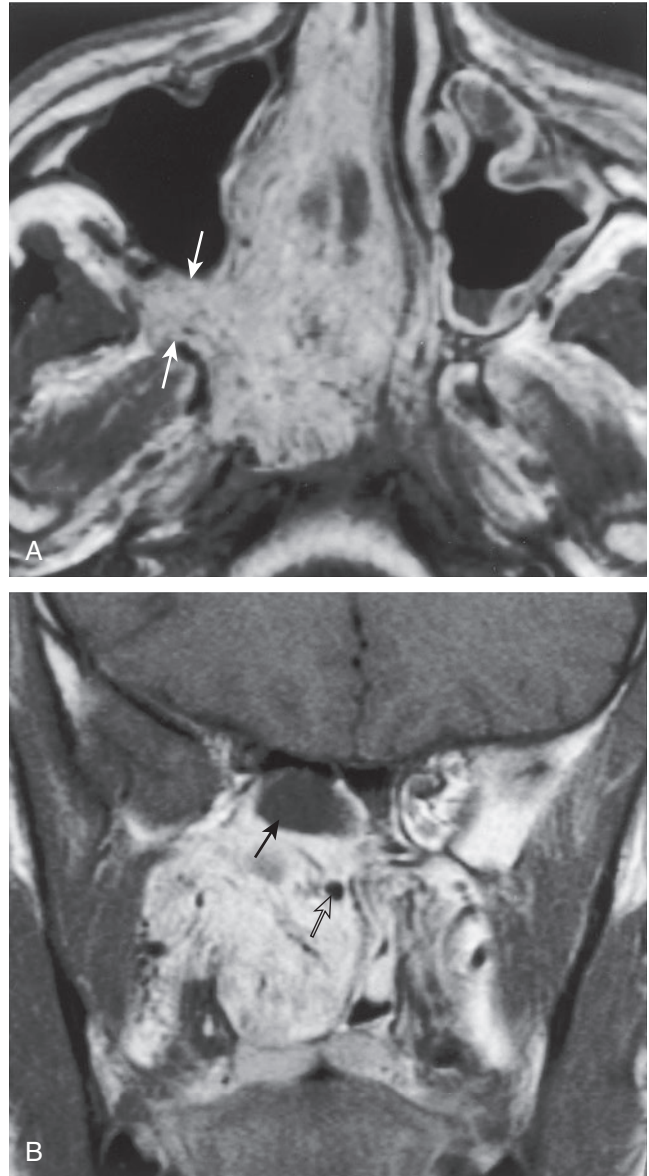


Fig. 10-3. Angiofibroma.

Juvenile nasopharyngeal angiofibroma (JNA) in a 14-year-old boy with chronic nasal obstruction and epistaxis.

A, Axial, contrast-enhanced, T1-weighted, MR image shows an intensely enhancing tumor filling the right nasal cavity and deviating the nasal septum. The pterygopalatine fossa and pterygomaxillary fissure are widened and filled with tumor (*arrows*). There is anterior displacement of the posterior wall of the right maxillary antrum. **B,** The coronal, contrast-enhanced, T1-weighted image reveals flow voids within the tumor (*open arrow*). The cephalad extent of the tumor is well seen on the coronal images. There are retained secretions within the sphenoid sinus (*arrow*).

(From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 30-106, p 1883.)

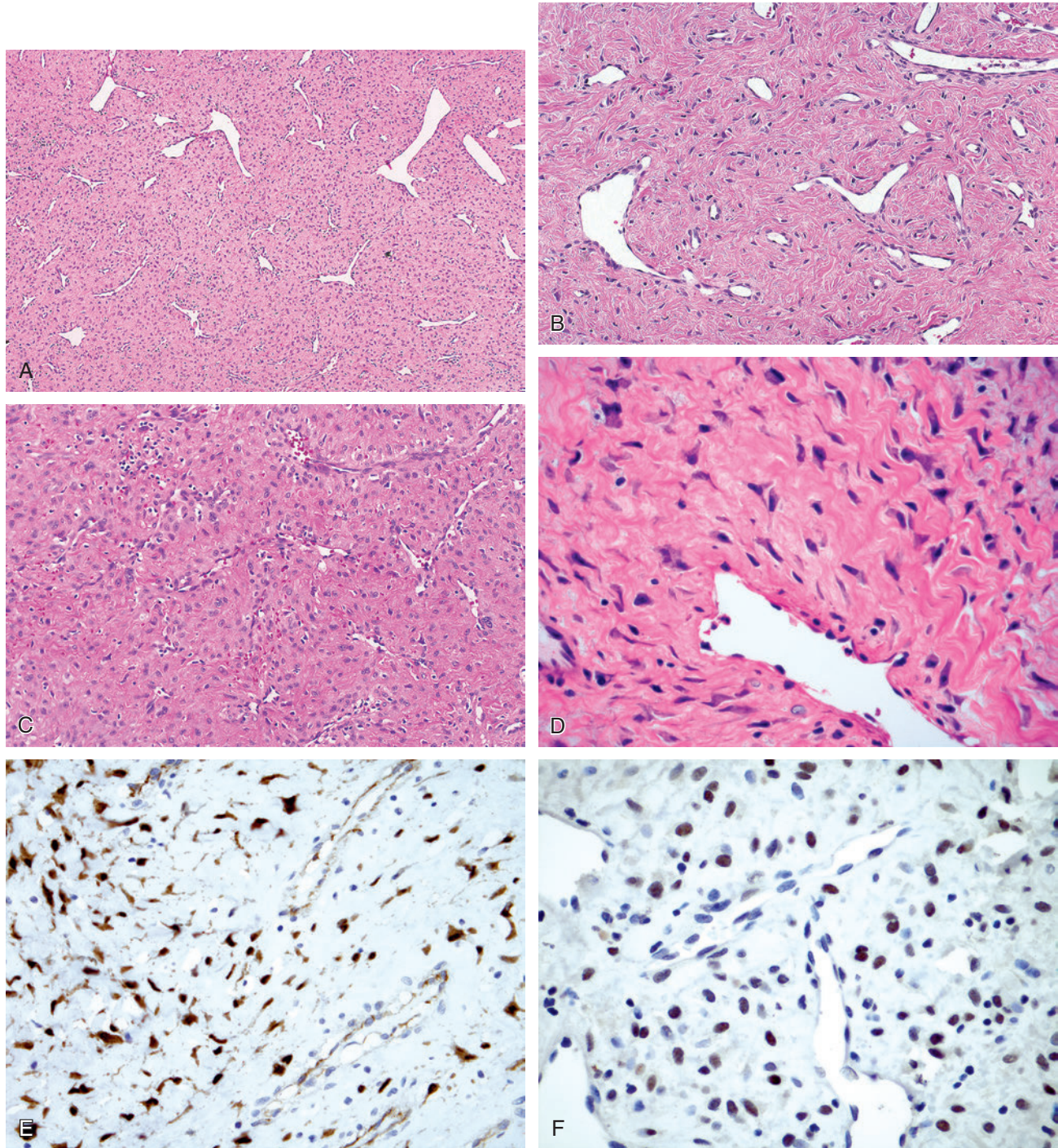


Fig. 10-4. Nasopharyngeal angiofibroma.

A through D, The tumor is composed of a variable admixture of blood vessels and fibrous tissue. The vascular component is composed of thin-walled blood vessels varying in appearance from stellate to staghorn to inconspicuous due to marked compression by stromal fibrous tissue; vessel walls are lined by flattened to plump endothelial cells forming a single layer and have an incomplete smooth muscle layer appearance. Stromal cells have spindle-shaped to stellate to plump nuclei with variable collagenized stroma. Immunohistochemical staining shows the spindle cells to be reactive for **(E)** β -catenin (nuclear staining) and **(F)** androgen receptor (nuclear staining).

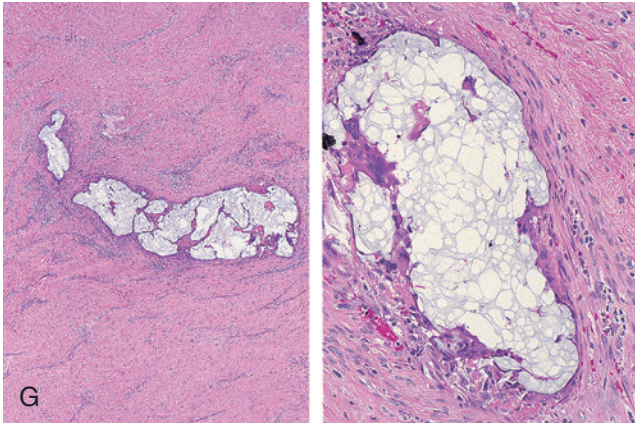


Fig. 10-4, cont'd

G, Intravascular foreign material with associated multinucleated (foreign body type) giant cells represents evidence of preoperative embolization in the attempt to infarct the tumor.

extending into the nasopharynx and other adjacent/contiguous anatomic sites:

- Given the presumed origin in the posterior nasal cavity, the use of the designation “nasopharyngeal” is questioned.
- These tumors are not strictly limited to juvenile ages so that the use of the designation “juvenile” is not recommended.

Clinical

- Relatively rare neoplasm accounting for less than 1% of all head and neck tumors
- Occurs almost exclusively in men, and some believe that it is a tumor limited to the male population; occurs over a wide age range but are most common in the second decade of life:
 - Uncommon over the age of 25 years
 - May occur in older ages, thereby negating the use of the designation “juvenile” angiofibroma
- Most common clinical complaints are persistent nasal obstruction and epistaxis:
 - Late signs and symptoms include facial swelling or deformity (swelling of the cheek), nasal discharge, proptosis, diplopia, headache, sinusitis, cranial nerve palsies, anosmia, and hearing deficits.
 - Pain may occur but is considered an unusual finding.
 - Typically, symptoms have been present for more than 1 year prior to diagnosis.
- Site of occurrence is usually the posterolateral portion of the roof of the nasal cavity in the area of the sphenopalatine foramen:
 - Large tumors may extend anteriorly into the nasal cavity, causing nasal obstruction and

simulating a primary intranasal or paranasal sinus tumor.

- Extension posteriorly may fill the nasopharynx and extend into the oropharynx, causing displacement of the soft palate.
- Extension can occur through the sphenopalatine foramen with involvement of the pterygomaxillary fossa and infratemporal fossa, resulting in facial deformities.
- Extension into the middle cranial fossa can occur if the tumor involves and destroys the pterygoid process.
- As a result of the overwhelming occurrence in males, this tumor is thought to be hormonally driven, being dependent on testosterone and inhibited with estrogen:
 - Androgen receptors have been found in these tumors but not estrogen receptors.
- Familial predisposition suggested in patients with familial adenomatous polyposis (FAP):
 - FAP results from germline mutations in the adenomatous polyposis coli (*APC*) gene that subsequently alters the β -catenin signaling pathway.
 - Patients with FAP develop nasopharyngeal angiofibroma 25 times more frequently than an age-matched population.
 - Role for the *APC*– β -catenin pathway has been suggested in patients with nasopharyngeal angiofibroma with the *APC* gene mutation.
 - Activating β -catenin mutation without the *APC* gene mutation has been reported in sporadic nasopharyngeal angiofibroma.
 - Immunohistochemical findings support the role of β -catenin in nasopharyngeal angiofibromas:
 - Expression of β -catenin, c-kit (CD117), and neural growth factor (NGF) higher and more frequent in stromal cells of nasopharyngeal angiofibromas than those of nasal polyps
 - Potential involvement of c-kit and neural growth factor (NGF) signaling pathways in the nasopharyngeal angiofibromas has been suggested.
 - Although the biologic significance of c-kit in nasopharyngeal angiofibromas has not been defined, the finding of frequent and high c-kit expression may have therapeutic importance.
 - In spite of the above findings, the association with nasopharyngeal angiofibroma and FAP has been disputed based on the absence of detectable mutations in *APC* gene in patients with nasopharyngeal angiofibroma.
- In a limited number of patients, consumptive coagulopathy has been found as a complication of nasopharyngeal angiofibromas, suggesting that

TABLE 10-1 Radiographic Staging of Nasopharyngeal Angiofibroma

Stage	Extent of Disease
I	Limited to nasopharynx with no bone destruction
II	Invasion into nasal cavity, maxillary, ethmoid or sphenoid sinuses with no bone destruction
III	Invasion of pterygopalatine fossa, infratemporal fossa, orbit, or parasellar region
IV	Massive invasion of the cranial cavity, cavernous sinus, optic chiasm, or pituitary fossa

preoperative coagulation studies may be useful in ensuring perioperative hemostasis.

- Radiology:
 - Routine radiographs show characteristic bowing of the posterior wall of the maxillary antrum, as well as distortion and posterior displacement of the pterygoid plates (Holman-Miller sign).
 - CT scan with contrast enhancement demonstrates the mass and its extension into adjacent areas.
 - Arteriographic findings are usually diagnostic and include a tumor with marked vascular hypertrophy and increased number of arteries without beading, dilatation, segmental narrowing, or aneurysmal dilatation.
 - Blood supply may be uni- or bilateral and typically comes from branches of the external carotid artery (internal maxillary or ascending pharyngeal branches).
 - Intracranial extension should be considered in cases where the internal carotid artery is the dominant vascular supply.
 - Various radiographic staging systems for nasopharyngeal angiofibroma based on extent of disease have been proposed (Table 10-1), with the two most often used proposed by Sessions (Table 10-2), which was subsequently modified by Radowski (Table 10-3).

Pathology

Gross

- May appear as sessile or lobulated masses but may occasionally be polypoid or pedunculated

Histology

- Unencapsulated and characterized by a fibrocollagenous stromal proliferation with an admixture of variably sized vascular spaces
- Vascular component is composed of thin-walled, small to large vessels varying in appearance from stellate or staghorn to barely conspicuous due to marked compression by stromal fibrous tissue.

TABLE 10-2 Sessions Staging of Nasopharyngeal Angiofibroma

Stage	Extent of Disease
IA	Tumor limited to posterior nares and/or nasopharyngeal vault; no paranasal sinus extension
IB	Same as IA but with extension into one or more paranasal sinuses
IIA	Minimal lateral extension through the sphenopalatine foramen, into and including a minimal part of the medialmost part of the pterygomaxillary fossa
IIB	Full occupation of pterygomaxillary fossa, displacing the posterior wall of the maxillary antrum forward. Lateral and/or anterior displacement of branches of the maxillary artery. Superior extension may occur, eroding the orbital bones
IIC	Extension through the pterygomaxillary fossa into the cheek and temporal fossa
III	Intracranial extension

Sessions RB et al: Radiographic staging of juvenile angiofibroma, *Head Neck Surg* 3:279-283, 1981.

TABLE 10-3 Modified (Radkowski) Staging of Nasopharyngeal Angiofibroma

Stage	Extent of Disease
IA	Limited to posterior nares and/or nasopharyngeal vault
IB	Tumor involving the posterior nares and/or nasopharyngeal vault with involvement of at least one paranasal sinus
IIA	Minimal lateral extension into pterygomaxillary fossa
IIB	Full occupation of pterygomaxillary fossa with or without superior erosion orbital bones
IIC	Extends into the infratemporal fossa or extension posterior to the pterygoid plates
IIIA	Erosion of base of skull (middle cranial fossa/base of pterygoids) – minimal intracranial extension
IIIB	Extensive intracranial extension with or without extension into cavernous sinus

Modified from Nicolai P, Schreiber A, Bolzoni Villaret A: Juvenile angiofibroma: evolution of management. *Int J Pediatr* 2012;412545, 2012.

- Endothelial cells form a single layer and are flat or plump in appearance.
- Vessel walls lack elastic fibers and are distinctive in having a smooth muscle layer which may be incomplete or discontinuous and which shows marked variation in thickness.

- Central aspects of the tumor may be relatively hypovascular.
- Stroma is composed of fibrous tissue with fine or coarse collagen fibers.
- Stromal cells are spindle-shaped and stellate with plump nuclei, and they tend to radiate around vessels.
- Nuclear pleomorphism and multinucleated giant cells may be seen; mitotic figures are rare.
- Stroma may be focally myxoid.
- Mast cells are common; however, other inflammatory cells are absent except near areas of surface ulceration.
- Evidence of preoperative embolization may be seen in tissue sections in the form of intravascular fibrin thrombi containing foreign material and tumor infarction.
- Tumors of longer duration tend to be more fibrous and less vascular.
- Immunohistochemistry:
 - Endothelial cells within the vascular spaces are reactive with:
 - Endothelial cell markers (e.g., CD31, Factor VIII–related antigen, CD34, others)
 - Smooth muscle actin-positive cells can be found around the circumference of the vascular spaces.
 - Spindle-shaped and stellate stromal cells are:
 - Vimentin positive
 - Nuclear β -catenin staining
 - Nuclear androgen receptor and testosterone positive
 - Estrogen and progesterone receptor negative
 - S100 protein negative
- Nonsurgical management has been proposed, including estrogen therapy, use of testosterone-receptor blockers such as flutamide, or radiation therapy:
 - These treatment modalities reduce the angiomatous component of the tumor and may be used in patients whose tumors are deemed unresectable.
- Complications associated with angiofibromas include excessive bleeding, recurrence of tumor, and extension of the tumor beyond the nasopharynx to involve adjacent anatomic compartments (sinonasal cavities, oropharynx, pterygomaxillary fossa, superior buccal sulcus, orbit, infratemporal fossa, and cranial cavity).
- Given their propensity to bleed, biopsies of the tumor should be performed with extreme caution.
- Recurrence rates vary from 6% to as high as 24%:
 - High recurrence rates and early recurrence may occur in nasopharyngeal angiofibromas involving the skull base.
 - Early postoperative contrast-enhanced helical CT is an accurate tool to evaluate excision of in the days after surgery.
 - Recurrences are more common in cases with intracranial extension.
 - Tumor recurrence in cases without intracranial extension usually occurs within 2 years of treatment.
- In general, the prognosis is excellent following surgical removal:
 - Mortality rates range from 3% to 9%.
 - Rarely, spontaneous regression may occur.
 - Malignant (sarcomatous) transformation is a rare event and has been linked to treatment with radiotherapy (post-irradiation sarcomas).

Differential Diagnosis

- Inflammatory nasal polyps
- Antrochoanal polyp
- Lobular capillary hemangioma
- Peripheral nerve sheath tumors
- Aggressive (desmoid) fibromatosis

Treatment and Prognosis

- In uncomplicated cases (with tumor limited to the nasopharynx), surgical excision via a transverse palatal approach is the preferred treatment.
- Vascular embolization usually precedes surgical intervention to control bleeding.
- Over the past two decades there has been a marked shift to less invasive endonasal approaches/procedures while the tumor stages of the patients treated remained the same.
- Successful management using less invasive techniques has been achieved with reduction in morbidity and without increasing the chance of recurrence.

CRANIOPHARYNGIOMA

(Figs. 10-5 and 10-6)

Definition: Rare benign epithelial tumor of the sellar region presumably derived from Rathke pouch epithelium.

Synonyms: Rathke pouch tumor; craniopharyngeal duct tumor; pituitary adamantinoma

- Considered to be a World Health Organization grade I (central nervous system) neoplasm (WHO grade I)

Clinical

- Most common non-neuroepithelial intracerebral neoplasm in children accounting for 5% to 10% of pediatric intracranial tumors
- Two clinicopathologic forms:
 - Adamantinomatous craniopharyngioma
 - Papillary craniopharyngioma

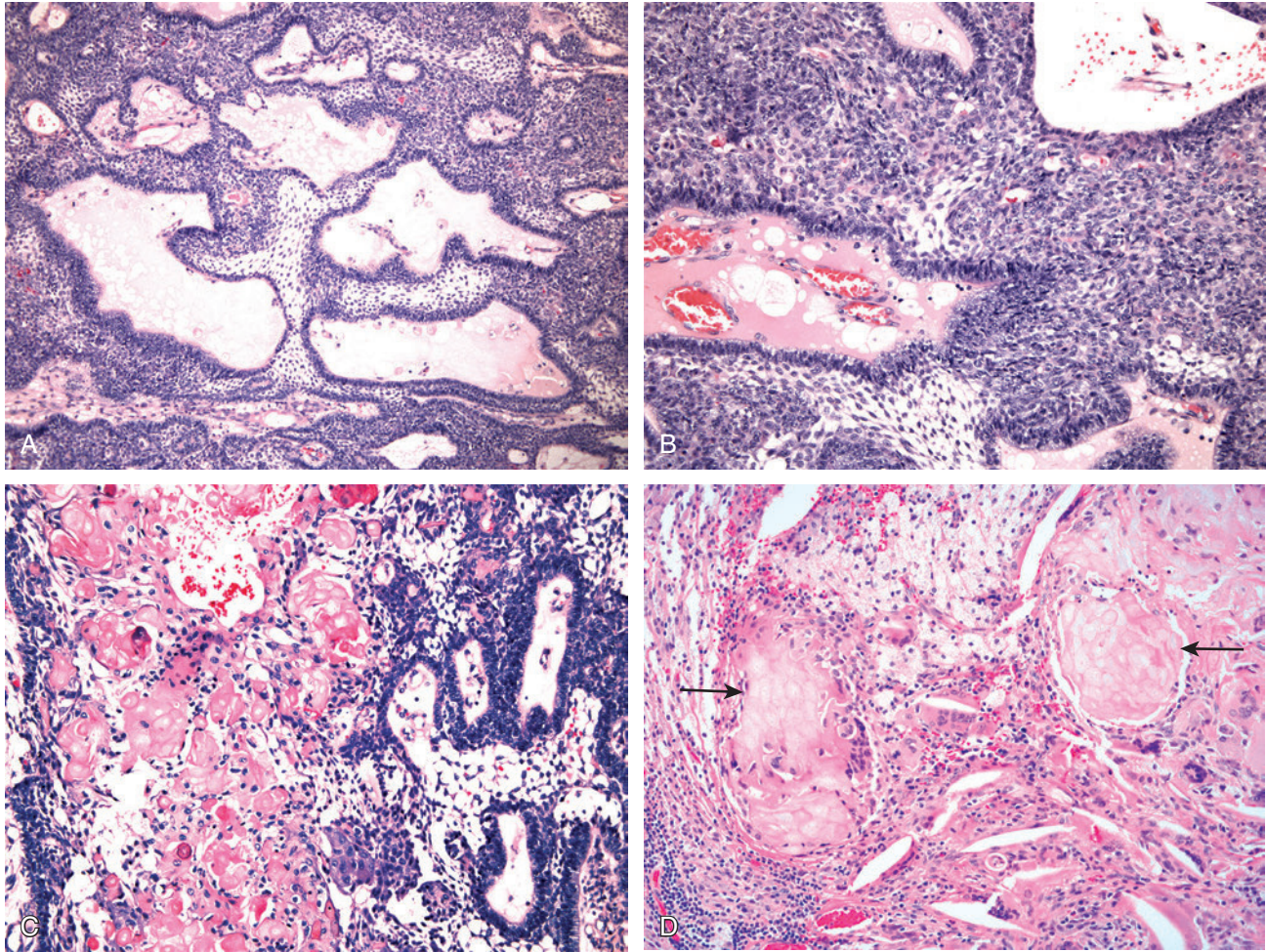


Fig. 10-5. Craniopharyngioma, adamantinomatous type.

A and B, Cellular proliferation with solid, cystic, and trabecular growth composed of multistratified squamous epithelium with peripheral palisading of nuclei resting on the basement membrane and foci showing a looser arrangement of the cells (stellate reticulum). **C,** Eosinophilic keratinized cells with ghost nuclei and associated calcification ("wet keratin") is present. **D,** Cholesterol granuloma formation is a common finding appearing as clear slit-like spaces with associated multinucleated giant cells (center and bottom of image); note the presence of foci of "wet keratin" (arrows) composed of eosinophilic acellular material with associated multinucleated giant cells as well as the presence of foamy histiocytes (top center).

- Adamantinomatous craniopharyngioma:
 - Slightly more common in males than females; bimodal age distribution including 5 to 14 years and adults over age 45 to 60 years
 - Most frequent is suprasellar with an intrasellar component
 - 20% restricted to suprasellar region
 - 5% entirely intrasellar
 - Extension of tumor may occur anteriorly into the middle cranial fossa and retroclival
 - Ectopic locations occur and include:
 - Optic nerves, pineal region, sphenoid bone, nasopharynx, and cerebellopontine angle
 - Symptoms include:
 - Visual disturbances:
 - More frequent in adults
 - Include loss of central vision
 - Headache
 - Endocrine deficiencies:
 - More common in children
 - More commonly seen in association with the papillary variant
 - Include deficiencies in growth hormone (75%), luteinizing hormone and/or follicle-stimulating hormone (40%), adrenocorticotrophic hormone (25%), and thyroid-stimulating hormone (25%)

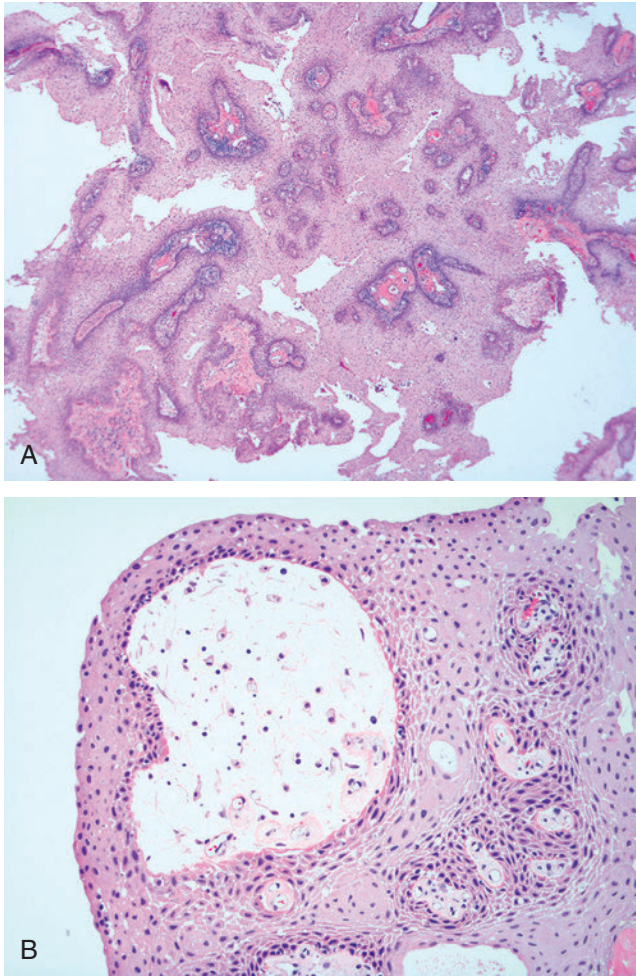


Fig. 10-6. Papillary craniopharyngioma.

Craniopharyngioma, papillary type, composed of sheets of well-differentiated squamous epithelium that separate to form pseudopapillae with anastomosing fibrovascular stroma; the epithelial proliferation lacks surface maturation, peripheral palisading, stellate reticulum, calcifications, wet keratin, and cholesterol clefts that are seen in adamantinomatous craniopharyngiomas.

- Diabetes insipidus noted in 17% of children and up to 30% of adults
- Dementia:
 - Cognitive impairment and personality changes occur in approximately 50% of patients.
- Radiology:
 - Adamantinomatous variant appears as a calcified, solid, and cystic mass:
 - CT scan:
 - Contrast enhancement of solid portions of the cyst capsule

- T1-weighted MRI:
 - Cystic areas appear well delineated, homogeneous, and hyperintense.
 - Solid components and mural nodules are iso-intense with heterogeneous aspect.
- T2-weighted MRI:
 - Cystic portion is iso-intense with an enhancing ring.
 - Solid component is hyperintense.
- Papillary craniopharyngioma:
 - No gender predilection; occurs almost exclusively in adults
 - Usually involves the third ventricle
 - Symptoms include:
 - Vision loss
 - Increased intracranial pressure
 - Diminished mental acuity and personality changes
 - Endocrine deficiencies (see above under adamantinomatous craniopharyngioma)
 - Radiology:
 - Noncalcified, vary from solid to cystic
 - More uniform appearance in CT and MRI than adamantinomatous craniopharyngioma
- Nasopharynx represents most common purely extra-sellar location for craniopharyngiomas:
 - Ectopic localization in the nasopharynx may be associated with headache, nasal obstruction epistaxis, or impaired vision.
 - Exceptionally may occur in the sinonasal tract:
 - Sphenoid sinus, maxillary sinus, ethmoid sinus
 - Multiple simultaneous sites of occurrence may be identified, including nasopharynx, sella turcica, and sinonasal tract.

Pathology

- Adamantinomatous craniopharyngioma (similar to ameloblastoma and calcifying odontogenic cyst):
 - Nodular and multicystic
 - Solid, nests, cords, strands, or anastomosing trabeculae of multistratified squamous epithelium with peripheral palisading of nuclei resting on the basement membrane, intercellular bridges, keratin pearls, and (dystrophic) calcification
 - Central aspects of the tumor nests/cords show a looser arrangement of the cells (stellate reticulum).
 - So-called wet keratin composed of eosinophilic keratinized cells with ghost nuclei and associated calcification
 - Cyst lining cells may include columnar basaloid cells and/or flattened stratified squamous epithelium.
 - Cholesterol clefts/deposits

- Papillary craniopharyngioma:
 - Sheets of squamous epithelium that separate to form pseudopapillae with anastomosing fibrovascular stroma:
 - Epithelium separates to form crude pseudopapillae.
 - Typically lacks surface maturation, peripheral palisading, stellate reticulum, calcifications, wet keratin, and cholesterol clefts
 - Ciliated epithelium and goblet cells may focally be present.
- Cytogenetics and molecular genetics:
 - A molecular hallmark of adamantinomatous craniopharyngioma is the activated Wnt signaling pathway indicated by nuclear β -catenin accumulation in a subset of tumor cells.
 - β -catenin nuclear translocation may occur in the absence of CTNNB1 mutations, suggesting that other genetic or epigenetic events can activate Wnt signaling in adamantinomatous craniopharyngioma.

Differential Diagnosis

- Ameloblastoma:
 - Histologic similarities exist between ameloblastoma and craniopharyngioma, and rare occurrence of a (peripheral) ameloblastoma in the nasopharynx and rare occurrence of craniopharyngioma in infratemporal (e.g., nasopharyngeal) locations may result in differential diagnostic difficulties.
 - Other than anatomic location, there are no specific findings differentiating craniopharyngioma from ameloblastoma.

Treatment and Prognosis

- Surgical resection is the preferred treatment for both types of craniopharyngiomas irrespective of location.
- Slow-growing, benign tumor that may have locally aggressive behavior but no tendency to metastasize
- Due to location and potential involvement of vital structures, complete surgical resection may prove challenging, resulting in:
 - Local recurrence in approximately 20% to 50%
 - Need for adjuvant radiotherapy
- Survival rates include:
 - Overall 5-year survival of 80% but negatively affected by increasing age:
 - 99% for under 20 years
 - 79% for 20 to 64 years
 - 37% for 65 years and older
 - 10-year recurrence-free survival of 60% to 93%
 - 10-year overall survival of 64% to 96%
- Purported better prognosis reported for the papillary rather than adamantinomatous type but such findings not substantiated in the literature
- Malignant transformation to squamous cell carcinoma following radiotherapy is an extraordinarily rare occurrence:
 - p53 overexpressed in the malignant component
 - p53 expression much lower in the benign component
- De novo malignant craniopharyngioma (i.e., not developing from a previously treated benign craniopharyngioma) may (extraordinarily) rarely occur
- Radiation-induced gliomas reported following treatment of craniopharyngioma

MALIGNANT TUMORS

EPITHELIAL MALIGNANT NEOPLASMS

Squamous Cell Carcinoma (SCC) of the Pharynx, Including Nasopharynx, Oropharynx, and Hypopharynx

General Considerations

- Etiologic factors linked to the development of pharyngeal carcinomas vary per site and include:
 - Oncogenic viruses, including Epstein-Barr virus (EBV) and human papillomavirus (HPV):
 - Epstein-Barr virus (EBV):
 - Found in association with nasopharyngeal carcinomas, in particular nonkeratinizing differentiated and undifferentiated types

- For more complete discussion see later in this chapter
- Human papillomavirus (HPV):
 - Found in association with oropharyngeal carcinomas, in particular carcinomas originating from the tonsil and base of tongue
 - Nonkeratinizing histomorphology
 - For more complete discussion see later in this chapter
- Tobacco and alcohol:
 - Tobacco use/abuse includes smoking and chewing (smokeless tobacco)
 - Alcohol potentiates the carcinogenic effect of tobacco
 - Linked to cancers of the hypopharynx as well as keratinizing carcinomas of the nasopharynx and oropharynx

- Still represents a significant risk factor in oropharyngeal carcinomas

Viral-Related Head and Neck Squamous Cell Carcinomas

- Increasing evidence that Epstein-Barr virus (EBV) and human papillomavirus (HPV) play a pathogenic role in a subset of pharyngeal head and neck squamous cell carcinomas (HNSCC).
- Viral-related HNSCCs may be termed:
 - EBV-associated head and neck squamous cell carcinoma (EBV-HNSCC)
 - HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC)
 - Such designations are not as yet universally accepted but have merit given the unique clinical, pathologic, therapeutic, and prognostic implications associated with these cancers.
- For nasopharyngeal carcinomas (NPC):
 - EBV is associated with the nonkeratinizing types of nasopharyngeal carcinomas, including differentiated and undifferentiated subtypes:
 - Consistent (near 100%) association in Asian populations
 - Less consistent association in Caucasian populations which, in a significant proportion of cases, may be associated with HPV
 - Most reliable detection method for EBV is in situ hybridization for EBV encoded early RNA (EBER) present in cells latently infected by EBV and can facilitate the diagnosis of NPC.
- For oropharyngeal carcinomas:
 - HPV, in particular, the high-risk type 16 (HPV-16), is present in most oropharyngeal carcinomas (i.e., base of tongue, tonsils).
 - For those oropharyngeal cancers positive for high-risk HPV, HPV-16 is detected in more than 90% of cases.
 - p16 immunohistochemical staining is a reliable and sensitive surrogate marker for HPV-16.

Nasopharyngeal Carcinoma (NPC)

Definition: NPC is a squamous cell carcinoma originating from the nasopharyngeal mucosa showing evidence of squamous differentiation by light microscopy, immunohistochemistry, or electron microscopy.

Nomenclature: NPC is classified according to the World Health Organization (WHO) into two histologic variants:

1. Keratinizing type (well, moderately, and poorly differentiated)

BOX 10-2 World Health Organization (WHO) Classification of Nasopharyngeal Carcinoma (NPC)

WHO Type I

- Keratinizing squamous cell carcinoma

WHO Type II

- Nonkeratinizing differentiated
- Nonkeratinizing undifferentiated
- Basaloid squamous cell carcinoma

2. Nonkeratinizing, which is further subdivided into:
 - Differentiated type
 - Undifferentiated type
- Current WHO classification retains the terminology of the 1991 classification and adds the category of basaloid squamous cell carcinoma to this classification (Box 10-2).
- Prior numeric designations of WHO types 1 (squamous cell carcinoma), 2 (nonkeratinizing carcinoma), and 3 (undifferentiated carcinoma) are no longer used.
- Use of the designation nasopharyngeal carcinoma is to the exclusion of all other malignant tumors that may arise in this region, including adenocarcinomas (minor salivary gland origin and nonsalivary gland origin).

Synonyms: EBV-associated head and neck squamous cell carcinoma; EBV-associated carcinoma; lymphoepithelioma, Rigaud and Schmincke types of lymphoepitheliomas; transitional carcinoma

NOTES:

- The designation lymphoepithelioma is a misnomer; this is a tumor entirely of epithelial origin with a secondary associated benign lymphoid component. Use of the term lymphoepithelioma may result in confusion with a diagnosis of malignant lymphoma.
- Rigaud and Schmincke refer to patterns of growth and have no practical significance in the diagnosis, treatment, or prognosis of NPC.
- Although they share the unfortunate designation of “undifferentiated,” as well as overlapping histomorphologic features, there is no relationship between the sinonasal undifferentiated carcinoma (see Section 1, Sinonasal Tract) and the nasopharyngeal carcinoma, nonkeratinizing undifferentiated type:
 - These two tumor types are anatomically distinct with differing therapeutic approaches, biologic outcomes, and causes:
 - Nasopharyngeal carcinoma nonkeratinizing types are associated with EBV.
 - Sinonasal undifferentiated carcinoma (SNUC) is not associated with EBV.

TABLE 10-4 Nasopharyngeal Carcinoma (NPC)

	Keratinizing	Nonkeratinizing, Differentiated	Keratinizing, Undifferentiated
Percent	Approximately 25%	Least common <15%	Most common >60%
Sex/Age	M > F; 4th-6th decades	M > F; 4th-6th decades	M > F; 4th-6th decades; may occur in children
Histology	Keratinization, intercellular bridges; conventional squamous carcinoma graded as well, moderately or poorly differentiated; desmoplastic response to invasion	Little to absent keratinization, growth pattern interconnecting cords (similar to transitional urothelial carcinoma); typically, limited to absent desmoplastic response to invasion	Absence of keratinization, syncytial growth, cohesive or noncohesive cells with round nuclei, prominent eosinophilic nucleoli, scant cytoplasm, and limited mitoses; prominent non-neoplastic lymphoid component; typically, absence of desmoplastic response to invasion
EBV	Weak association	Strong association	Strong association
Treatment	Radio-responsiveness is not good	Radioresponsive	Radioresponsive
Prognosis	20% to 40% 5-year survival	75% 5-year survival	75% 5-year survival

Clinical (Table 10-4)

- Overall, NPC is an uncommon neoplasm in the United States, accounting for approximately 0.25% of all cancers:
 - In China, NPC accounts for 18% of all cancers, and 1 in 40 men develop NPC before the age of 72 years.
- Affects men more than women; occurs over a wide age range but is most common in the fourth to sixth decades of life:
 - Less than 20% of cases occur in pediatric age groups.
 - Pediatric NPC is most common in northern and central Africa, accounting for 10% to 20% of all cases, whereas only approximately 2% of NPC in China occurs in children.
- Signs and symptoms are often subtle and nonspecific and thereby may cause a delay in the diagnosis, resulting in clinical presentation at an advanced stage of disease.
- Clinical presentation may include:
 - Presence of an asymptomatic cervical neck mass typically localized to the posterior cervical triangle or the superior jugular nodal chain:
 - Can be present in up to 50% of patients as initial presentation for NPC
 - Primary carcinoma often occult
 - No correlation to size of primary NPC, which may be extremely small (millimeters), and size of nodal metastasis, which may be large (centimeters)
 - Bilateral cervical neck metastasis may be seen in up to 25% of cases.
 - A finding associated with WHO nonkeratinizing types of NPCs but typically not seen in association with WHO keratinizing types of NPCs.
 - Additional clinical signs and symptoms include nasal obstruction, nasal discharge, epistaxis, pain, serous otitis media, otalgia, hearing loss, and headache.
- Up to 25% of patients may experience cranial nerve involvement:
 - Cranial nerve involvement occurs by spread of tumor laterally through the cavernous sinus, with involvement of cranial nerves III, IV, ophthalmic branch of V and VI, and by direct tumor extension with involvement of cranial nerves IX, X, XI, XII and the third division of V nerve through the parapharyngeal space in proximity to the lateral nasopharyngeal wall.
- Lateral wall of the nasopharynx (fossa of Rosenmüller) is the most common site of occurrence followed by the superior posterior wall:
 - May result in unilateral otitis media and conductive hearing loss due to obstruction of the orifice of the eustachian tube opening into the lateral wall of the nasopharynx
 - Anecdotally, unilateral otitis media in an adult unresponsive to antibiotic therapy is NPC until proven otherwise.
- Radiology (Figs. 10-7 and 10-8):
 - Represents an important diagnostic aid in assessing the extent of disease and presence of metastatic disease
 - Magnetic resonance imaging (MRI) is the preferred study to computed tomography (CT) for the detection of invasion into soft tissues, intracranial extension, and invasion into bone:
 - Care must be taken with fat suppression because this often produces artifacts at air-bone interfaces at the skull base.
 - CT is very good for showing cortical bone erosion.

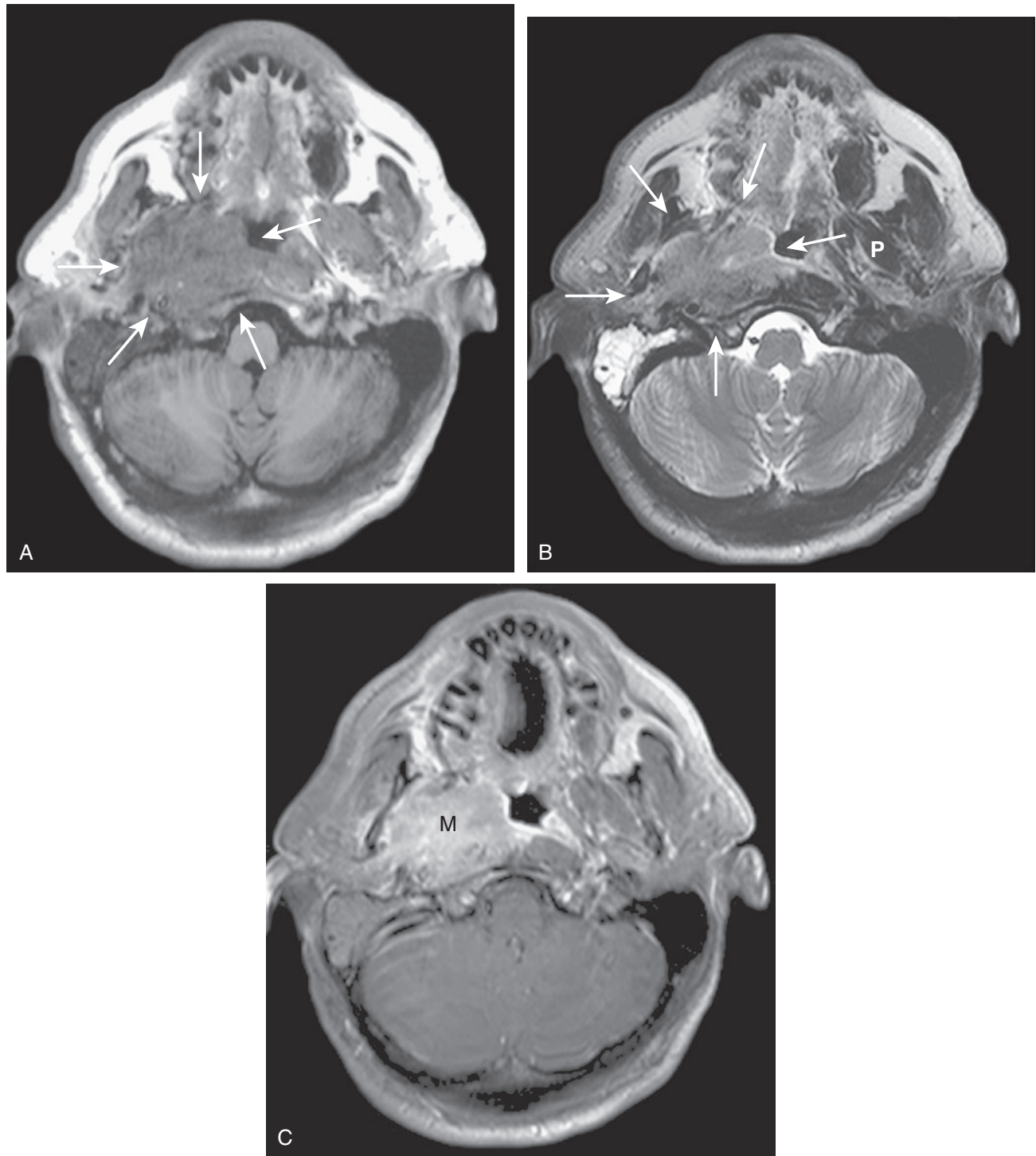


Fig. 10-7. Nasopharyngeal carcinoma.

A, Axial T1 precontrast MR image through an infiltrating right-sided nasopharyngeal mass (*arrows*). **B**, Axial T2-weighted image shows that the mass (*arrows*) extends laterally to involve the lateral pterygoid muscle, indicating a T4b lesion. Note the normal left lateral pterygoid muscle (*P*). **C**, T1-weighted, fat-suppressed, contrast-enhanced image demonstrates contrast enhancement of the tumor (*M*). This patient had a nasopharyngeal carcinoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 29-2, p 1751.)

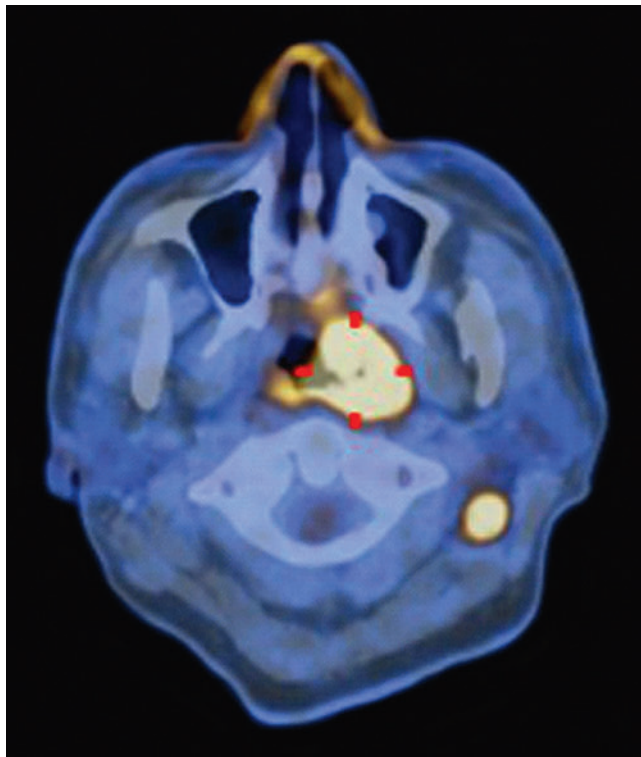


Fig. 10-8. Nasopharyngeal carcinoma.

Axial PET/CT scan shows a primarily left-sided nasopharyngeal mass that has spread along the mucosa to the right side. The standard uptake value of this tumor was 19. Also seen is a high right level IIB node. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 29-11, p 1757.)

- In addition to other imaging studies (e.g., conventional x-ray, ultrasound, computed tomography), positron emission tomography and computed tomography (PET-CT) are used in the detection of locoregional and distant spread of tumor.
- Multiple interactive etiologic factors have been linked to the development of NPC:
 - Genetic and geographic factors play an important role in the genesis of NPC:
 - Increased incidence of NPC in China, especially in southern (Kwantung province) and northern provinces and Taiwan
 - Although the incidence among Chinese people decreases after emigration to low-incidence areas, it remains higher than in non-Chinese populations.
 - HLA-A2, HLA-B17, HLA-Bw46, and HLA-BW58 histocompatibility loci have been suggested as the marker for genetic susceptibility to nasopharyngeal carcinoma.
 - Most important link to the development of NPC is the Epstein-Barr virus (EBV):
 - There is a strong association between nasopharyngeal nonkeratinizing carcinomas (differentiated and undifferentiated types) and the presence of EBV, indicating an oncogenic role of EBV in the development of NPC.
- Elevated titers of IgA antibodies (against viral capsid antigen [VCA]) and IgG antibodies (against early antigen [EA]) are seen in patients with NPC, with detection rates for NPC ranging up to 93%.
- Elevated titers have been used as a marker to screen populations in high-risk areas and as a potential indicator of disease relapse.
- Positive serology against EBV in 90% of patients with nonkeratinizing carcinoma has been reported.
- Newer antibody tests based on recombinant EBV antigens (e.g., EBV nuclear antigens [EBNA], membrane antigen [MA], others) have been used in the diagnosis of NPC as has quantitative PCR to test for elevated circulating EBV DNA in plasma and serum and have reported sensitivity rates in NPC of up to 96%.
- Molecular biologic analysis of NPC by either in situ hybridization or polymerase chain reaction (PCR) detects EBV DNA or RNA in from 75% to 100% of NPC:
 - This fact is not true of the keratinizing subtype, in which the detection of EBV genomes is variable and, if present, is generally limited to scattered dysplastic intraepithelial cells.
- EBV is an early initiating event in the development of NPC:
 - EBV has been found in preinvasive (precursor) nasopharyngeal lesions, and the EBV-DNA identified was clonal, suggesting that the preinvasive lesions arose from a single EBV-infected cell, and that these preinvasive lesions progressed to invasive cancer within 1 year.
- EBV infection in NPC shows expression of EBV nuclear antigen-1 (EBNA-1) and latent membrane protein-1 (LMP-1) with an abundance of EBV encoded early RNAs (EBERs).
- Elevated levels of circulating cell-free Epstein-Barr virus (EBV) DNA detected in plasma and serum samples from NPC patients:
 - Good sensitivity and specificity and might be helpful for the screening of NPC
- Human papillomavirus (HPV) has been reported in nasopharyngeal carcinomas of keratinizing and nonkeratinizing types:
 - HPV may have a pathogenetic role for some nasopharyngeal carcinomas.
 - HPV-associated nasopharyngeal cancers may be morphologically similar to the EBV-associated carcinomas but are negative for EBER and positive for p16.
 - Tend to occur in nonendemic populations, including Caucasians with history of smoking

- Other suggested factors implicated in NPC include diet (salted fish high in nitrosamines), poor hygiene, and nondietary environmental factors, including atmospheric agents such as dust, smoke, chemical fumes, domestic smoke from burning wood, grass, and incense, and inhalation (active or passive) of tobacco smoke, the use of herbal medicines, and the use of nasal inhalants in the treatment of nasal disease.

Pathology

Gross

- Varies from a mucosal bulge with an overlying intact epithelium to a clearly demonstrable mass with extensive involvement of the surface epithelium and/or frankly infiltrative to a totally unidentifiable lesion fortuitously sampled and identified by microscopic evaluation

Histology

Nasopharyngeal Carcinoma, Keratinizing Type (Fig. 10-9)

- Represents approximately 25% of all NPC and rarely occurs in patients under 40 years of age
- Characterized by the presence of keratinization and intercellular bridges and graded as well, moderately, or poorly differentiated

- A desmoplastic response is typically found in response to invasive growth by this histologic type of NPC.

Nasopharyngeal Carcinoma, Nonkeratinizing Differentiated Type (Fig. 10-10)

- Least common type of NPC, representing approximately 12% of all NPC
- Growth includes the presence of interconnecting cords or trabeculae
- Predominantly nonkeratinizing stratified cellular proliferation with absent to focal keratinization and interconnecting and ramifying cords with sharp delineation from the surrounding stroma
- Well-defined cell borders and vague intercellular bridges may be present; in any given case foci of keratinization may be present.
- Typically, there is an absence of a desmoplastic response to invasive growth.
- Highly associated with EBV
- May undergo cyst formation with associated necrosis:
 - May metastasize as cystic metastatic nonkeratinizing carcinoma to cervical neck region
 - Overall histologic features similar if not identical to oropharyngeal nonkeratinizing (HPV-associated) squamous cell carcinoma

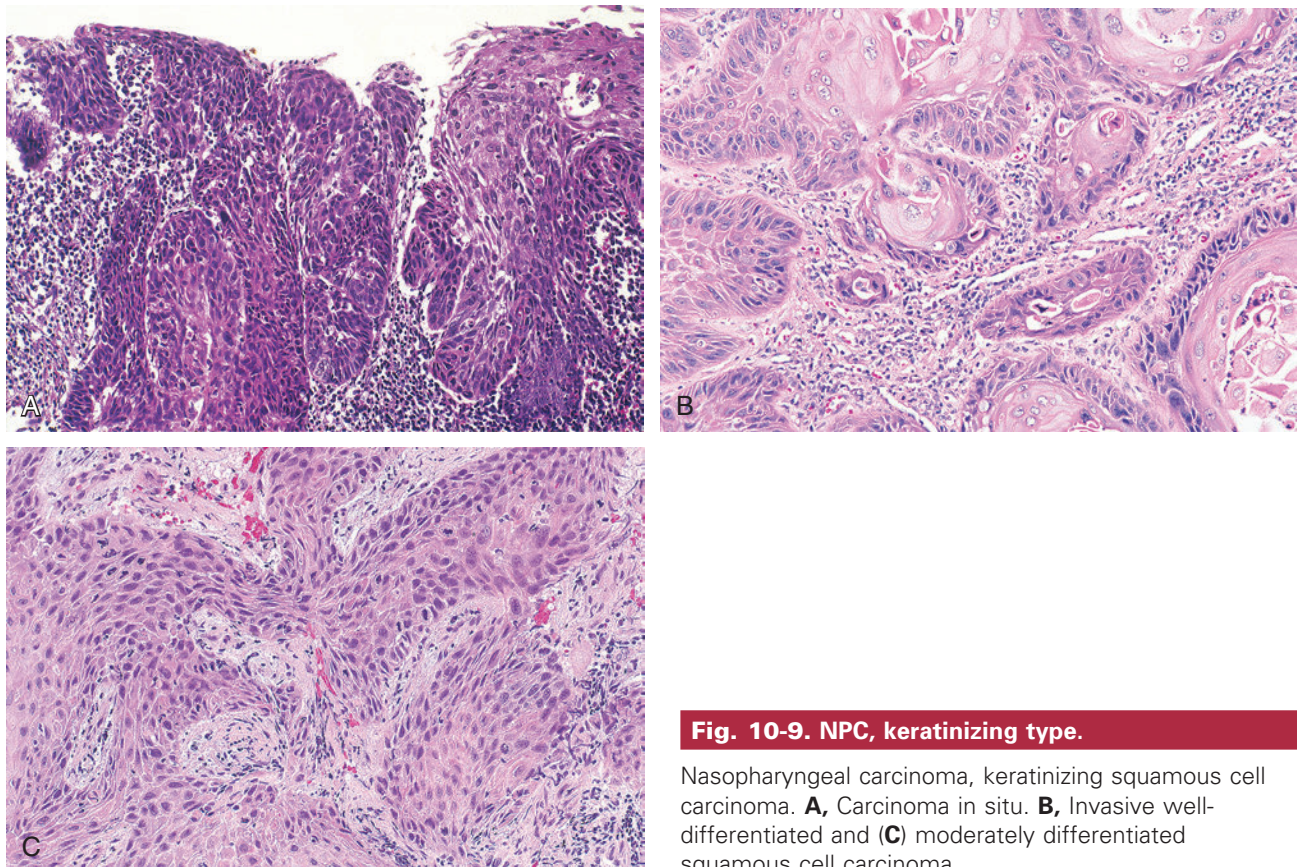


Fig. 10-9. NPC, keratinizing type.

Nasopharyngeal carcinoma, keratinizing squamous cell carcinoma. **A**, Carcinoma in situ. **B**, Invasive well-differentiated and (**C**) moderately differentiated squamous cell carcinoma.

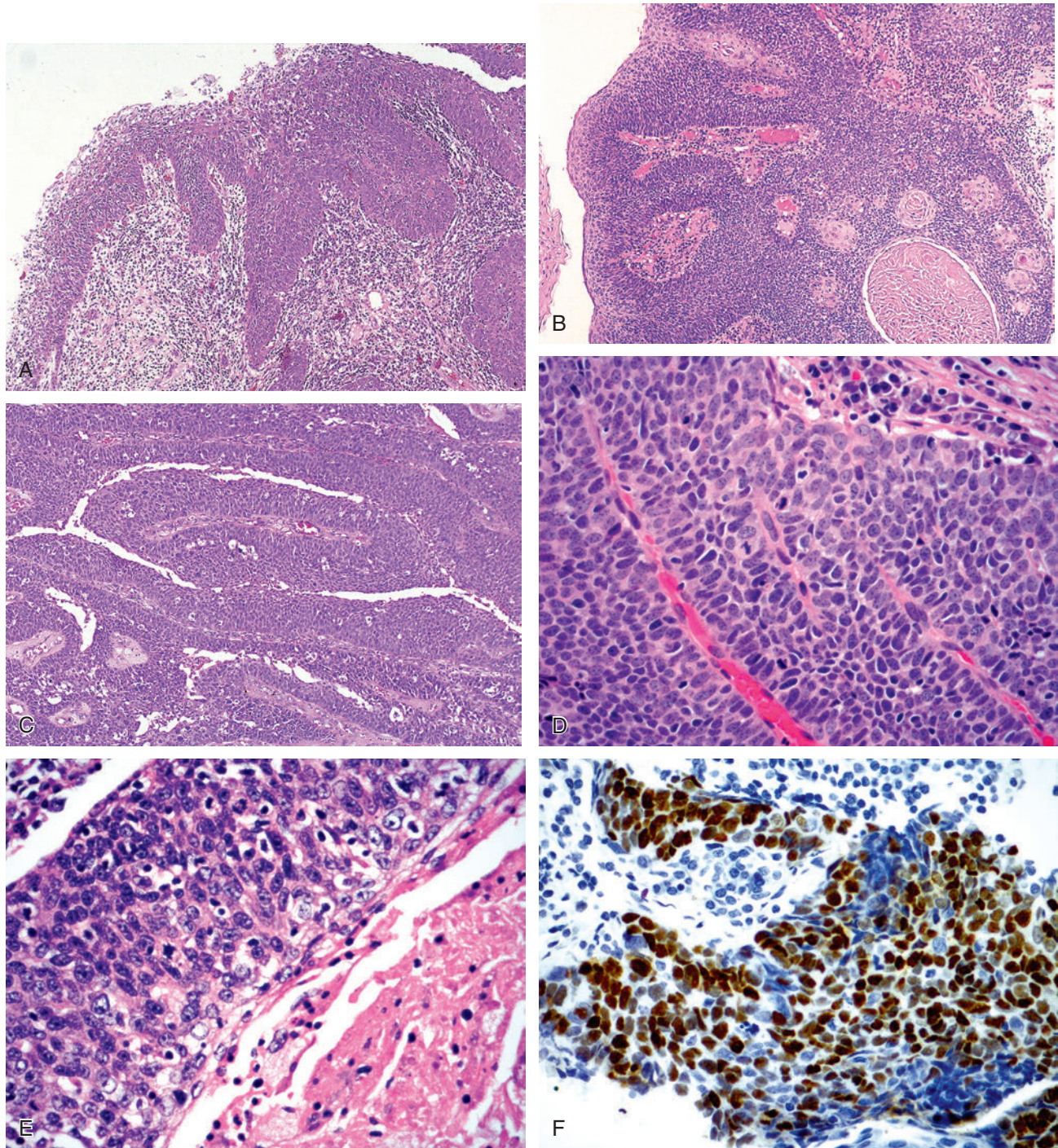


Fig. 10-10. Nasopharyngeal carcinoma, nonkeratinizing differentiated.

A, Carcinoma in situ. **B** and **C**, Interconnecting cords and trabeculae of infiltrative carcinoma originating from the surface epithelium and maintaining this pattern of growth in its depth. **D**, Higher magnification showing stratified cells delineated from the surrounding stroma with absent keratinization and increased mitotic activity. **E**, Cystic degeneration showing cyst filled with necrotic material (*bottom right*). This carcinoma may metastasize to cervical lymph nodes as cystic metastatic nonkeratinizing carcinoma from an occult primary carcinoma. The overall histologic features are similar if not identical to oropharyngeal nonkeratinizing (HPV-associated) squamous cell carcinoma. Differentiation predicated on the presence or absence of EBER and p16. **F**, Lesional cells are EBER positive (nuclear staining).

- Presence of EBER and absence of p16 confirm diagnosis and generally would establish nasopharynx as primary source for such metastatic carcinoma; however:
 - Examples of nasopharyngeal carcinoma, non-keratinizing type may be p16 positive and EBER negative (see below), especially in nodal metastasis from occult primary.
- No correlation between the size of the primary carcinoma, which may be only a few millimeters, and the neck metastasis, which may be large (several centimeters)

Nasopharyngeal Carcinoma, Nonkeratinizing Undifferentiated Type (Figs. 10-11 through 10-13)

- Represents approximately 60% of all NPC and is the most frequent tumor type seen in pediatric age groups
- Neoplastic cells are characterized by the presence of round nuclei, prominent eosinophilic nucleoli, dispersed nuclear chromatin, and scant eosinophilic to amphophilic cytoplasm.
- Keratinization is typically absent.
- Increased mitoses, including atypical forms, may be present.
- A prominent non-neoplastic lymphoid component composed of mature lymphocytes and plasma cells is seen in association with the malignant epithelial cellular infiltrate, although in any given example there may be a relative absence of an associated lymphoplasmacytic cell infiltrate:
 - Other inflammatory cell types that can be present include eosinophils and neutrophils, and scattered epithelioid granulomas may be present.
- May have a syncytial growth with cohesive or nested cells or has a diffuse cellular infiltrate composed of noncohesive cells:
 - Diffuse pattern is the one that is difficult to differentiate from a malignant lymphoma by light microscopy.
- Regaud and Schmincke patterns in nonkeratinizing carcinoma, undifferentiated type, refer to specific growth patterns, including:
 - Regaud pattern:
 - Cohesive (syncytial) nests and cords sharply distinct from surrounding lymphoid stroma
- Schmincke pattern:
 - Noncohesive cells (individual/single neoplastic cells or small tumor nests) infiltrated and potentially obscured by lymphoid infiltrate
 - These eponyms and their correlated growth have no bearing on the biology of the disease but may affect, especially with the Schmincke pattern, the diagnosis and differential diagnosis.
- Other uncommon cell types and/or growth patterns include:
 - Spindle-shaped neoplastic cells (Fig. 10-14)
 - Reticulated growth pattern (see Fig. 10-14)
- Infiltrative growth of this tumor generally does not produce a host desmoplastic response:
 - Absence of desmoplasia may be problematic in biopsy samples because the tumor may be overrun by the benign lymphoplasmacytic cell infiltrate and thus is easily overlooked.
 - Similarly, metastasis to cervical lymph nodes may not elicit a desmoplastic response in the involved lymph node.
- Because the distinction between the nonkeratinizing differentiated from the nonkeratinizing undifferentiated is of no clinical or prognostic significance, subclassification into differentiated and undifferentiated subtypes is optional:
 - Histologically, 26% of the NPC had features of more than one tumor type so that classification in such a situation is according to the dominant component.
 - Histologic distinction among the three types of NPCs may not always be clear, with overlapping histology in any given tumor.
- It is uncommon to identify the presence of a precursor lesion in the form of intraepithelial dysplasia or an in situ carcinoma:
 - If such a precursor lesion is present, the changes are similar to those of other upper aerodigestive tract sites and is characterized by the presence of a variably thickened epithelium with nuclear hyperchromasia, loss of cell polarity with nuclear crowding, increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and increased mitotic activity:
 - These changes can be seen in the surface or crypt epithelium.
 - In most examples an invasive carcinoma is present without identification of surface epithelial dysplasia and/or carcinoma in situ; nevertheless, NPC originates from nasopharyngeal surface or crypt epithelium.
- Immunohistochemistry (for all three histologic types):
 - Strong immunoreactivity for cytokeratins, including AE1/AE3, CAM5.2, CK5/6, OSCAR, and EMA
 - p63 (nuclear) strongly and diffusely reactive
 - No immunoreactivity for hematolymphoid markers (positive in non-neoplastic lymphoplasmacytic infiltrate, including CD45, CD3, and CD20), melanocytic markers, myogenic markers

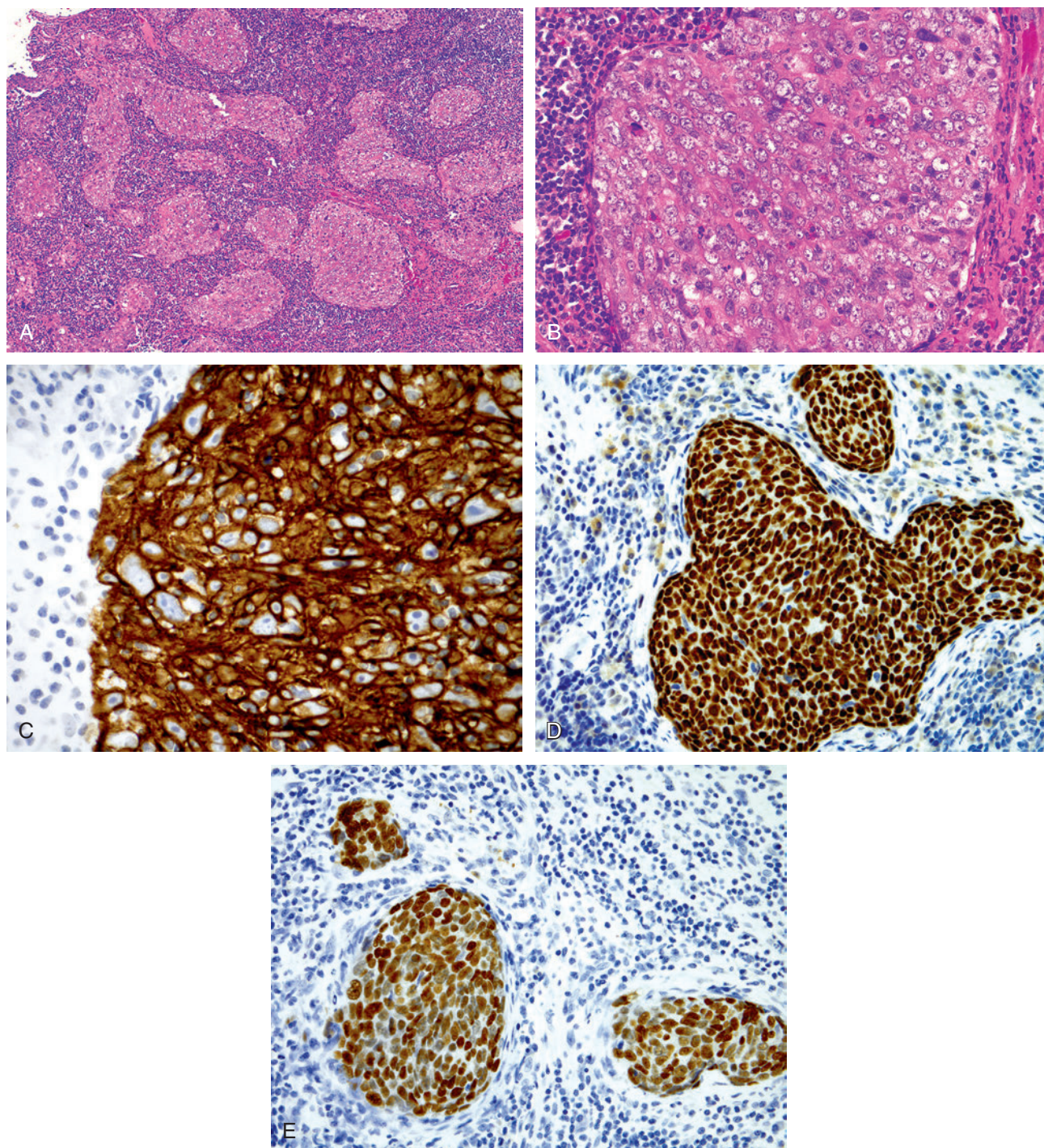


Fig. 10-11. Nasopharyngeal carcinoma, nonkeratinizing undifferentiated.

A, Infiltrating round to oval tumor nests surrounded by non-neoplastic lymphoid proliferation. Note the absence of a desmoplastic response to the invasive carcinoma. **B**, Syncytial neoplastic nests composed of cells with enlarged round to oval nuclei with vesicular chromatin, prominent eosinophilic nucleoli, and scant cytoplasm with indistinct cell margins; neoplastic cells are **(C)** cytokeratin positive, **(D)** p63 (nuclear) positive, and **(E)** EBER (nuclear) positive.

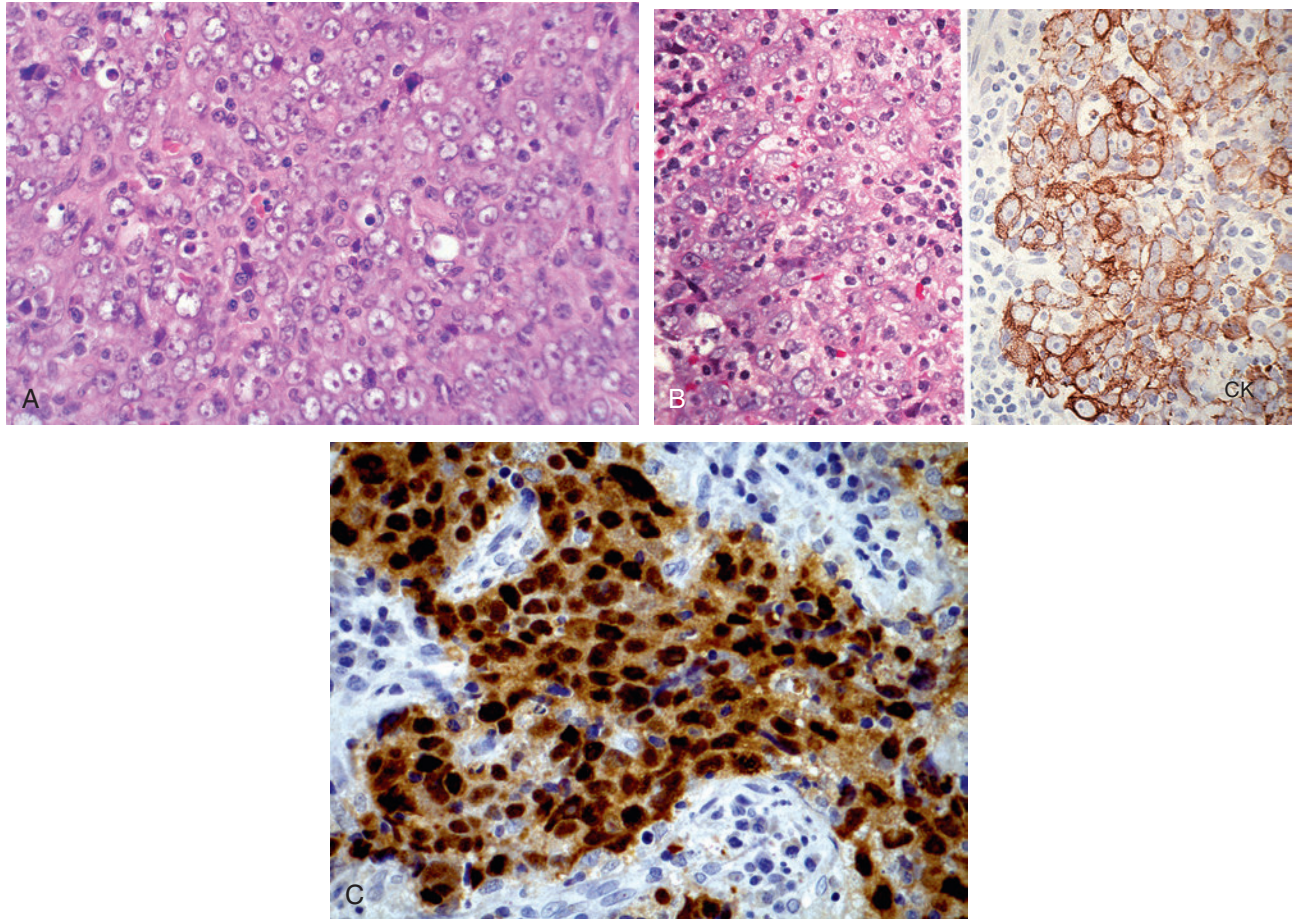


Fig. 10-12. Nasopharyngeal carcinoma, nonkeratinizing undifferentiated.

A and B (left panel), Diffuse, noncohesive cellular infiltrate composed of cells with oval or round vesicular nuclei, prominent eosinophilic nucleoli, scant cytoplasm, indistinct cell margins; the growth characteristics and cell types raise concern for a large cell B-cell lymphoma but **(B, right panel)** the neoplastic cells are cytokeratin positive with meshwork pattern of staining) confirming the diagnosis of carcinoma. **C,** Lesional cells are EBV positive (nuclear staining).

- Identification of EBV:
 - Immunohistochemistry:
 - Latent membrane protein 1 (LMP-1) reactivity:
 - Considered to lack sensitivity
 - In situ hybridization for Epstein-Barr encoded RNA (EBER):
 - Considered “gold standard”
 - Strong and diffuse nuclear staining
 - Invariably present in nonkeratinizing subtypes (i.e., differentiated, undifferentiated) but not true of the keratinizing subtype in which the detection of EBV genomes is variable and, if present, is generally limited to scattered dysplastic intraepithelial cells
- p16 immunoreactivity may be present in NPC (Fig. 10-15):
 - Morphologically similar to the EBV-associated carcinomas but will be negative for EBER and positive for p16
 - Cytogenetics and molecular genetics:
 - Consistent nonrandom deletions and rearrangement of the short arm of chromosome 3 found in NPC
 - Genetic instabilities (losses and gains) are common molecular events in NPC and play an important role in the development and progression of NPC:
 - Loss of heterozygosity (LOH) and comparative genomic hybridization (CGH) have shown high frequent allelic losses on chromosomes 1p, 3p, 9p, 9q, 11q, 13q, 14q, 16q, and 19q
 - CGH analysis has shown gains on chromosome 1q, 8q, 18q, and loss on 9p closely related to advanced stage of NPC
 - High frequent LOH on 3p in normal nasopharyngeal epithelium (74%) and dysplasia lesions (75%) from the southern Chinese have been found, suggesting that LOH at 3p may be an earlier genetic event of NPC tumorigenesis.

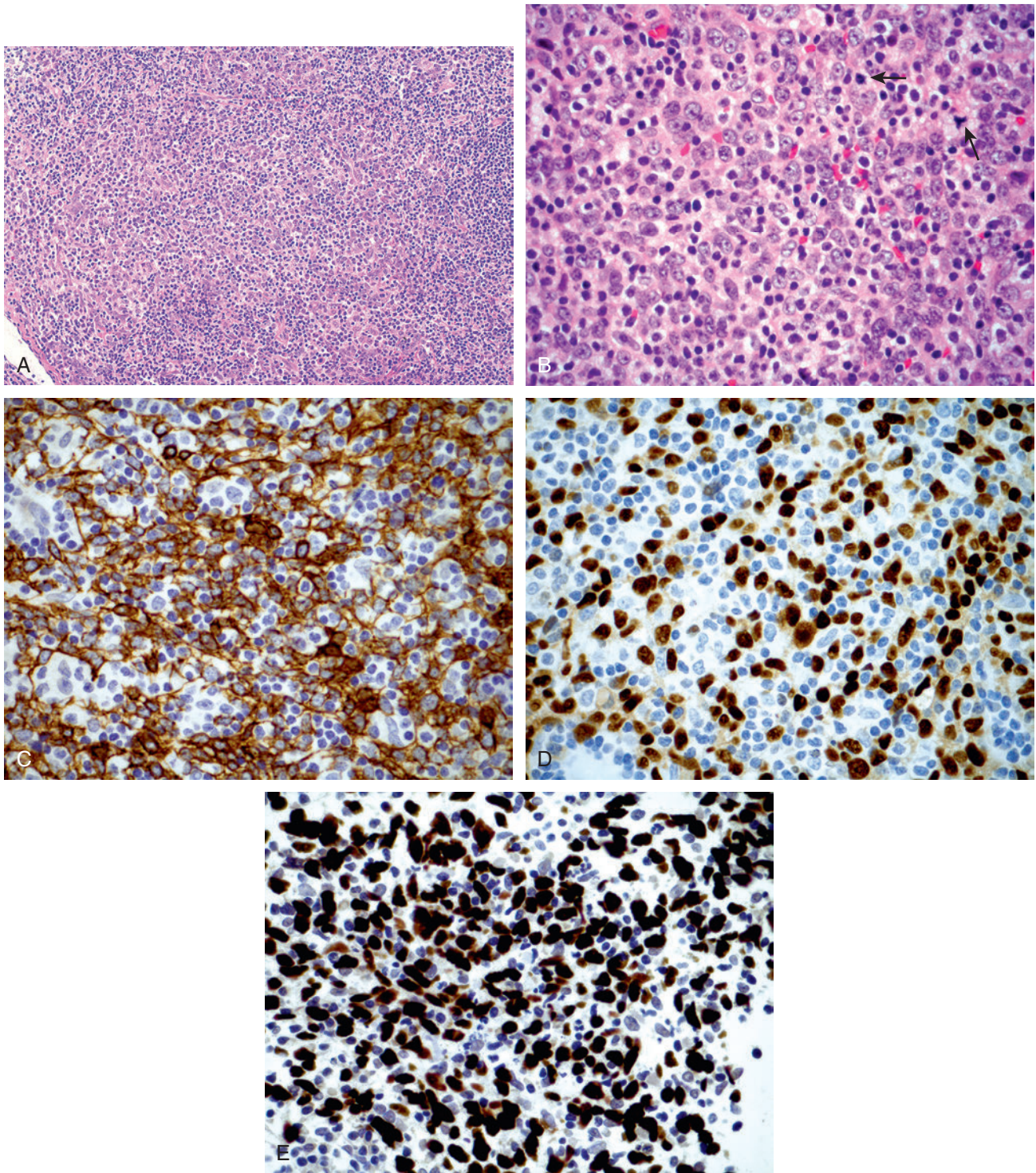


Fig. 10-13. Nasopharyngeal carcinoma, nonkeratinizing undifferentiated.

A, Owing to the absence of a host desmoplastic response to invasive carcinoma, at low magnification these findings appear to be those of a mixed inflammatory cell infiltrate with no suggestion that an invasive carcinoma is present. **B**, At higher magnification numerous neoplastic cells are seen but have the appearance of histiocytic cells as part of a mixed inflammatory cell infiltrate; scattered mitotic figures are present (*arrows*); the epithelial nature of the lesional cells are confirmed by the presence of (**C**) cytokeratin immunoreactivity showing a meshwork pattern of staining and (**D**) p63 (nuclear) staining. **E**, Strong association of the neoplasm with Epstein-Barr virus is confirmed by EBER positivity (nuclear staining).

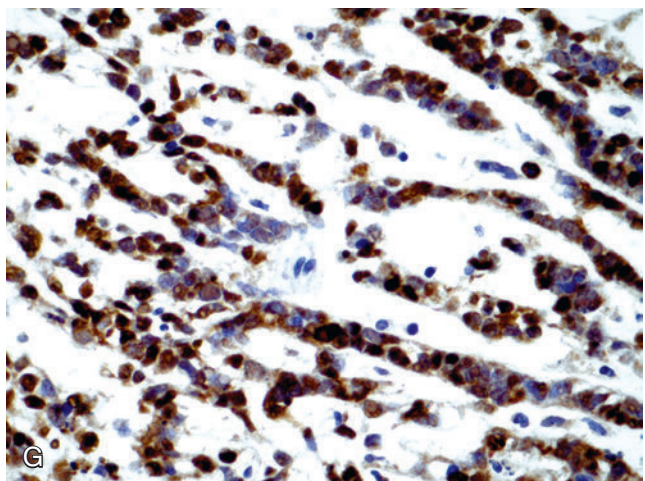
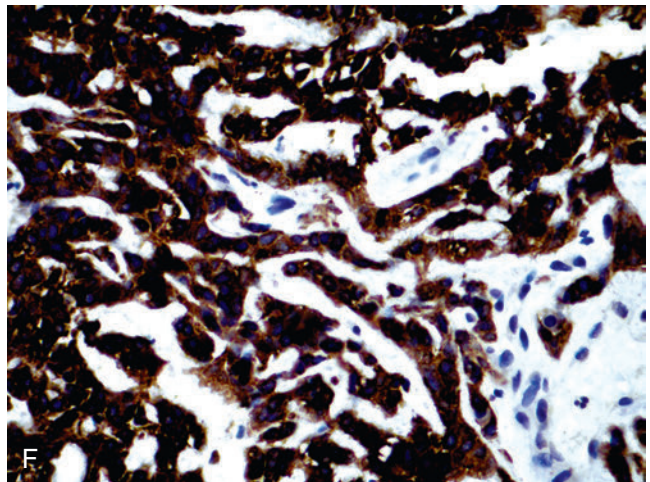
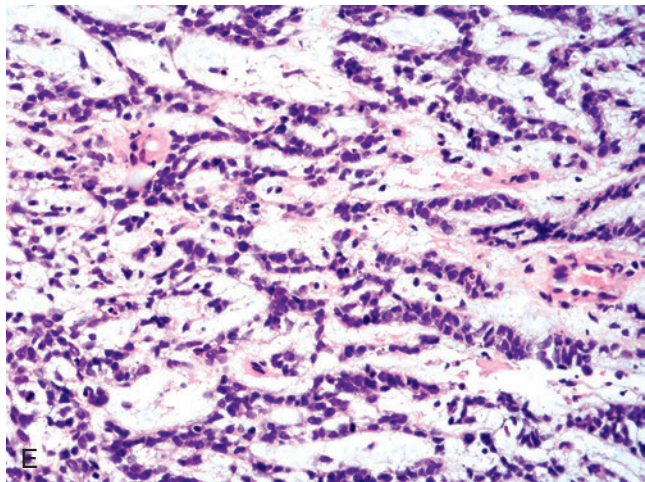
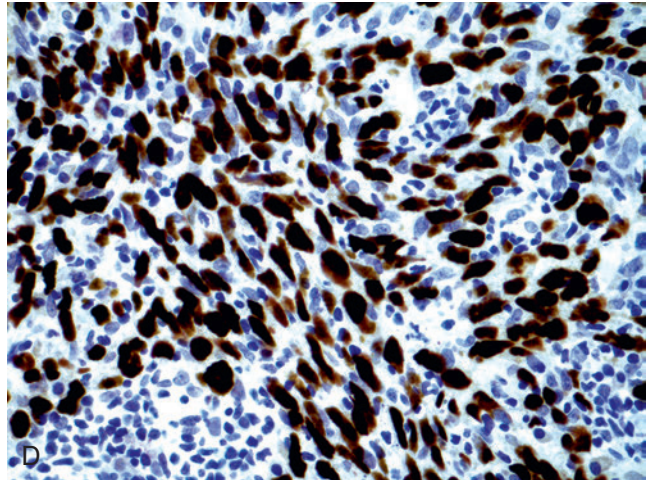
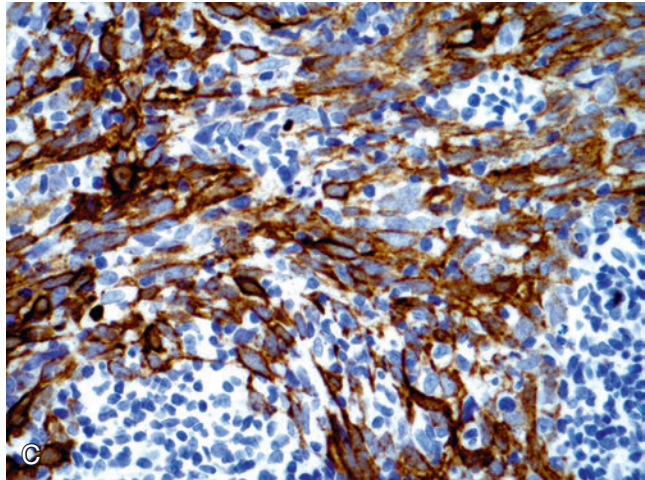
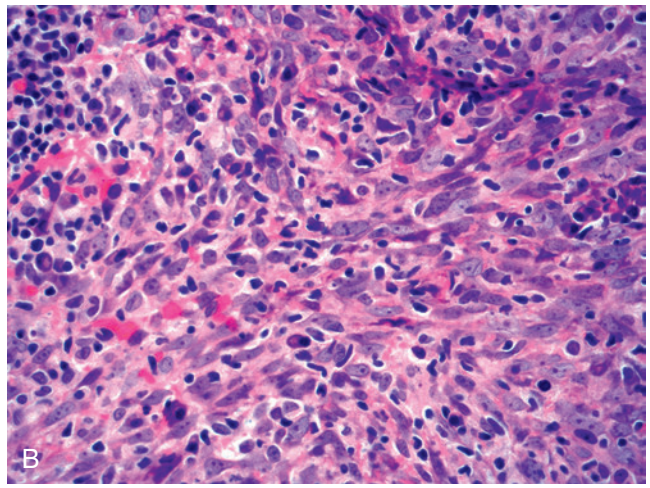
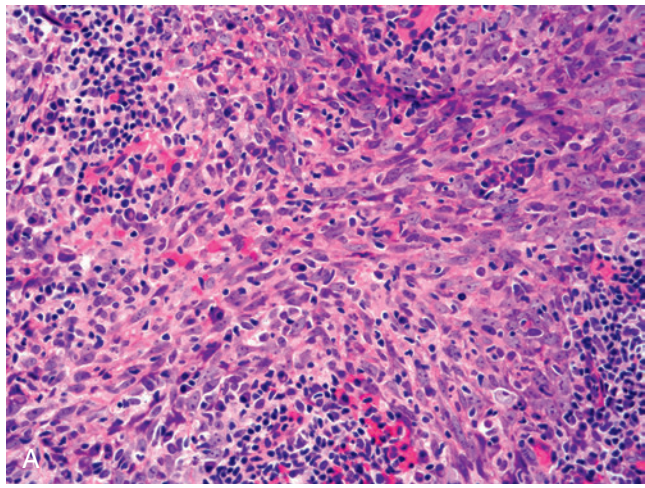


Fig. 10-14. NPC, variant histology.

A and B, Nasopharyngeal carcinoma, undifferentiated with fascicular growth composed of spindle-shaped cells; an associated mixed inflammatory cell infiltrate is present. The spindle-shaped cells are **(C)** cytokeratin positive and **(D)** EBER positive (nuclear staining). **E**, Nasopharyngeal carcinoma, undifferentiated with reticulated growth; lesional cells are **(F)** cytokeratin positive and **(G)** EBER positive (nuclear staining). (Slides from reticulated growth pattern provided courtesy of Fredrik Petersson, MD.)

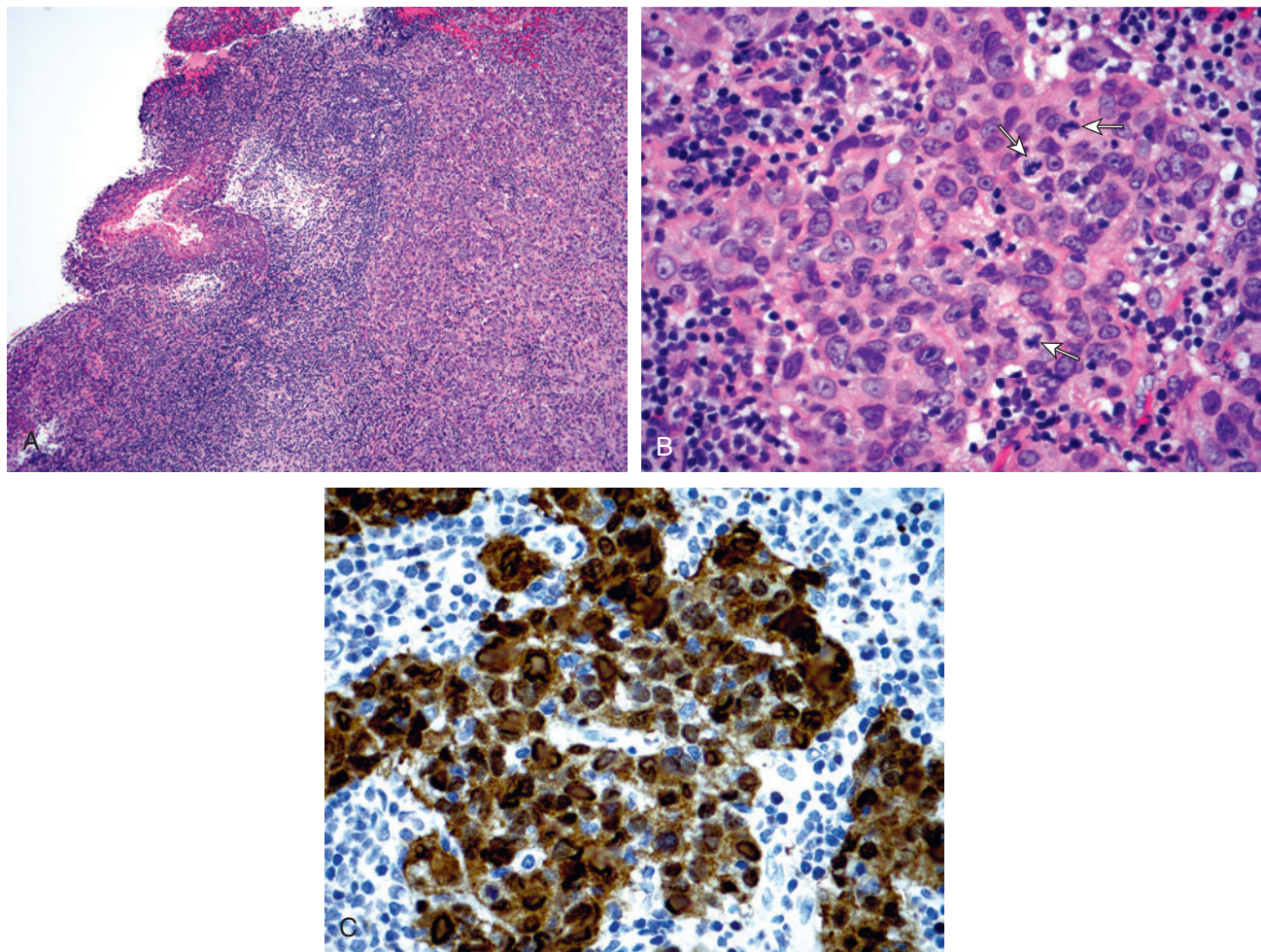


Fig. 10-15. Example of HPV-associated nasopharyngeal carcinoma.

A, Nasopharyngeal carcinoma characterized by the presence of a submucosal neoplastic infiltrate (*right side of image*). **B**, High magnification showing cytomorphic features of nonkeratinizing undifferentiated carcinoma; scattered mitoses are present (*arrows*). **C**, Lesional cells are immunoreactive for p16. EBER staining was negative (not shown).

- Development of NPC likely involves cumulative genetic and epigenetic changes in a background of predisposed genetic and environmental factors.
- Genome-wide studies have identified multiple chromosomal abnormalities with involvement of specific oncogenes and tumor suppressor genes, including inactivation of the p16 tumor suppressor gene on 9p21, the most common molecular alteration in NPC tumorigenesis.
- Alterations of genes such as Ras association domain family 1A (RASSF1A), p16/INK4A, p14/ARF suggest that multiple cellular pathways are dysregulated in the NPC cells.
- Findings on the precancerous lesions revealed early genetic changes and a critical role of EBV latent infection in the development of this cancer.

Differential Diagnosis

- Diagnosis of the keratinizing and nonkeratinizing types of NPC is usually straightforward.
- NPC, nonkeratinizing undifferentiated type, primarily when it occurs as a diffuse cellular infiltrate composed of dyscohesive cells, may be difficult to distinguish from non-Hodgkin malignant lymphoma ([Table 10-5](#)):
 - Differentiation is readily accomplished by immunohistochemical stains:
 - NPC will be reactive with cytokeratins and not negative for leukocyte common antigen (LCA).
 - Non-Hodgkin malignant lymphomas of the nasopharynx are predominantly of B-cell lineage and will be reactive with LCA and B-cell lineage markers (e.g., CD20, others).

TABLE 10-5 NPC, Nonkeratinizing Undifferentiated: Differential Diagnosis

Tumor	Gender/Age	Clinical	Histology	IHC	Treatment and Prognosis
NPC, UND	M > F; >6th decade	Airway obstruction; aural symptoms; neck mass	Cohesive vs dyscohesive; large cells with round nuclei, prominent eosinophilic nucleoli; increase mitotic activity	Epithelial markers +; EBV positive	Radioresponsive; 75% 5-year survival
SNUC	M > F; wide age range 3rd-9th decade with mean in 6th decade	Rapid onset (weeks to months); multiple symptoms include nasal obstruction, epistaxis, proptosis, visual disturbances (e.g., diplopia), facial pain, and symptoms of cranial nerve involvement	Overlapping histology with NPC, UND	Epithelial markers +; EBV negative	Not radioresponsive; poor prognosis often lethal over relatively short time periods
DLBCL	M > F; 5th-6th decade	Airway obstruction; aural symptoms; neck mass	Dyscohesive; diffuse growth; pleomorphic large cells and immunoblasts; large cells with round nuclei, prominent eosinophilic nucleoli; increased mitotic activity; necrosis	CD45, CD20, CD79a, PAX5, MUM1 positive; surface Ig (IGM>IgG>IgA) +	Multiagent chemotherapy and radiotherapy; prognosis is dependent on the clinical stage: overall 10-year disease-free survival (for all treatment modalities) is approximately 66%; overall survival rate of 82%; relapse occurs in from 30% to 45% of patients
MMM	M > F; 5th-6th decade	Airway obstruction; aural symptoms; pain; epistaxis	Varied growth including solid, organoid, alveolar and storiform; pleomorphic epithelioid and spindle cells; numerous mitoses	S100 protein, HMB-45, melan-A, tyrosinase, SOX10, vimentin positive	Surgery plus radiotherapy; overall poor prognosis
RMS	M = F; 1st-2nd decades but can be seen in adults	Airway obstruction; aural symptoms; pain	Various histologic types: embryonal, alveolar, pleomorphic; small round cells to large pleomorphic cells	Desmin, myoglobin, myogenin (myf-4) positive	Surgery, multiagent chemotherapy with or without radiotherapy Overall survival rates based on data from IRS-IV includes: 95% for low-risk patients; 75% for intermediate-risk patients; 27% for high-risk patients

DLBCL, Diffuse large B-cell lymphoma; MMM, mucosal malignant melanoma; NPC, UND, nasopharyngeal undifferentiated carcinoma; RMS, rhabdomyosarcoma; SNUC, sinonasal undifferentiated carcinoma.

- p63 is typically a marker of squamous cell lineage but may also be present in lymphomas.
- Sinonasal undifferentiated carcinoma (SNUC):
 - Overlapping histology especially with NPC, nonkeratinizing undifferentiated type
 - SNUCs are EBER negative.
 - Critically important to differentiate NPC from SNUC given the stark differences in treatment and prognosis between these tumor types:
- NPC: radioresponsive; good overall prognosis
- SNUC: not radioresponsive; poor prognosis often lethal over relatively short time periods
- HPV-associated HNSCC:
 - Overlapping histology with NPC, nonkeratinizing differentiated and undifferentiated types
 - EBV-associated HNSCC and HPV-associated NPC may present with cervical neck metastasis in the face of an occult primary neoplasm such

that differentiation cannot be made by light microscopic features and immunohistochemical staining for cytokeratins and p63; in this setting:

- Presence of EBV would support nasopharyngeal origin.
- Presence of HPV would support oropharyngeal origin.
- Other tumor types that might be included in the differential diagnosis include mucosal malignant melanoma and rhabdomyosarcoma:
 - Differentiation easily achieved by immunohistochemical staining:
 - Melanoma: S100 protein, HMB45, SOX10, MITF1, melan-A, tyrosinase positive; cytokeratins, EBER negative
 - Rhabdomyosarcoma: desmin, myogenin, myoglobin positive; cytokeratins, EBER negative; cytokeratins, EBER negative

Treatment and Prognosis

- As a result of the anatomic constraints imposed by the nasopharynx and the tendency of these neoplasms to present at an advanced stage, supervoltage radiotherapy (50 to 60 to 80 Gy) with or without adjuvant chemotherapy is considered the preferred treatment for all histologic subtypes:
 - Patients with early stage tumors (T1/T2) amenable to treatment with radiation therapy alone
 - Patients with T3/T4 lesions or significant nodal disease require more intensive treatments, including chemotherapy either sequentially concurrently or both with radiation therapy, as outcomes with radiation alone lead to higher rates of locoregional failure.
 - Surgical intervention reserved for patients who fail radiation therapy
- Technical advances in treatment planning systems incorporating CT have led to development of conformational therapies, including three-dimensional conformal therapy and intensity-modulated radiation therapy (IMRT):
 - Provides accurate delineation of tumor volumes and adjacent critical structures allowing for achieving maximal therapeutic benefit
 - Fusion with MRI or PET/CT crucial to accurately follow tumor spread three dimensionally
- Overall 5-year survival:
 - 20% to 40% for keratinizing squamous cell carcinoma.
 - Approximately 75% for nonkeratinizing carcinomas (differentiated and undifferentiated).
- TNM classification for NPC is detailed in [Table 10-6](#).

TABLE 10-6 TNM Classification: Pharyngeal Carcinoma

Primary Tumor (T)		Hypopharynx	
TX	Primary tumor cannot be assessed	T1	Tumor limited to one subsite of the hypopharynx and 2 cm or less in greatest dimension
T0	No evidence of primary tumor	T2	Tumor invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of the hemilarynx
Tis	Carcinoma in situ	T3	Tumor more than 4 cm in greatest dimension or with fixation of the hemilarynx or extension to esophagus
Nasopharynx		T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue [†]
T1	Tumor confined to nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*	T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
T2	Tumor with parapharyngeal extension*	Regional Lymph Nodes (N)	
T3	Tumor involves bony structures of skull base and/or paranasal sinuses		
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space	The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.	
Oropharynx			
T1	Tumor 2 cm or less in greatest dimension		
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis		
T4a	Moderately advanced local disease Tumor invades the larynx, deep extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible [†]		
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery		

TABLE 10-6 TNM Classification: Pharyngeal Carcinoma—cont'd

Regional Lymph Nodes (N) ^f		Distant Metastasis (M)	
NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
N0	No regional lymph node metastasis	M1	Distant metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension ^g	Anatomic Stage/Prognostic Indicators	
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa ^g	Nasopharynx	
N3	Metastasis in a lymph node(s)* >6 cm and/or to the supraclavicular fossa ^g	Stage 0	
N3a	Greater than 6 cm in greatest dimension	Stage I	
N3b	Extension to the supraclavicular fossa ^h	Stage II	
		Stage III	
		Stage IVA	
		Stage IVB	
		Stage IVC	
		Oropharynx, Hypopharynx	
		Stage 0	
		Stage I	
		Stage II	
		Stage III	
		Stage IVA	
		Stage IVB	
		Stage IVC	

Used with permission from Edge et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer-Verlag, 2010, pp 45-46.

*Parapharyngeal extension denotes posterolateral infiltration of tumor.

^fMucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

^gCentral compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

^hMidline nodes are considered ipsilateral nodes.

ⁱSupraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points:

- (1) The superior margin of the sternal end of the clavicle
- (2) The superior margin of the lateral end of the clavicle
- (3) The point where the neck meets the shoulder

Note that this would include caudal portions of levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

^fMetastases at level VII are considered regional lymph node metastases.

- Clinical stage at presentation represents the most important prognostic factor:
 - 5-year disease-specific survival (DSS) for:
 - Stage I is 98%.
 - Stage IIA-B is 95%.
 - Stage III is 86%.
 - Stage IVA-B is 73%.
- Factors that may affect prognosis include the clinical stage, patient age and gender, presence of keratinization, lymph node metastasis, and possibly genetic factors:
 - Better prognosis is associated with early (lower) clinical stage, younger patient age, and nonkeratinizing histology.

- Worse prognosis is seen with higher stage tumors, older patients, and male gender, as well as patients with the HLA-Aw33-C3-B58/DR3 haplotype, whereas patients with A2-Cw11-Bw46/DR9 haplotype have longer survival.
- Children and adolescents tend to present at a more advanced clinical stage but still retain a relatively good rate of long-term survival but are prone to serious long-term treatment-related morbidities.
- Patients with the keratinizing type of NPC tend to have a higher incidence of locally advanced tumor but a lower incidence of lymphatic and/or distant spread:
 - Despite the above findings, patients with the keratinizing NPC had a poorer 5-year survival rate than those with the other histologic subtypes due to a higher incidence of deaths secondary to local uncontrollable disease and nodal metastases.
- NPC frequently metastasizes to regional lymph nodes and the presence of lymph node metastasis decreases survival by approximately 10% to 20%.
- A large percentage of NPC, particularly of the undifferentiated type, metastasize to sites below the clavicle, including the lungs, bone (ribs and spine), and liver.
- Patterns of spread include invasion into adjacent soft tissues, sinonasal tract, paranasal sinuses, posteriorly to the carotid sheath with involvement of cranial nerves IX, X, or XI, and skull base as well as spreading intracranially (Fig. 10-16):
 - Risk of developing a synchronous or metachronous second primary malignancy in patients with NPC is approximately 4%:
 - Incidence is lower than in other head and neck sites.
 - Quantitative real-time PCR test (qPCR) for circulating EBV DNA found to be useful in the clinical management of NPC patients:
 - EBV DNA qPCR has good sensitivity and specificity in the detection of NPC at disease onset.
 - Increased viral DNA load found in NPC patients at late stages of disease
 - High EBV DNA load at disease onset or detectable viral load post-treatment associated with poor survival or frequent relapse
 - Residual EBV DNA load after primary treatment could be a useful indicator to justify adjuvant chemotherapy.
 - qPCR test may also be applied to define a poor prognostic group in patients at early stage (I/II) for implementing concurrent chemo-radiotherapy (chemo-RT) to improve patients' outcome.
 - Also useful to monitor distant metastases or response to radiotherapy, chemo-RT, or surgery
 - EBV serologic biomarkers may enhance accuracy of TNM staging:
 - Serum VCA-IgA/EA-IgA titers and plasma EBV DNA correlated strongly with TNM classification:
 - VCA-IgA-positive rate significantly associated with advanced N classification and stage
 - EA-IgA-positive rate significantly associated with advanced T and N classifications and stage
 - EBV-DNA-positive rate significantly associated with advanced T, N, and M classifications and stage
 - Percentage of triple-positive patients higher in patients with advanced TNM classification
 - Plasma EBV DNA load could accurately predict metastatic disease.

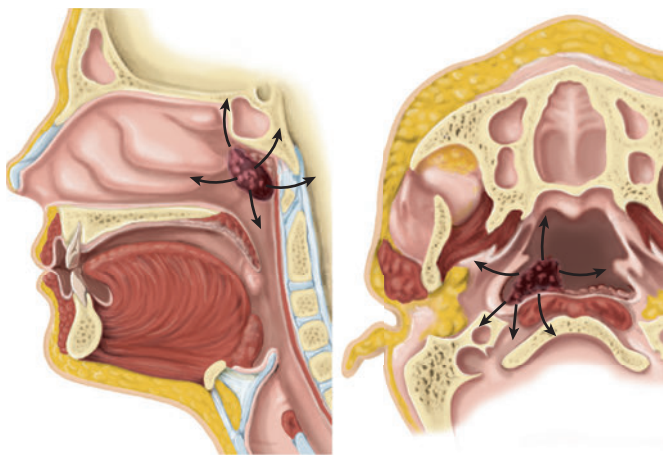


Fig. 10-16. Patterns of spread in NPC.

Sagittal and axial schematic illustrations demonstrate the potential pathways of spread (arrows) for nasopharyngeal carcinomas. (From Mukherji SK, Pillsbury H, Castillo M: *Imaging squamous cell carcinomas of the upper aerodigestive tract: what the clinicians need to know*, Radiology 205:629-646, 1997.)

Basaloid Squamous Cell Carcinoma (BSCC) of the Nasopharynx

- Uncommon type of nasopharyngeal carcinoma
- Morphologically similar to BSCC of other (more common) head and neck sites
- Reported to show lower biologic aggressiveness as compared with BSCC of other head and neck sites
- Mixed reports identifying association with EBV:
 - Asian patients positive
 - Non-Asian patients negative
- Not associated with HPV unlike oropharyngeal BSCC; see later in this chapter.
- For more complete discussion see Section 5, Larynx.

Oropharyngeal Squamous Cell Carcinoma

- Oropharynx encompasses multiple different sites, including:
 - Soft palate and uvula
 - Palatine (faucial) tonsillar region, including tonsillar fossa encasing the palatine tonsils and pillars
 - Base of tongue extends inferiorly from circumvallate papillae to the vallecula (base of epiglottis)
 - Posterior and lateral oropharyngeal walls between the nasopharynx and pharyngoepiglottic fold
- Retromolar trigone is part of the oral cavity, and although carcinomas of the retromolar trigone often involve the oropharynx and behave like oropharyngeal cancers, it is discussed in Section 2, Oral Cavity.
- Hypopharyngeal carcinoma, including the piriform sinus, is often lumped with laryngeal carcinomas but will be discussed below under the general category of pharyngeal carcinomas.
- In the head and neck, HPV has emerged as a major pathogen associated with squamous cell carcinomas, in particular of the tonsil and base of tongue.
- Oropharyngeal squamous cell carcinomas other than those of the tonsil and base of tongue are associated with tobacco and alcohol use/abuse.
- Oropharyngeal squamous cell carcinoma can be classified into morphologic subtypes, including:
 - Nonkeratinizing type:
 - Very strong association with HPV (HPV-associated SCC)
 - Most common

- Typically invades without associated desmoplasia
- Nonkeratinizing with squamous differentiation (maturation or hybrid carcinoma):
 - Intermediate association with HPV but considered closely related to the nonkeratinizing type
- Keratinizing type (“conventional” SCC):
 - Weak to no association with HPV (non-HPV-associated SCC)
- TNM classification for oropharyngeal carcinoma is detailed in Table 10-6.

HPV-Associated Squamous Cell Carcinoma of the Tonsil and Base of Tongue

Definition: Squamous cell carcinoma predominantly but not exclusively nonkeratinizing with basaloid cell morphology that is strongly associated with HPV-16 with overall better outcome than non-HPV associated HNSCCs (Table 10-7).

Synonyms: Nonkeratinizing squamous cell carcinoma; basaloid carcinoma; basal-like carcinoma; poorly differentiated carcinoma

NOTE:

- Initial designation for these cancers as basaloid may result in confusion with basaloid SCC, which is a high-grade variant of conventional SCC predilecting to the hypopharynx (i.e., piriform sinus) and supraglottic larynx not typically associated with HPV (or EBV); see Section 6, Larynx
- HPV-associated squamous cell carcinomas originating from tonsillar crypt epithelium may be viewed and diagnosed as “poorly differentiated”

TABLE 10-7 Comparison Between HPV-Positive and HPV-Negative SCC

	HPV-Positive SCC	HPV-Negative SCC
Age	Younger	Older
Gender	M = F	M > F
Race	Caucasian >>>> African American	Caucasian = African American
Risk factors (Tobacco/alcohol)	No known risk factors (usually nonsmokers, nondrinkers)	Associated with tobacco and/or alcohol use/abuse
Primary location	Oropharynx (base of tongue; tonsil)	All mucosal sites of the UADT
Histology	Nonkeratinizing carcinoma predominantly composed of basaloid cells	Keratinizing squamous cell carcinoma
p16	Positive	Negative
Prognosis	Better disease-free and overall survival	Worse disease-free and overall survival
Tumor stage at presentation	Often higher (more nodal metastasis)	Often lower

HPV, Human papillomavirus; SCC, squamous cell carcinoma; UADT, upper aerodigestive tract.

given the immature appearance of the lesional cells as well as the absence of differentiation in the form of keratinization and intercellular bridges; however, such cancers are in fact differentiated, originating and recapitulating the features of its cell of origin—that of the specialized tonsillar crypt reticulated epithelium.

Clinical

- Approximately 20% to 25% of squamous cell carcinomas of the upper aerodigestive tract are related to HPV infection:
 - Incidence of HPV-associated HNSCC is rising:
 - Increase in the prevalence of HPV-associated oropharyngeal squamous cell carcinoma from:
 - 21% in the pre-1990 time period
 - To 51% in 1990 to 1999
 - To 65% for 2000 to present
 - In contrast, incidence of HPV-unrelated HNSCC has stabilized or is decreasing with the decreasing use of tobacco products.
- Majority of HPV-associated SCC of the upper aerodigestive occurs in the oropharynx predominantly arising at the base of the tongue or palatine tonsil:
 - Propensity for HPV to infect the base of tongue and tonsil may be due to greater accessibility of the virus to the basal and proliferating squamous cells in these locations possibly secondary to epithelial disruption
- HPV-associated oropharyngeal SCC represents a unique subtype of HNSCC characterized by (see [Table 10-7](#)):
 - Absence (usually but not always) of known risk factors for HNSCC (i.e., nonsmokers and nondrinkers)
 - Patients who are younger patients than those with non-HPV-associated HNSCC
 - Better outcome (better overall and disease-specific survival) than non-HPV-associated HNSCCs
 - Their tendency to be highly curable even in presence of advanced disease
- Lower prevalence of HPV reported in African-American populations:
 - Largely accounts for poorer survival in African-American populations from oropharyngeal cancer but not other HNSCC
- Symptoms associated with HPV-associated oropharyngeal SCC:
 - Often relate to a mass; however, these cancers may be small and clinically/radiographically difficult to detect
 - Frequently develop early neck metastasis and may present as metastatic cancer to a cervical neck lymph node from an unknown primary site:
 - There is no correlation between the size of the primary carcinoma and the size of the metastatic carcinoma; a primary carcinoma may be tiny/small, measuring only a few millimeters but give rise to a large metastasis measuring several centimeters.
 - Similar lack of size correlation between the primary carcinoma and its metastasis seen in association to nasopharyngeal nonkeratinizing carcinomas
- Common presenting symptoms for tonsillar carcinomas may include:
 - Ipsilateral referred otalgia, odynophagia, sensation of a lump or foreign body in the throat
- Base of tongue carcinomas tend to be highly insidious:
 - Base of tongue is almost devoid of pain fibers.
 - Such carcinomas are frequently asymptomatic, presenting with higher clinical stage disease.
 - Such carcinomas often present with neck node metastases only to have base of tongue lesion found on full evaluation.
 - Visualization of this area on physical examination can be difficult and lesions may be missed.
 - Referred otalgia may represent the first symptoms.
 - Patients may experience sensation of a mass or discomfort in the throat, bleeding, difficulty with speech and swallowing, and pain in later stages.
- Radiology ([Figs. 10-17 to 10-19](#)):
 - PET/CT scan:
 - Plays an important role in the imaging evaluation of these cancers, in particular in trying to localize/identify the primary oropharyngeal carcinoma.
 - Combination of the two modalities has highest yield in discovering the primary head and neck cancer
 - PET/CT superior to either PET or CT alone
 - Metabolic imaging:
 - Neoplasms have increased metabolic activity with respect to surrounding normal mucosa:
 - Isotope ^{18}F -fluorodeoxyglucose (FDG), a glucose analog, enters cells using normal transport mechanisms.
 - The application of FDG uses the fact that glucose metabolism (i.e., FDG uptake) is increased in malignant cells but cannot be further metabolized, remaining in the tumor tissues.
 - Imaging modalities using FDG include positron emission tomography (PET) (FDG-PET):
 - ◻ Increases the detection of primary cancer site by up to 54%

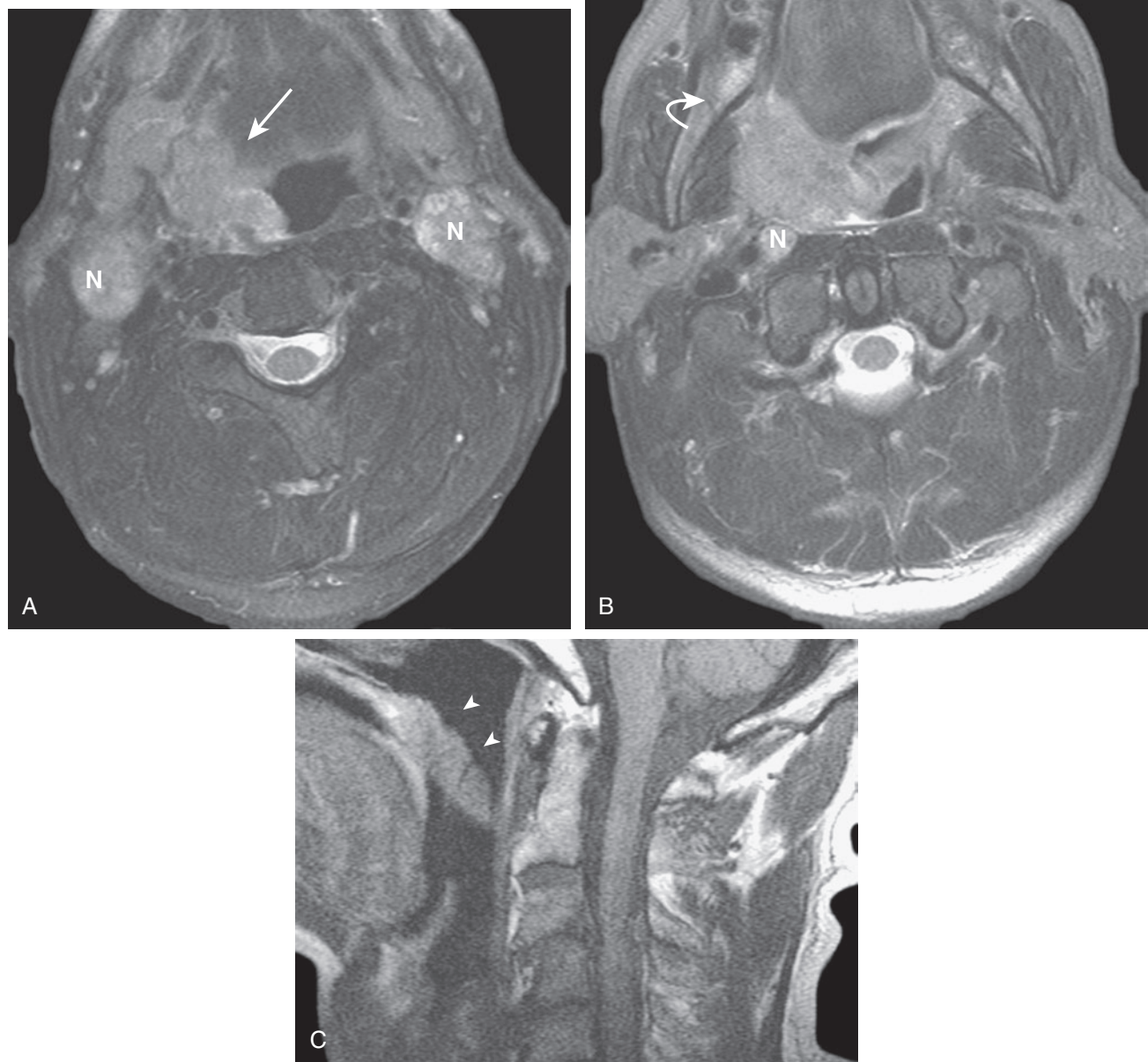


Fig. 10-17. Radiologic imaging in tonsillar carcinoma.

A, Axial T2-weighted image through an exophytic right tonsillar fossa SCC (*arrow*) with bilateral cervical metastases (*N*). **B**, Axial image slightly cranial to **A**, demonstrating subtle marrow involvement (*curved arrow*) and right lateral retropharyngeal lymph node disease. **C**, Sagittal precontrast T1-weighted image demonstrates extension to the soft palate (*arrowheads*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-15, p 1761.)

Pathology

Nonkeratinizing Carcinoma

Cytomorphology (see Section 4, Fig. 13-39)

- Cohesive and dyscohesive clusters or groups of malignant epithelial cells with basaloid cytomorphology, including:
 - Hyperchromatic nuclei with coarse nuclear chromatin, nuclear pleomorphism
 - Increased nuclear-to-cytoplasmic ratio

- Increased mitotic activity, including atypical mitoses
- Necrosis (individual cell and confluent areas) may be present.
- Typically, absence of keratinization, although focal keratinization may be present

NOTE: Given their basaloid morphology, including features of a histologic higher-grade carcinoma, such carcinomas (whether on fine-needle aspiration or biopsy) have been erroneously designated as poorly

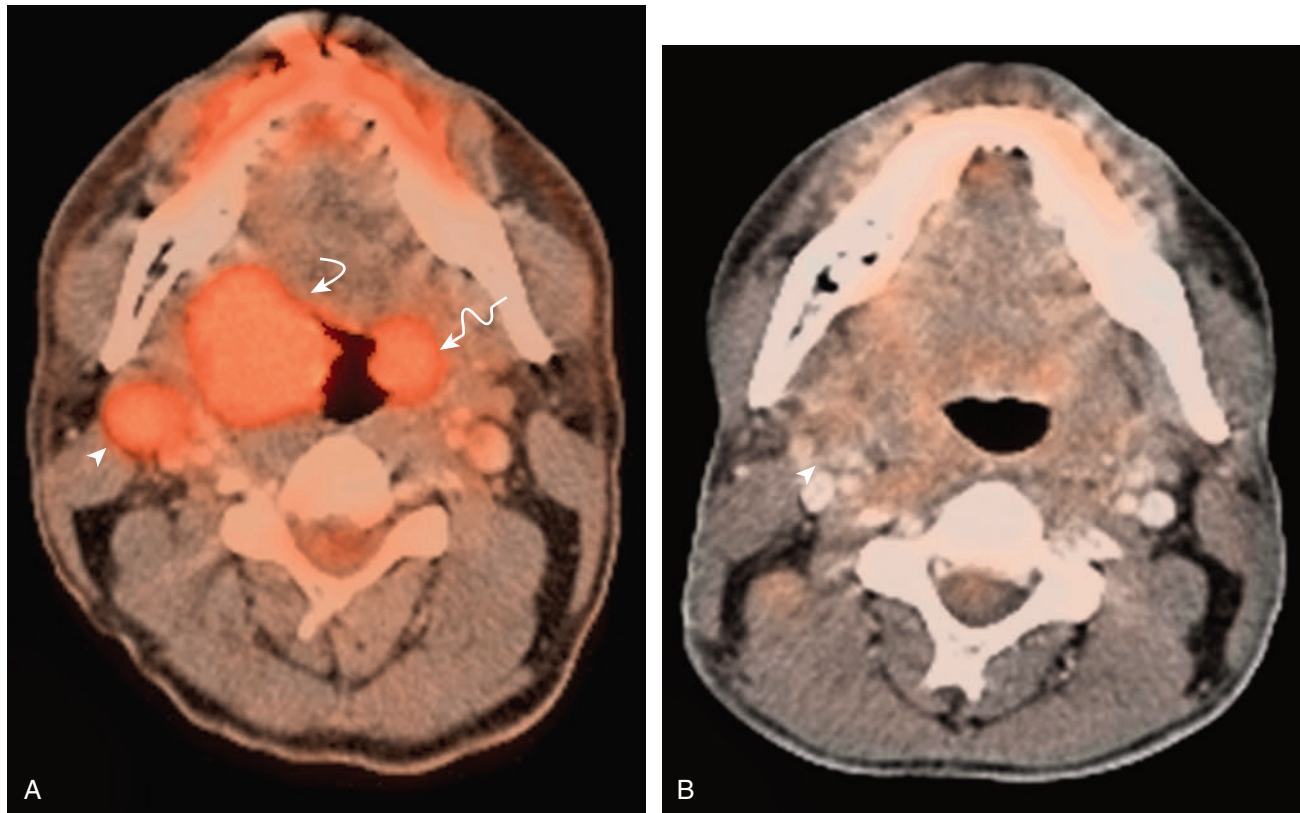


Fig. 10-18. PET/CT scan in tonsillar carcinoma.

A, Axial pretreatment PET/CT demonstrates a large right tonsillar carcinoma (*curved arrow*) that extended across the tongue base to involve the left tonsil (*wavy arrow*). Note the metastatic right level II node (*arrowhead*). **B**, Following chemoradiation, there is a marked reduction in the right tonsillar size. The pharyngeal mucosa, although prominent, is symmetric. The right level II node (*arrowhead*) has a low-attenuation center, consistent with necrosis. No FDG activity is present. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-23, p 1765.)

differentiated. In fact, these nonkeratinizing carcinomas are considered better differentiated carcinomas, recapitulating the crypt epithelium from which they may arise.

Gross

- No specific macroscopic findings:
 - Often clinical presentation is with cervical lymph node metastasis without known primary carcinoma.
 - Identification of primary carcinoma may occur in biopsy material without macroscopic evidence of a lesion.
- Carcinomas of anterior tonsillar pillar can be erythroplakic and/or exophytic.
- Carcinomas of tonsillar fossa in contrast to tonsillar pillar tend to be either exophytic or ulcerative.

Histology (Figs. 10-20 and 10-21)

- Arise from tonsillar crypts located within the depth of the tonsil (palatine or lingual):

- Involvement of surface epithelium not commonly present
- When there is involvement of surface epithelium, it usually occurs by contiguous extension from the crypts.
- Transition from surface epithelial intraepithelial dysplasia to invasive carcinoma that typifies most of the squamous cell carcinomas of mucosal sites of the upper aerodigestive tract is not typically evident in HPV-associated carcinoma.
- Invasive growth may include solid sheets, trabeculae, cords, and nests, but individual infiltrative cells can be seen:
 - Often are cystic with central areas of necrosis and frequently metastasize as cystic metastatic carcinomas (see Section 5, The Neck):
 - In the absence of a known primary carcinoma, such cystic neck masses may be considered branchial cleft cysts with malignant transformation, a diagnosis of questionable existence.

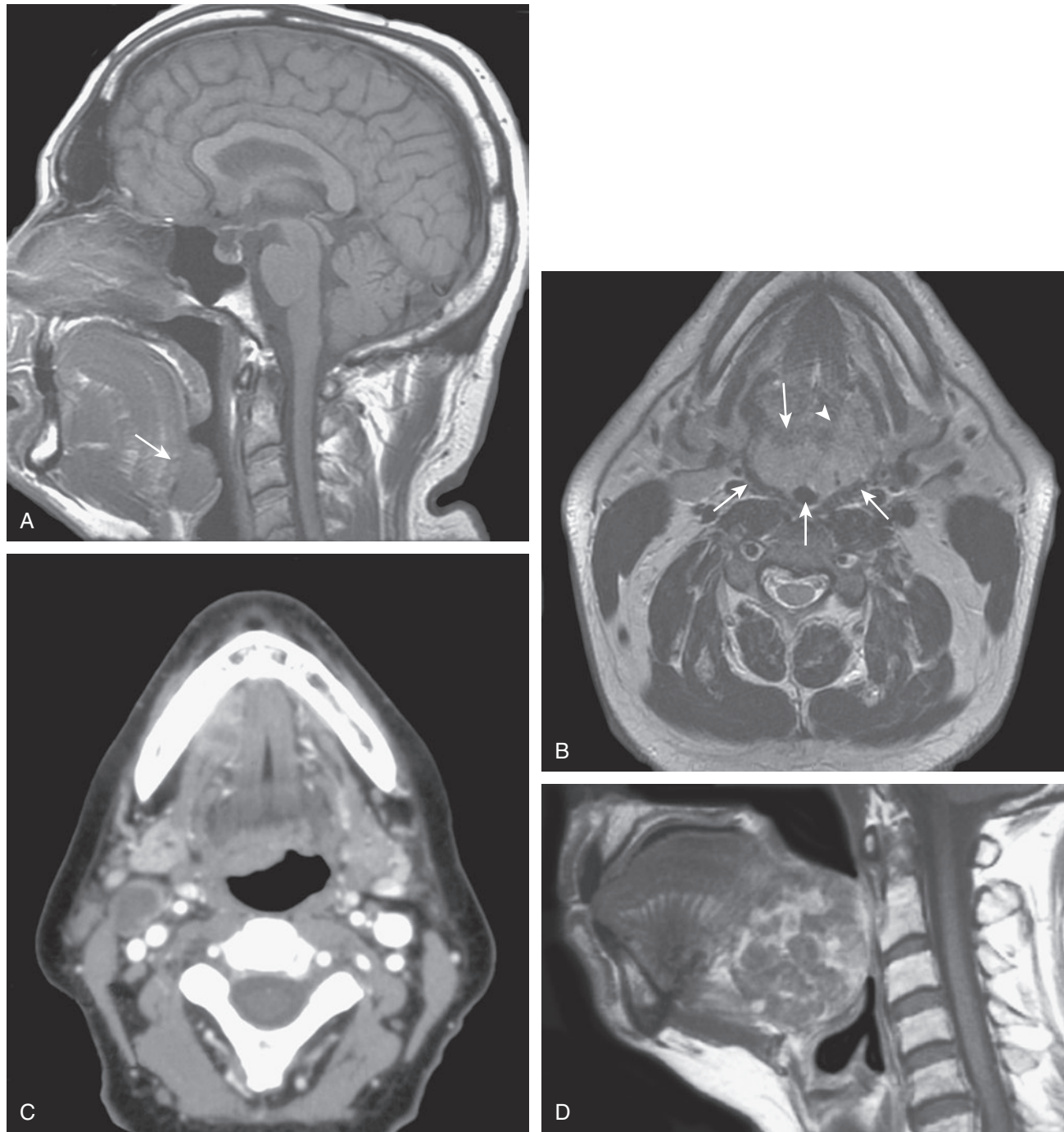


Fig. 10-19. Radiologic imaging in base of tongue carcinoma.

A, Sagittal T1-weighted image with prominent mass at the base of the tongue (*arrow*). **B**, Mass involves the entire tongue base, right to left (*arrows*) on T2-weighted image, with extension into the left-sided deep tongue musculature (*arrowhead*). **C**, Axial, contrast-enhanced CT scan shows an asymmetric soft-tissue fullness in the right base of the tongue. This asymmetry should raise concern. This was a SCC of the base of the tongue. **D**, Sagittal, T1-weighted MR image shows a large noninfiltrating mass in the base of the tongue. The mass is nonhomogeneous. This patient had a goiter of a lingual tonsil. This is an example of a nonmalignant mass in the base of the tongue. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-20, p 1763.)

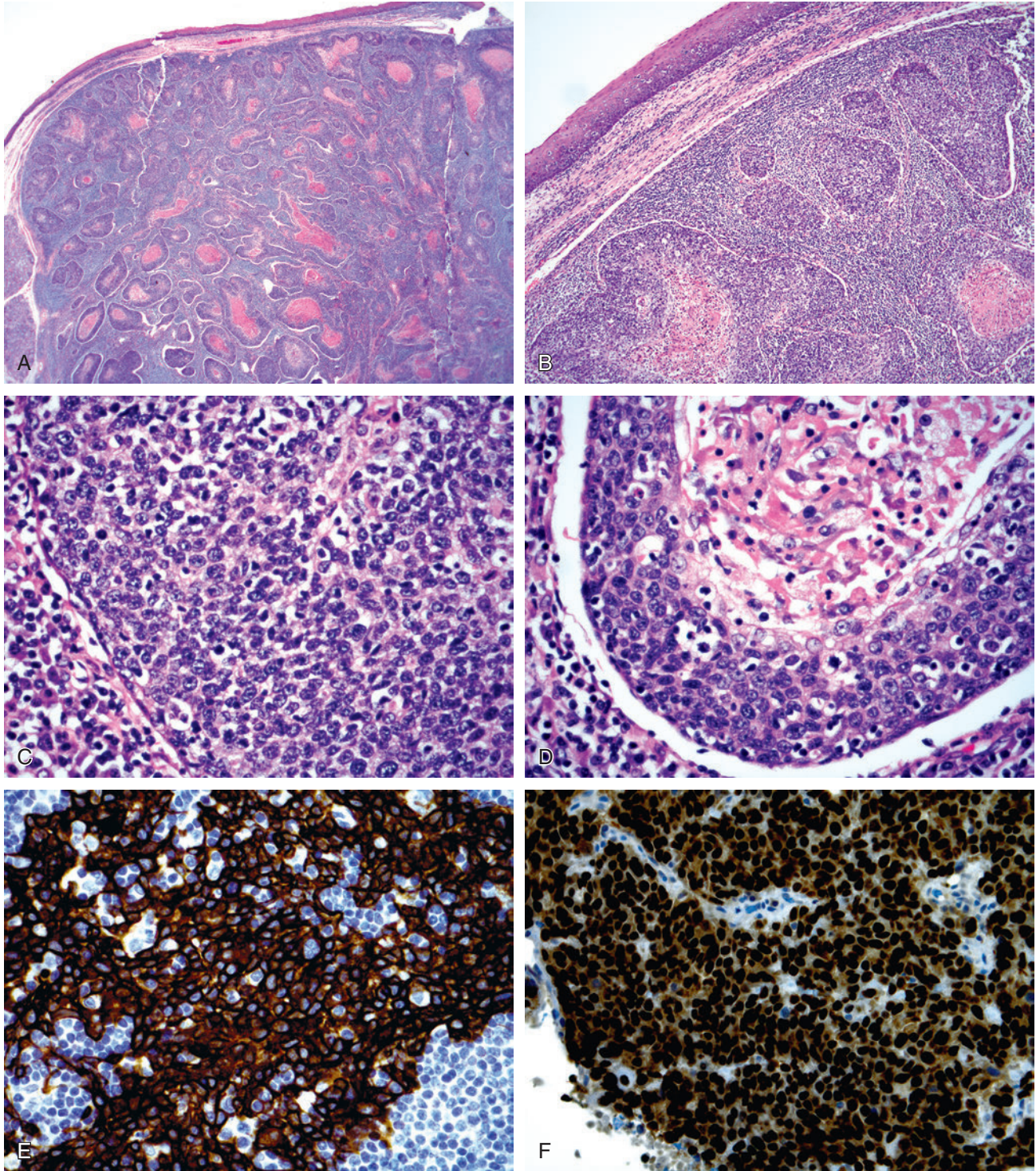


Fig. 10-20. Histology of oropharyngeal HPV-associated SCC.

Oropharyngeal (tonsillar) HPV-associated nonkeratinizing squamous cell carcinoma characterized by the presence of (A) submucosal invasive neoplasm including solid nests as well as nests with cystic change and central areas of necrosis; (B) the overlying surface squamous epithelium is intact and uninvolved by the invasive carcinoma. An inflammatory cell infiltrate is present in and around the carcinoma but there is an absence of associated desmoplastic stromal response to the invasive carcinoma. C and D, The neoplastic cells whether in the solid foci or in the cystic foci are characterized by a basaloid cell morphology, including nuclear pleomorphism with increased mitotic activity and absence of keratinization. However, in other examples focal keratinization may be present but typically the extent of keratinization is limited. E, The epithelial nature of the lesion is confirmed by the presence of cytokeratin (AE1/AE3) immunoreactivity and (F) diffuse p63 (nuclear) staining.

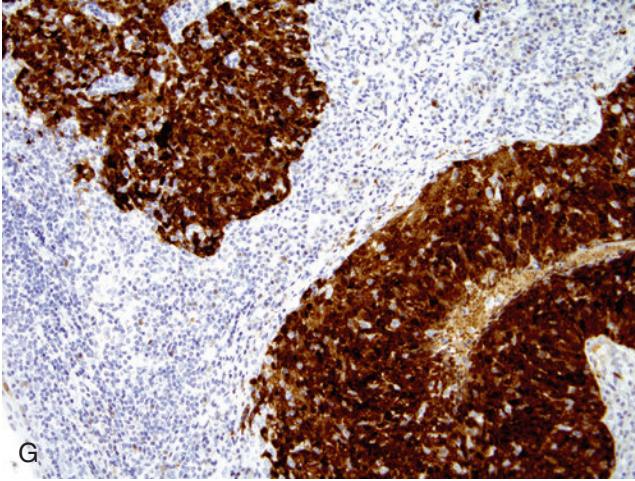


Fig. 10-20, cont'd

G, Lesional cells are diffusely and strongly positive for p16 (nuclear and cytoplasmic staining).

- Invasive growth often without associated desmoplasia that typifies most other invasive carcinomas (with the exception of nasopharyngeal nonkeratinizing carcinomas).
- Typical histologic features are those of a nonkeratinizing carcinomas characterized by basaloid cell morphology:
 - Neoplastic cells include marked nuclear pleomorphism with increased mitotic activity, including atypical mitoses.
 - Focal keratinization may present:
 - Typically the extent of keratinization is limited, with the majority of the neoplastic cells lacking evidence of keratinization.
 - Not more than 10% maturing squamous differentiation
 - Often associated with a dense benign lymphocytic cell infiltrate (tumor infiltrating lymphocytes [TIL]):
 - Given the propensity for this carcinoma to invade without associated desmoplasia, the associated dense lymphocytic cell infiltrate may obscure the presence of the malignant cells.
 - Cytokeratin and p16 staining are invaluable in evaluating for the presence of invasive carcinoma.
 - May include papillary growth or may show growth and cytomorphic characteristics similar to nasopharyngeal nonkeratinizing carcinoma, undifferentiated type, including syncytial growth and cells with enlarged vesicular nuclei and prominent nucleoli:
 - Although this morphology overlaps with the EBV-associated nasopharyngeal carcinomas, this subset of oropharyngeal carcinomas is associated with HPV rather than EBV.
- Carcinoma in situ versus invasive carcinoma (Fig. 10-22):
 - Determining whether an HPV-associated carcinoma represents carcinoma in situ or invasive carcinoma can be problematic due to:
 - Origin from tonsillar crypt reticulated epithelium, which is penetrated by lymphocytes, thereby blurring the junction between the epithelium and the lymphoid stroma
 - Porous nature of the epithelial-to-lymphoid junction, where the basal cell layer is incomplete as well as the disruption and noncontinuous nature of its basement membrane
 - Absence of associated desmoplasia
 - In addition, very small foci of HPV-associated SCC may metastasize to regional lymph nodes in the absence of definitive evidence of invasion.
 - Given the challenges in any given case to determine if a focus of HPV-associated carcinoma is or is not invasive yet nodal metastasis may be present, a prudent approach would include regarding all such foci to be malignant and invasive even in the absence of unequivocal evidence of invasion.
- Large pleomorphic cells (tumor cell anaplasia) and multinucleation may be present, which has correlated to poorer clinical outcomes (Fig. 10-23).

Nonkeratinizing Carcinoma with Squamous Differentiation (Maturation or Hybrid Type) (Fig. 10-24)

- Oropharyngeal carcinoma with histologic features of keratinizing and nonkeratinizing squamous cell carcinomas:
 - Histology composed of predominantly classic nonkeratinizing carcinoma with a component of squamous differentiation, the latter identified in more than 10% of the overall surface area of maturing squamous differentiation:
 - Basaloid cells show a trend toward differentiation to a keratinizing phenotype at the periphery of the cell nests and trabeculae.
 - Strong association with HPV but the virus is slightly less frequently detected than in the oropharyngeal nonkeratinizing carcinoma
 - Immunohistochemistry for HPV-associated SCC:
 - Neoplastic cells express cytokeratins, including AE1/AE3, CAM5.2, and CK5/6, as well as p63 (diffuse and strong nuclear staining):
 - Extremely helpful in identifying the malignant cells in the presence of obscuring benign lymphoid infiltrate
 - p16 positive:
 - Surrogate marker for HPV16 (i.e., presence of p16 immunostaining correlates to the presence of HPV16)

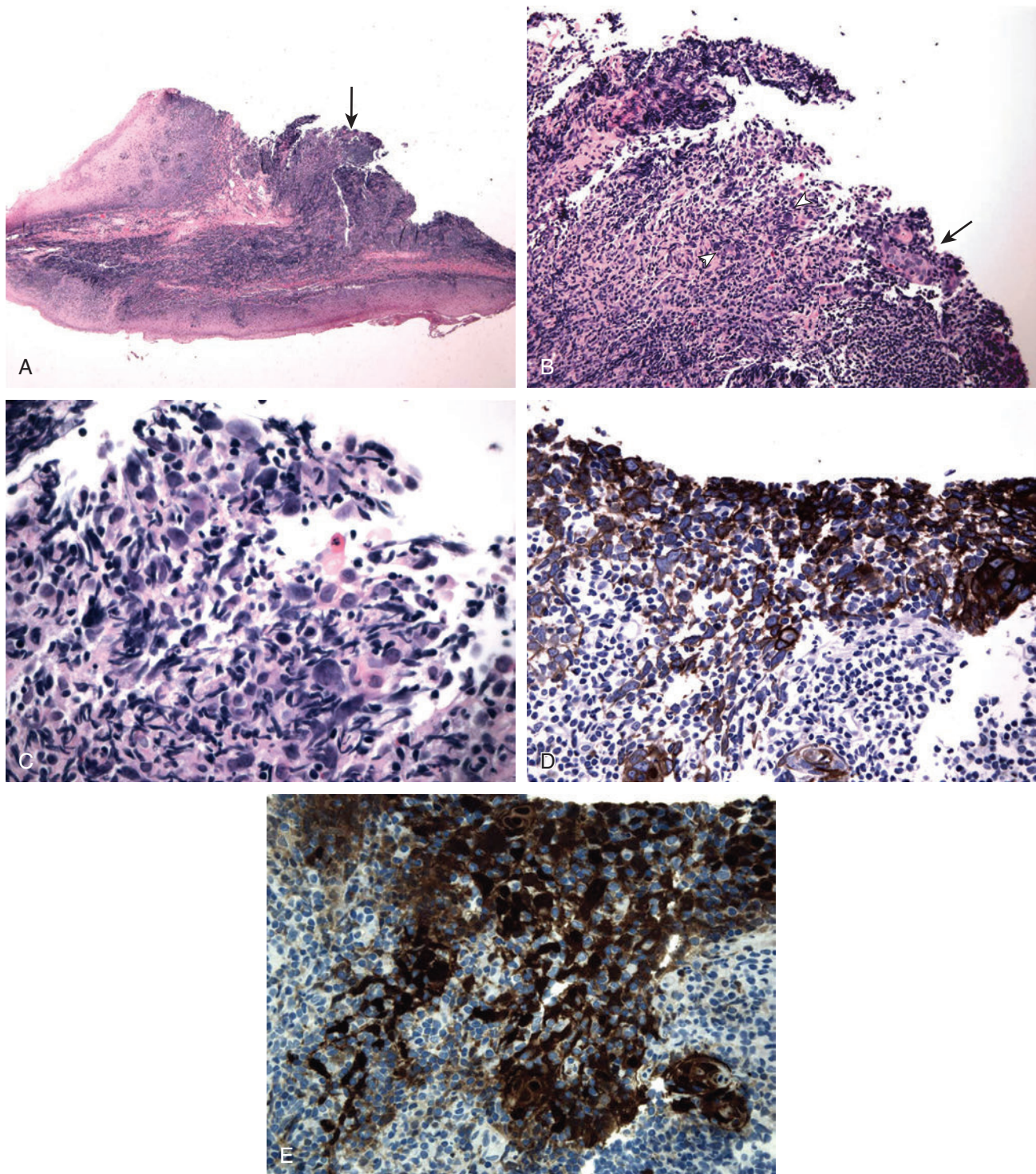


Fig. 10-21. Biopsy of base of tongue HPV-associated SCC.

Base of tongue biopsy in a patient with cervical lymph node metastatic carcinoma diagnosed by fine-needle aspiration as poorly differentiated carcinoma. **A**, At low magnification a fragment of squamous mucosa with submucosal dense lymphoid infiltrate is present. At this magnification there is no suggestion that an invasive carcinoma is present in the form of readily identifiable infiltrative tumor nests (see Fig. 10-20 in comparison) and/or the presence of identifiable stromal desmoplasia. However, an invasive carcinoma is present along the deep edge of the specimen (*arrow*). **B** and **C**, At higher magnification, the invasive carcinoma becomes more evident as seen by a small cohesive cluster of malignant cells including focal keratinization (*arrow*) but also as individual tumor cells (between arrowheads) overrun and obscured by the lymphoid infiltrate. **C**, Higher magnification shows the individual malignant cells with basaloid nuclei. **D**, In deeper levels performed for immunohistochemical staining, a greater amount of carcinoma becomes evident by the strong cytokeratin (CAM5.2) immunoreactivity. **E**, Lesional cells are diffusely and strongly positive for p16 (nuclear and cytoplasmic staining). In spite of the very small focus of the primary base of tongue carcinoma (that parenthetically can be quite difficult to detect by clinical and radiologic evaluation), nodal metastatic disease can be large (several centimeters).

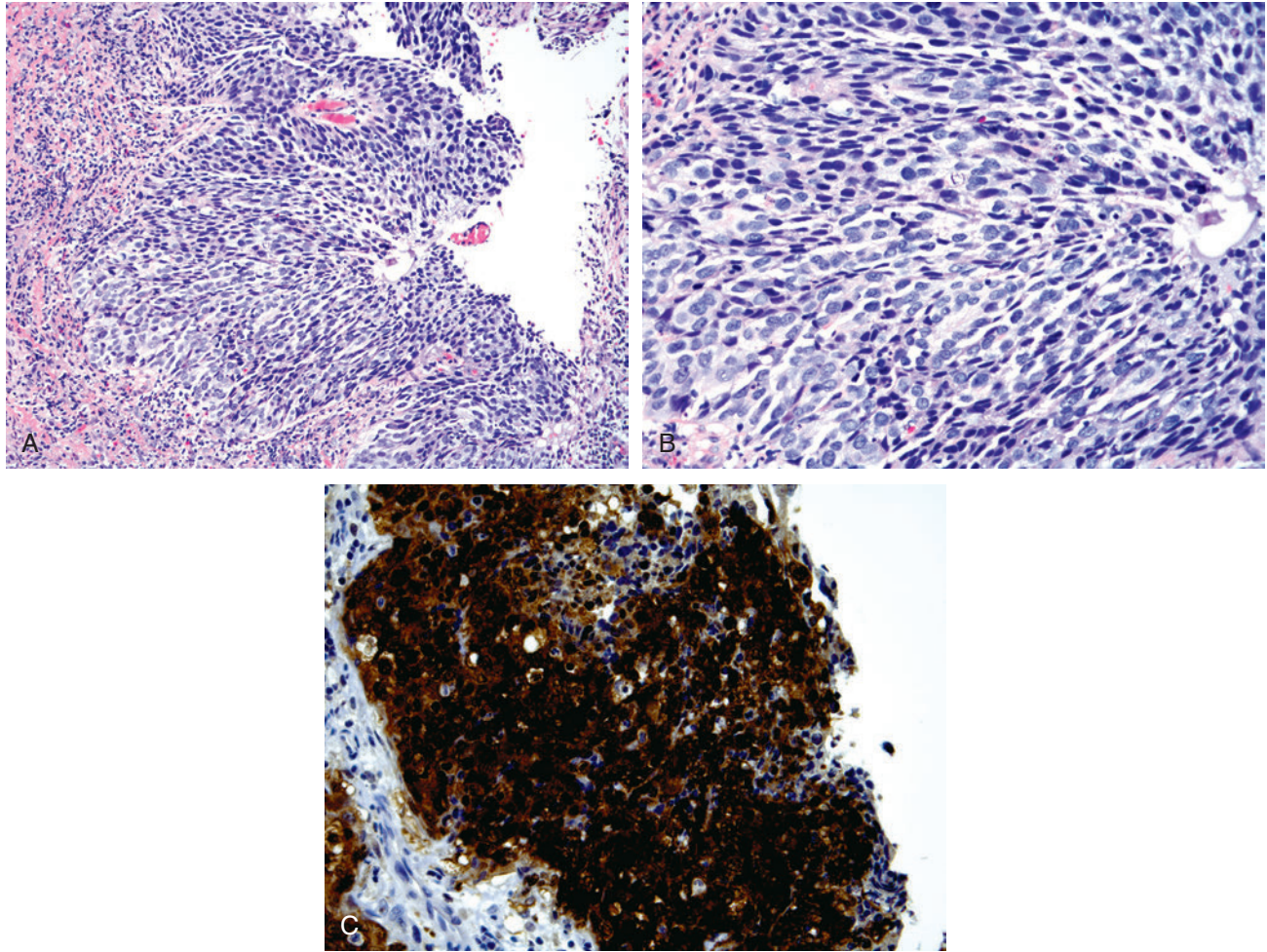


Fig. 10-22. In-situ versus invasive oropharyngeal HPV-associated SCC.

A and **B**, Areas in a tonsillar biopsy showing what appears to be carcinoma in situ (CIS) with the neoplastic basaloid cells apparently confined to crypt epithelium without evidence of invasion. **C**, Lesional cells are diffusely and strongly positive for p16 (nuclear and cytoplasmic staining). Determining whether an HPV-associated carcinoma represents carcinoma in situ or invasive carcinoma is problematic. Given the challenges in any given case to determine if a focus of HPV-associated carcinoma is or is not invasive, a prudent approach would include regarding all such foci to be malignant and invasive even in the absence of unequivocal evidence of invasion. Reasons for this approach include the facts that origin from tonsillar crypt reticulated epithelium penetrated by lymphocytes results in the blurring of the junction between the epithelium and the lymphoid stroma; the porous nature of the epithelial-to-lymphoid junction where the basal cell layer is incomplete as well as the disruption and noncontinuous nature of its basement membrane; very small foci of HPV-associated SCC including foci depicted in this image may metastasize to regional lymph nodes in the absence of definitive evidence of invasion.

- Reactivity pattern includes nuclear and cytoplasmic staining and is usually diffuse and strongly reactive; should be positive in $\geq 75\%$ of lesional cells.
- Considered a reliable predictor of a carcinoma originating from the oropharynx
- Can be performed on aspiration material and on tissue sampling
- High proliferation rate as seen by Ki67 (MIB1) staining
- EBER negative
- S100 protein negative
- No immunoreactivity for hematolymphoid markers and melanoma-specific markers
- Detection methods for HPV16 include:
 - Immunohistochemical (IHC) staining for p16, a surrogate marker for HPV16
 - HPV specific molecular tests:
 - DNA in situ hybridization (ISH)
 - mRNA techniques for identification of transcripts of viral oncogenes E6/E7 (at present considered gold-standard test to determine oncogenic role of HPV in a given tumor)

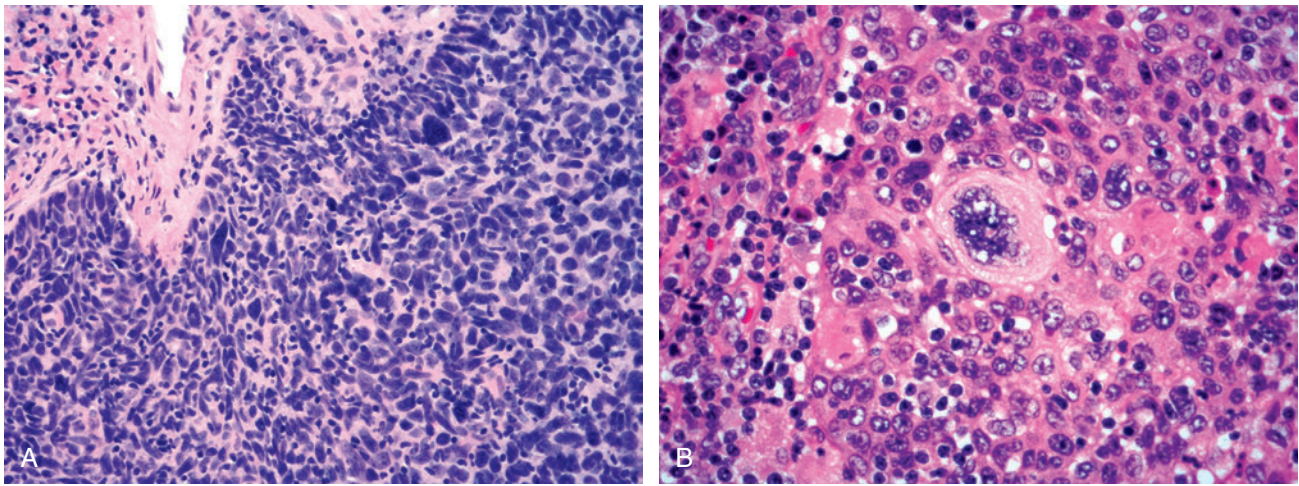


Fig. 10-23. Tumor cell anaplasia in oropharyngeal HPV-associated SCC.

Tonsillar HPV-associated nonkeratinizing squamous cell carcinoma with (A) large pleomorphic cells and (B) multinucleation may be present and have been reported to correlate to poorer clinical outcomes.

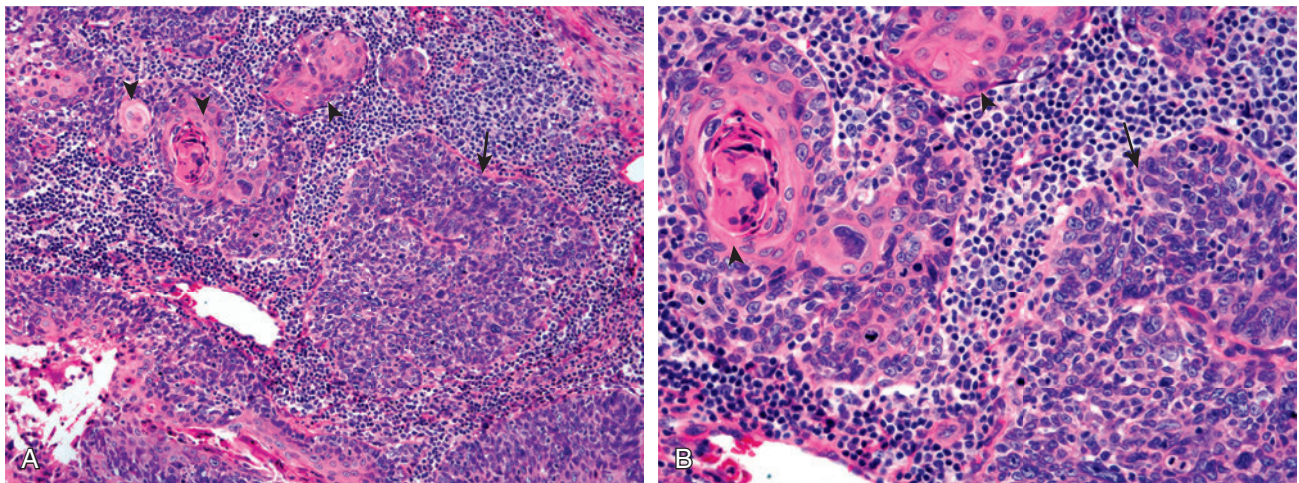
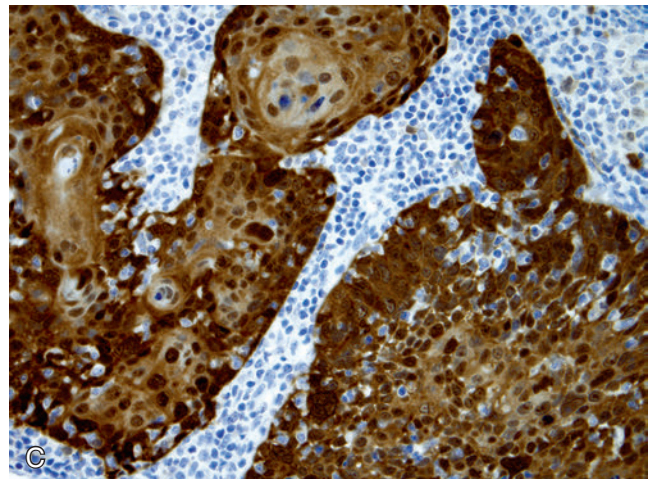


Fig. 10-24. Hybrid type of oropharyngeal HPV-associated SCC.

Oropharyngeal nonkeratinizing carcinoma with squamous differentiation (maturation or hybrid type) showing histologic features of both keratinizing and nonkeratinizing squamous cell carcinomas. A and B, Histologic features include foci of classic nonkeratinizing carcinoma (arrows) with a component of mature squamous differentiation (arrowheads), the latter identified in more than 10% of the overall surface area of maturing squamous differentiation. C, Strong association with HPV as evidenced by the presence of p16 immunoreactivity. Molecular analysis confirmed the presence of HPV (not shown).



- PCR-based (consensus and type-specific; real-time assays to quantify viral load)
- Some authorities advocate a combined approach to include IHC and ISH.
- p16 as a stand-alone test has validity based on:
 - Overexpression is very sensitive for the presence of transcriptionally active HPV (i.e., high correlation with detectable HPV RNA) with moderate to high specificity:
 - Approximately 10% of p16 positive tumors are HPV DNA negative due to either misclassification as HPV DNA negative because of insufficient sensitivity of the HPV DNA test or cases represent tumors in which p16 overexpression triggered by other cellular signaling pathways
 - Correlates strongly with patient outcomes (i.e., strong risk stratification for patient survival)
 - In addition, p16 IHC staining is:
 - Widely available
 - Easy to interpret
 - Focal/weak p16 staining should be confirmed by molecular testing
- Some authorities advocate a combined approach to include p16IHC with additional molecular testing especially in oropharyngeal cancers:
 - That are p16 negative but show classic HPV-associated histomorphology
 - That are p16 focal and weakly positive in presence of classic HPV-associated histomorphology
 - That are p16 positive oropharyngeal cancers without classic histomorphology
 - For enrollment/selection for clinical (therapeutic) protocols requiring confirmation of transcriptionally active virus
- Guidelines for p16 and/or HPV testing in head and neck carcinomas may include:
 - In an oropharyngeal biopsy showing atypical basaloid cells, the presence of p16 confirms the diagnosis of HPV-associated HNSCC.
 - In tumors with overlapping morphology, presence of p16 helps confirm the diagnosis of HPV-associated HNSCC.
 - In the presence of cervical nodal metastatic disease of unknown primary origin, p16 staining would:
 - Confirm the diagnosis of metastatic cystic SCC
 - Localize the primary site of origin to the oropharynx
 - Establish tumor classification, which then would reflex to specific treatment protocols
- Hybrid Capture 2 and Cervista reported to be as sensitive as PCR with fewer false positives than p16 immunohistochemical staining

Conventional Keratinizing Squamous Cell Carcinoma

- Oropharyngeal carcinoma typically composed of infiltrative nests with prominent stromal desmoplasia:
 - Characterized by polygonal cells with distinct cell borders, abundant eosinophilic cytoplasm
 - Squamous maturation in the form of keratin pearl formation, individual cell keratinization, and intercellular bridges
 - Squamous maturation is diffusely seen even in poorly differentiated carcinomas.
 - Typically not associated with HPV and are usually p16 negative.

Differential Diagnosis for Nonkeratinizing Carcinoma

- Basaloid squamous cell carcinoma (BSCC):
 - Non-HPV-associated BSCC has aggressive clinical behavior
 - Overlapping growth patterns and cell type between non-HPV-associated BSCC and HPV-associated carcinoma make differentiation between these two similar-appearing but biologically distinct cancers problematic.
 - Presence or absence of HPV represents the key feature in distinguishing these two tumor types.

Treatment and Prognosis

- Currently, there is no single standardized treatment strategy for HPV-associated HNSCC, and treatment regimens may include:
 - Radiation therapy alone
 - Combination of radiotherapy and chemotherapy (given concurrently or an induction therapy)
 - Surgery with or without adjuvant radiotherapy:
 - Surgical options include minimally invasive approaches, obviating the need for mandibulotomy, including transoral robotic surgery (TORS).
 - As compared with traditional open surgical techniques, TORS may:
 - Achieve complete surgical resection with associated reduced morbidity
 - Be associated with better quality of life
 - Further, TORS may improve functional outcomes when compared with nonsurgical treatment with radiation with or without chemotherapy.
- Patterns of spread for tonsillar carcinoma (Fig. 10-25):
 - Anterior tonsillar pillar carcinomas may spread:
 - Laterally to buccal mucosa
 - Along the superior constrictor muscle to the pterygomandibular raphe and from there to the buccinator muscle and retromolar trigone

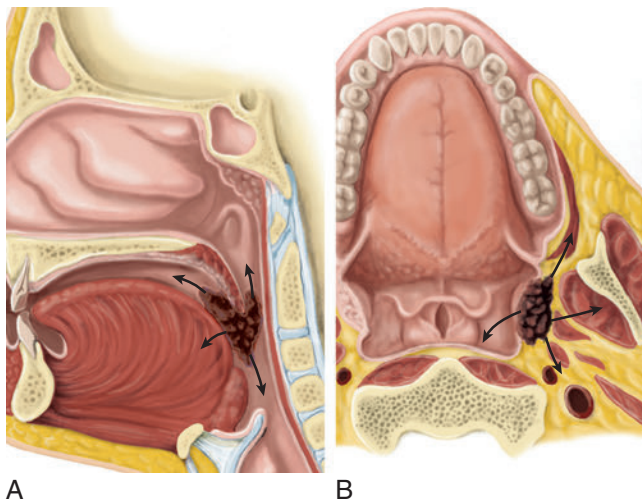


Fig. 10-25. Patterns of spread for tonsillar carcinoma.

Sagittal and axial illustrations demonstrate the potential spread patterns of a tonsillar carcinoma (arrows). (From Mukherji SK, Pillsbury H, Castillo M: *Imaging squamous cell carcinomas of the upper aerodigestive tract: what the clinicians need to know*, Radiology 205:629-646, 1997.)

- Inferiorly base of tongue invasion may likely occur as a result of growth along the palatoglossus muscle.
- Superior extension can involve the hard palate.
- Medial extension may involve the oral tongue.
- Close proximity to mandible increased risk for periosteal and bone involvement
- Posterior and superior extension can lead to involvement of the pterygoid muscles with subsequent trismus and pain.
- Tonsillar fossa carcinomas may have patterns of spread similar to those of the anterior tonsillar pillar but may also include:
 - Lateral extension to parapharyngeal space toward the base of skull, causing neurologic signs and symptoms
 - Carcinomas of the posterior tonsillar pillar can extend inferiorly and involve the pharyngoepiglottic fold and posterior aspect of the thyroid cartilage.
- Patterns of spread for base of tongue carcinoma may include (Fig. 10-26):
 - Inferior spread to involve the vallecula, epiglottis, and preepiglottic fat:
 - More advanced cancers may extend to the hypopharynx and larynx.
 - Lateral and superior spread to involve the tonsil and pharyngeal mucosa:
 - Deeper extension can occur along the pterygo-mandibular raphe toward the mandible.
 - Lateral and posterior spread can also occur into parapharyngeal space and carotid sheath.

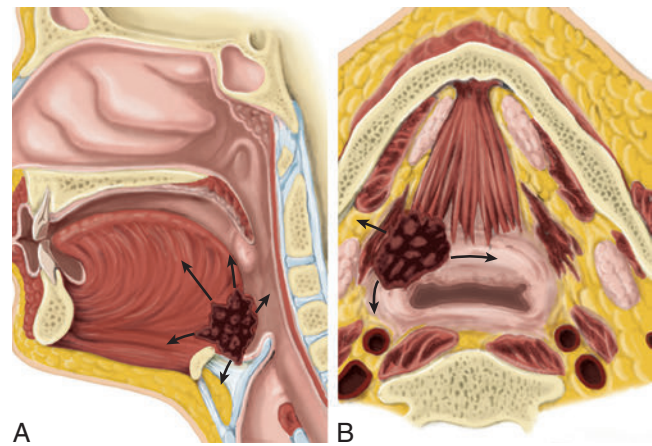


Fig. 10-26. Patterns of spread for tongue base carcinoma.

Sagittal and axial illustrations demonstrate the potential spread patterns of a tongue base carcinoma (arrows). (From Mukherji SK, Pillsbury H, Castillo M: *Imaging squamous cell carcinomas of the upper aerodigestive tract: what the clinicians need to know*, Radiology 205:629-646, 1997.)

- Anterior spread to floor of mouth and oral tongue
- Local advanced cancers can infiltrate deep muscle and cause fixation.
- As compared with non-HPV-associated HNSCC, HPV-associated HNSCC is:
 - Associated with a better outcome (better overall and disease-specific survival)
 - Highly curable even in presence of advanced clinical stage disease
- Factors that may be in play relative to their better outcome include the possibility of absence of field cancerization and presence of enhanced radiation sensitivity.
- Factors affecting prognosis include:
 - Positive prognostic benefit of HPV in HNSCC mitigated by negative prognostic effects of smoking
 - Increasing evidence TP53 mutation and high EGFR expression can increase resistance of HPV-associated carcinoma to therapy.
 - Current therapies associated with excess morbidities, including long-term swallowing dysfunction, reduced saliva production, and dysgeusia
 - Second primary malignancies may be less common in patients with HPV-associated tumors than HPV-negative tumors.
 - Rates of death from second primary cancers in HPV-associated HNSCC similar to rates associated with HPV-negative HNSCC
- HPV vaccines are expected to protect against most HPV-induced cancers:

- Primarily directed against development of cervical cancer
- Effects of HPV vaccine on incidence of HPV-associated HNSCC yet to be determined and with ongoing trials will be determined over time
- Targeted therapy:
 - Potential use of targeted therapy based on genomic findings including somatic mutations currently subject of clinical trials and potentially could be used in treatment of these cancers

HPV-Associated Basaloid Squamous Cell Carcinoma of the Oropharynx

- Histologically similar to basaloid squamous cell carcinoma arising in other mucosal sites of the upper aerodigestive tract; for more details including images see Section 5, Larynx.
- In contrast to non-oropharyngeal basaloid squamous cell carcinoma, many but not all of the oropharyngeal basaloid squamous cell carcinomas are associated with HPV16 (p16 positive).
- Overlapping growth patterns and cell types between non-HPV-associated basaloid squamous cell carcinoma and HPV-associated basaloid squamous cell carcinoma make differentiation between these two similar-appearing but biologically distinct cancers problematic.
 - Presence or absence of HPV represents the key feature in distinguishing these two tumor types.
- HPV-associated basaloid squamous cell carcinoma of the oropharynx:
 - Predilects to the base of tongue > tonsil
 - More common in men than women
 - Are immunoreactive for p16
 - Confers a better prognosis than non-HPV-associated basaloid squamous cell carcinoma

Nonkeratinizing (Lymphoepithelial-Like) Undifferentiated Carcinoma of the Oropharynx (Fig. 10-27)

- Represents a rare variant of nonkeratinizing carcinoma
- More than 90% occur in tonsils and base of tongue.
- Symptoms may include oropharyngeal mass and/or neck mass:
 - Cervical lymph node involvement occurs in approximately 70% of cases at presentation.
- Histomorphologic features similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated (see previously in this chapter)

- Immunohistochemistry:
 - Cytokeratins positive
 - Hematolymphoid markers negative
 - p16 positive
 - EBER negative
- Radiosensitive cancers:
 - Local failure: 3%
 - Regional failure: 5%
 - Distant failure: 19%

Conventional Keratinizing (Non-Viral-Associated) Squamous Cell Carcinoma of the Pharynx

- Incidence stabilized or decreasing with the decreasing use of tobacco products
- Clinical findings differ per site of occurrence (see below).
- Histology similar regardless of site of occurrence

Squamous Cell Carcinoma of the Soft Palate and Uvula

Anatomic Considerations

- Soft palate includes the uvula and incompletely separates the oral cavity and oropharynx from the nasopharynx:
 - Continuous laterally with the tonsillar pillars and attaches anteriorly to the hard palate
 - Forms the roof of the oropharynx and floor of the nasopharynx
 - Demarcates the oral cavity from the oropharynx as well as the oropharynx from the nasopharynx

Clinical

- More common in men than women; most frequently occurs in the fifth through eighth decades of life
- Symptoms include sore throat, sensation of a lump or foreign body in the throat, dysphagia, bleeding, trismus, and referred pain (e.g., otalgia):
 - Referred otalgia can be one of the first symptoms a patient experiences with a mass of the oropharynx
 - Mediated by cranial nerves IX and X
- Carcinomas of the soft palate almost exclusively found on the oropharyngeal rather than nasopharyngeal surface and may be localized at presentation or spread to adjacent structures, including tonsillar pillars and base of tongue:
 - Occasionally may extend laterally and superiorly as far as the nasopharynx

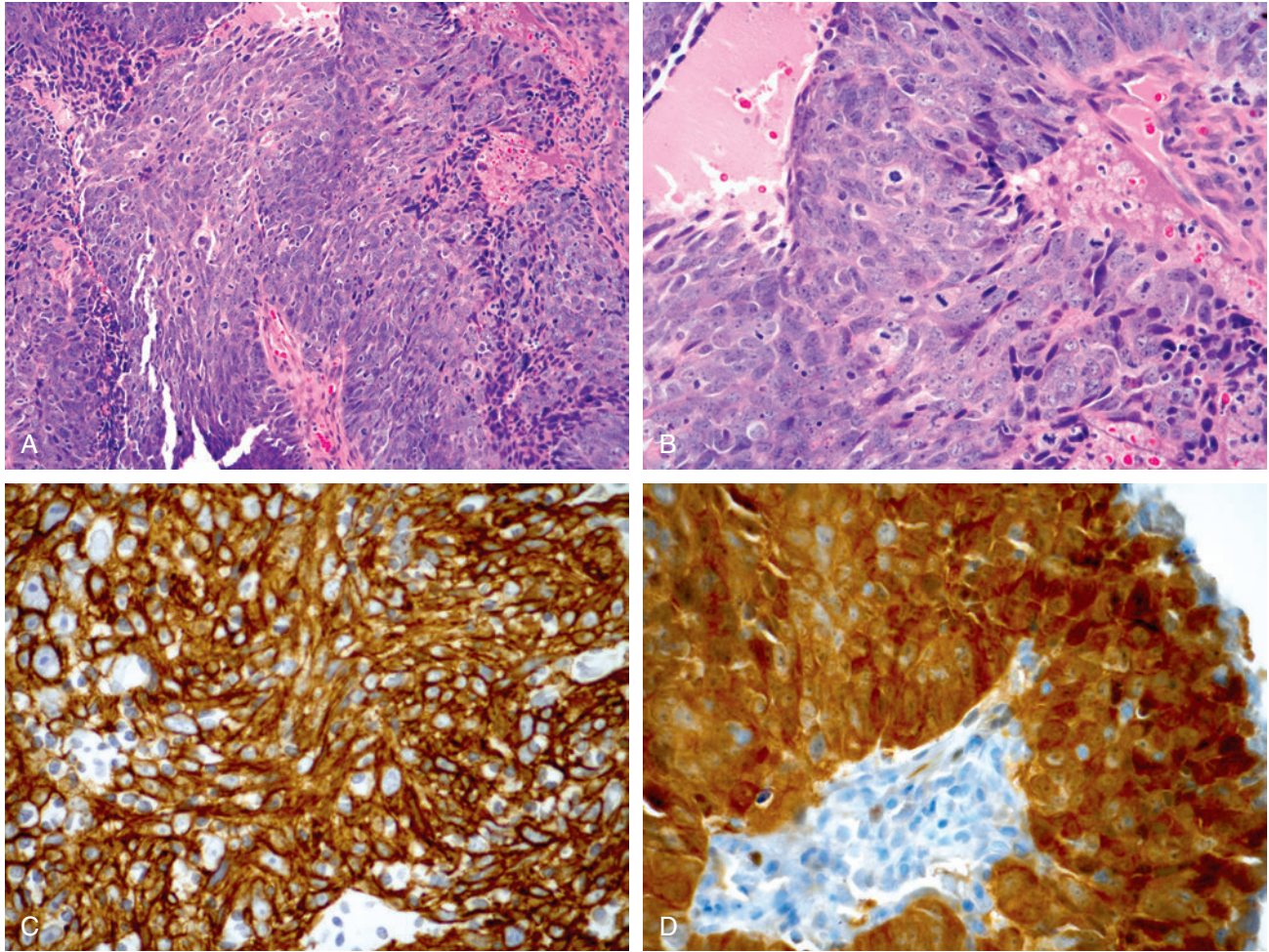


Fig. 10-27. Nonkeratinizing (lymphoepithelial-like) undifferentiated carcinoma of the oropharynx.

A and B, Histomorphologic features are similar to those of nasopharyngeal carcinoma, nonkeratinizing undifferentiated type, including syncytial growth composed of neoplastic cells with enlarged pleomorphic and vesicular nuclei and prominent nucleoli. **C,** Lesional cells are cytokeratin positive. In addition to localization to the base of tongue, **(D)** the lesional cells are p16 positive. EBER staining was negative (not shown). Molecular analysis confirmed the presence of HPV (not shown). This carcinoma can metastasize to cervical neck lymph nodes as an occult primary carcinoma. In such a scenario, purely based on the light microscopic features, a primary nasopharyngeal carcinoma would be the most likely consideration. EBER staining would be negative, and unless consideration was given for a possible oropharyngeal origin, p16 staining, which would be diagnostic, may not be performed.

- Involvement of the palatine nerve can result in carcinoma tracking along this pathway with extension to the base of the skull.
- Lymphatic involvement primarily to level II
- Carcinoma of the midline or uvula can result in bilateral neck metastases
- Retropharyngeal nodes are at risk
- Causes include primarily tobacco and alcohol use/abuse; other risk factors include:
 - Diet poor in fruits and vegetables
 - Chewing betel quid

Pathology Histology

- Originates from surface epithelium
 - Conventional keratinizing squamous cell carcinoma is the most common histologic type.
- Conventional invasive keratinizing squamous cell carcinoma is the most common histologic type:
 - Originates from surface epithelium, so intraepithelial dysplasia is often present and identifiable in the absence of ulceration.

- May be well, moderately, or poorly differentiated
- Desmoplastic stromal response present
- Histologic variants of squamous cell carcinoma may occur.

Treatment and Prognosis

- TNM classification for pharyngeal carcinoma is detailed in [Table 10-6](#).
- Treatment options for early stage disease (T1, T2) include:
 - Primary radiotherapy:
 - Increasing use of intensity-modulated radiotherapy (IMRT) with addition of image-guided radiotherapy (IGRT) has led to high rates of locoregional control with low incidence of long-term functional morbidity.
 - Primary surgery:
 - Primary surgery involves transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) for the primary site and must be combined with a separate procedure to remove neck nodes:
 - Must be combined with (separate) procedure to remove neck nodes
 - May not be the only treatment needed and may require additional treatment with radiotherapy or concomitant chemotherapy-radiotherapy, depending on the pathologic findings in the primary tumor and the neck (e.g., lymph-vascular invasion, neurotropism, extranodal extension)
 - Surgery does not address the retropharyngeal nodes, which is an area at risk.
- Outcomes for early stage disease:
 - Primary RT:
 - 5-year initial and ultimate (after successful salvage) local control rates for stage I 84% and 89%, respectively
 - 5-year initial and ultimate (after successful salvage) local control rates for stage II 85% and 88%, respectively
 - 90% locoregional control rates for T1 and T2
 - 5-year disease-specific survival for stages I and II of 89% and 87%, respectively
 - 90% 5-year nodal control rate for N0 disease
 - 5-year freedom from distant metastases rate of 95% for stage I and 97% for stage II
 - Primary surgery:
 - 5-year disease-specific survival for stages I and II 70% and 53%, respectively
 - 5-year local control for stages I and II 83% and 74%, respectively
 - 5-year distant control for stages I and II 96% and 81%, respectively
 - 5-year disease-specific survival for stages I and II 87% and 66%, respectively
- Treatment options for advanced stage disease (T3, T4) includes:
 - Combined therapy options are preferred:
 - Concomitant chemotherapy and radiation therapy preferred management for most patient with stages III and IVA/B disease
 - Stage III disease:
 - Radiation therapy alone considered for certain patients with low bulk stage III lesions (i.e., T1-2N1M)
 - Primary surgery alone may be used for select patients with low bulk stage III disease
 - If there are negative margins on primary site surgery and negative neck specimens, surgery alone may be adequate.
 - Stage III patients with positive margins, positive nodes, or other adverse findings (neurotropism, lymph-vascular invasion) trigger postoperative radiotherapy or concomitant chemotherapy-radiotherapy especially if margins are positive or there is extranodal extension.
 - Stage IVA/B disease:
 - Concomitant chemotherapy and radiation therapy (i.e., cisplatin and IMRT) are the mainstays of treatment.
 - Stage IVC:
 - Determined by the extent of locoregional disease, resectability presence and extent of distant metastases, and performance status of the patient
- Outcomes for advanced stage disease:
 - 5-year outcomes for patients receiving primary surgery, surgery plus postoperative radiotherapy, or primary radiotherapy with or without chemotherapy include:
 - Local control for stages III and IV of 88% and 54%, respectively
 - Regional control local control for stages III and IV of 77% and 73%, respectively
 - Distant control for stages III and IV of 72% and 83%, respectively
 - Disease-free survival for stages III and IV of 54% and 36%, respectively
 - Overall survival for stages III and IV of 55% and 37%, respectively
 - Disease-specific survival for stages III and IV of 65% and 55%, respectively

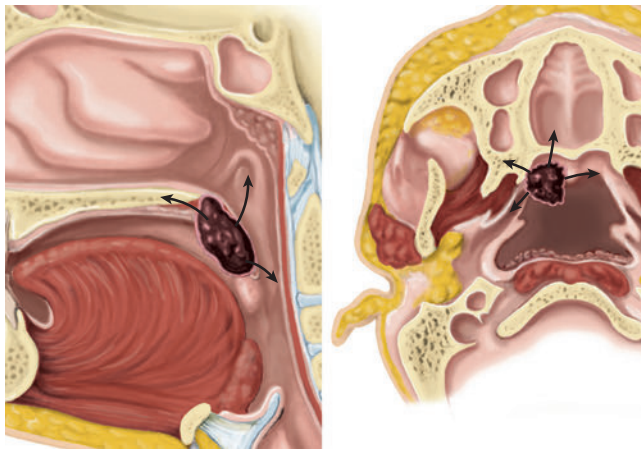


Fig. 10-28. Patterns of spread for soft palate carcinoma.

Sagittal and axial illustrations demonstrate the potential spread patterns of a soft palate carcinoma (arrows). (From Mukherji SK, Pillsbury H, Castillo M: *Imaging squamous cell carcinomas of the upper aerodigestive tract: what the clinicians need to know*, *Radiology* 205:629-646.)

- Patterns of spread for soft palate carcinoma (Fig. 10-28):
 - Inferiorly to tonsillar pillars
 - Anteriorly to hard palate
 - Laterally deep invasion can occur into the parapharyngeal space
 - Superiorly, extension along the nasopharynx into the skull base

Squamous Cell Carcinoma of the Oropharyngeal Wall

Anatomic Considerations

- Posterior pharyngeal wall starts at the inferior aspect of the nasopharynx in the region of the soft palate and extends to the level of the epiglottis inferiorly:
 - Makes up the posterolateral surfaces of the oropharynx
 - Pharyngeal constrictor muscles constitute the framework of the pharyngeal walls.
 - Lateral aspect continuous with the pharyngoepiglottic fold and continues to the lateral aspect of the piriform sinus
 - Nerve supply from cranial nerves IX and X
 - Rich in lymphatics with primary drainage directed to retropharyngeal nodes and levels II and III

Clinical

- More common in men than women; most common in the seventh decade of life

- Clinically “silent” region resulting in tumors presenting at a more advanced stage (e.g., T3, T4):
 - Symptoms may include dysphagia, odynophagia, bleeding, and a neck mass.
 - Otalgia which represents referred pain in the ear region may be an initial symptom of oropharyngeal cancers is mediated by cranial nerves IX and X.
 - Clinically palpable lymph nodes present in:
 - 25% of T1 lesions
 - 30% of T2 lesions
 - 66% of T3 lesions
 - >75% of T4 lesions
 - Most pharyngeal wall tumors extend across the midline, commonly resulting in bilateral cervical metastases; retropharyngeal lymph nodes are also at increased risk.

Pathology

Histology

- Conventional invasive keratinizing squamous cell carcinoma is the most common histologic type:
 - Originates from surface epithelium, so intraepithelial dysplasia is often present and identifiable in the absence of ulceration
 - May be well, moderately, or poorly differentiated
 - Desmoplastic stromal response present
- Histologic variants of squamous cell carcinoma may occur.

Treatment and Prognosis

- TNM classification for pharyngeal carcinoma is detailed in Table 10-6.
- Treatment options must address the primary site and both sides of the neck, including the bilateral retropharyngeal nodes:
- Outcomes for early stage disease:
 - Primary RT:
 - Local control rates of 93% and 82% for T1 and T2, respectively
 - 5-year disease-specific survival and overall survival:
 - Stage I: 88% and 50%, respectively
 - Stage II: 89% and 75%, respectively
- Outcomes for advanced stage disease:
 - Primary RT:
 - 5-year local control rates of 59% and 44% to 50% for T3 and T4, respectively
 - 5-year disease-specific survival and overall survival:
 - Stage III: 49% and 31%, respectively
 - Stage IV: 35% and 21%, respectively
 - Outcomes for primary surgery with or without radiotherapy include:

- For combined therapy:
 - Local failure of 11%
 - 5-year survival rate of 35%
- For patients with local failure post-primary radiotherapy, 16% 5-year survival rate
- Patterns of spread for pharyngeal wall carcinoma:
 - Superiorly to nasopharynx
 - Posteriorly to prevertebral fascia
 - Inferiorly to piriform sinus and hypopharyngeal wall

Squamous Cell Carcinoma of the Hypopharynx

Definition: Hypopharyngeal carcinoma involves the piriform sinus, posterior pharyngeal wall, and postcricoid area.

Anatomic Considerations

- Piriform sinus: Inverted pyramid- or pear-shaped sinus composed of anterior, medial, and lateral walls converging inferiorly toward an apex at the level of the inferior border of the cricoid cartilage:
 - Superior border: at level of pharyngoepiglottic fold
 - Lateral wall: inner surface of thyroid cartilage and thyrohyoid membrane
 - Medial wall: posterior surface of the aryepiglottic fold and the arytenoids and cricoid cartilages
- Posterior pharyngeal wall: three levels of the pharynx are recognized, including the nasopharynx, oropharynx, and hypopharynx with no specific anatomic barriers between these levels; tumors of the pharynx tend to be large at presentation with involvement of more than one level
- Postcricoid area: bounded laterally by the piriform sinuses and extends from the posterior surface of the arytenoid cartilage to the inferior surface of the cricoid cartilage

Clinical

- More common in men than in women; peak incidence in the sixth to seventh decades of life:
 - 80% to 85% occur in men
 - For postcricoid specific carcinomas, 50% to 90% occur in women
- In descending order of occurrence, hypopharyngeal carcinomas involve the piriform sinus > posterior pharyngeal wall > postcricoid region:
 - Piriform sinus accounts for approximately 65% to 85% of the carcinomas in this region.
 - Posterior pharyngeal wall accounts for approximately 10% to 20% of the carcinomas in this region.
 - Postcricoid region accounts for approximately 5% to 15% of the carcinomas in this region.

- Symptoms include:
 - Dysphagia: most common presenting symptom, present in up to 85% of cases
 - Palpable neck mass most common physical finding
 - Other symptoms may include odynophagia, sore throat, sensation of a foreign body in the throat, hoarseness, referred otalgia, hemoptysis, and weight loss.
- Hypopharyngeal carcinomas tend to remain quiescent for longer periods and present with more advanced disease (i.e., T3 and T4):
 - Carcinomas of the postcricoid area are commonly extensive at presentation and portend a worse prognosis in comparison with carcinomas from other hypopharyngeal locations.
- Uncommonly, early stage hypopharyngeal carcinomas diagnosed in the evaluation of new-onset reflux symptoms
- Cause linked to:
 - Tobacco smoking
 - Excessive alcohol use
- Plummer-Vinson syndrome characterized by:
 - Dysphagia due to webs, stenosis, or mucosal atrophy:
 - Webs arise from anterior esophageal wall distal to the cricoid cartilage.
 - Carcinomas develop immediately proximal to the webs and not within the webs.
 - Carcinomas may develop in other sites including the oral cavity and esophagus.
 - Treatment with dietary supplements, particularly iron, may result in disappearance of the webs, thereby decreasing the incidence of carcinoma.
 - Iron-deficiency anemia
 - Glossitis
 - Cheilitis
 - Achlorhydria

Pathology

Gross

- Tumors of all hypopharyngeal sites tend to be large at presentation:
 - Those of the posterior hypopharyngeal wall often are greater than 5 cm in greatest dimension.

Histology

- Majority are invasive keratinizing moderately to poorly differentiated squamous cell carcinomas.

Treatment and Prognosis

- TNM classification for pharyngeal carcinoma is detailed in [Table 10-6](#).
- For early stage patients, including stage I or II (T1-2, N0), constituting approximately 10% to 15% of

hypopharyngeal carcinomas, important goal in management is to obtain local control while optimizing functional outcome:

- Curative radiation is preferred as definitive treatment approach, provides good chance for organ preservation.
- Alternatively, open or endoscopic surgery (partial laryngopharyngectomy) with ipsilateral or bilateral neck dissection may be performed.
- More recently, transoral laser microsurgeries used with promising results
- For advanced stage patients, including stage III to IVa (T1-2, node positive, or T3-4a):
 - Desire for organ preservation in locally advanced disease is primary indication for nonoperative management in patients who may be technically respectable
 - Definitive chemoradiotherapy represents treatment most used:
 - Induction chemotherapy can be used prior to definitive therapy.
 - For patients undergoing primary radiation or chemotherapy, consideration should be given to postradiation neck dissection.
 - Generally not used for N0-N1 necks
 - Used for patients with N2-N3 neck disease in attempt to enhance regional disease control
 - Primary surgery and postoperative radiation:
 - Total laryngectomy and partial pharyngectomy with bilateral neck dissections was historical mainstay of treatment for locally advanced hypopharyngeal cancers.
 - Postoperative radiation:
 - Indications for postoperative radiation therapy include:
 - Pathologic T3-T4 tumors (bulky T-stage disease)
 - N2-N3 disease
 - Positive surgical margins
 - Perineural invasion
 - Lymph-vascular invasion
 - Extranodal extension of involved lymph nodes
 - Induction chemotherapy
 - Can be used to facilitate organ preservation in some patients who require total laryngectomy for adequate surgical resection
- For unresectable, nonmetastatic disease:
 - May warrant aggressive treatment with curative intent or may be best served by a palliative approach with decision making predicated on tumor burden, patient motivation, and performance status
 - Curative intent therapy may include chemoradiation:
 - For patients with high motivation and good performance status, induction chemotherapy followed by chemoradiation may be considered.
 - Patients with advanced disease and poor performance status who are not considered appropriate for aggressive radiation or chemoradiation can be offered palliative radiotherapy alone.
 - In conjunction with radiation therapy represents a potential legitimate alternative therapy to surgery in:
 - Patients with advanced hypopharyngeal carcinoma who want to avoid total laryngectomy
 - Patients with unresectable M0 hypopharyngeal carcinoma:
 - Unresectability (or not resectable for cure) includes tumor fixed to the cervical spine, massive T4 disease, bulky lymphadenopathy fixed to neurovascular bundle
 - Patients with M1 hypopharyngeal carcinoma
- Outcomes:
 - Outcomes for hypopharyngeal carcinomas are poor:
 - 5-year overall survival rates of approximately 30%
 - 5-year stage-specific overall survival includes:
 - Stage I: 51.3%
 - Stage II: 34.8%
 - Stage III: 34.8%
 - Stage IV: 19.8%
 - Poor prognostic factors include:
 - Increasing age (>70 years)
 - Male gender
 - Carcinomas of the posterior wall and postcricoid area
- Hypopharynx is rich in lymphatic spaces and many patients (65% to 80%) have node-positive disease:
 - Greater than 50% present with clinically positive cervical lymph nodes
 - Additional 30% to 40% of N0 necks found to show pathologic involvement when dissected electively
 - Lymphatic drainage includes jugular chain nodes (levels II to IV) as well as retropharyngeal nodes
 - In addition, paratracheal lymph nodes also at risk in hypopharyngeal cancers with surgical specimens showing involvement in 20% to 25% of cases
 - Bilateral neck disease is common owing to presence of cross-draining lymphatics.
- Hypopharyngeal carcinomas have higher rates of distant metastatic disease than primary carcinomas of other head and neck subsites:
 - Approximately 16% present with distant metastasis at diagnosis

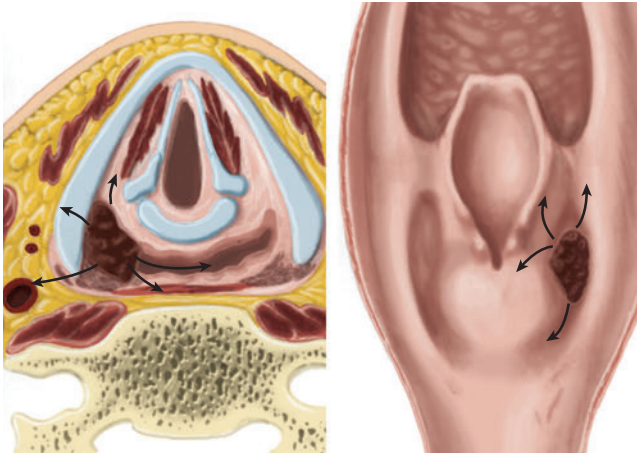


Fig. 10-29. Patterns of spread for piriform sinus carcinoma.

Sagittal and axial illustrations demonstrate the potential spread patterns of a piriform sinus carcinoma (arrows). (From Mukherji SK, Pillsbury H, Castillo M: *Imaging squamous cell carcinomas of the upper aerodigestive tract: what the clinicians need to know*, Radiology 205:629-646, 1997.)

- Lung is most common site of distant metastases followed by mediastinal lymph nodes, liver, and bone
- Hypopharyngeal carcinomas tend to grow submucosally, spreading beneath intact mucosa and beyond grossly apparent margins.

Patterns of Spread

- Piriform sinus carcinomas (Fig. 10-29):
 - Medially to invade the lateral wall of the supra-glottic larynx with invasion of the cricoarytenoid joint and/or muscle or the recurrent laryngeal nerve resulting in vocal cord fixation
 - Laterally to invade posterolateral portion of the thyroid cartilage and/or invasion of the superior lobe of the thyroid gland
 - Superiorly to involve aryepiglottic folds, arytenoids, paraglottic space, and base of tongue
 - Across the postcricoid areas with involvement of the opposite piriform sinus
 - Into the contiguous posterior pharyngeal wall, which is common as the tumor grows laterally
- Posterior hypopharyngeal wall carcinomas:
 - May spread circumferentially to involve the larynx
 - Advanced carcinomas may extend superiorly with involvement of the tonsillar pillars, soft palate, and nasopharynx.

- Advanced carcinomas may extend inferiorly with involvement of the piriform sinus, cricopharyngeus, and cervical esophagus.
- Postcricoid area carcinomas:
 - Inferiorly to involve cervical esophagus
 - Circumferential growth frequently occurs with invasion of cricoid cartilage and cricoarytenoid muscles and resultant vocal cord fixation.
 - May spread circumferentially to involve the larynx
 - Advanced carcinomas may extend superiorly with involvement of the tonsillar pillars, soft palate, and nasopharynx.
 - Advanced carcinomas may extend inferiorly with involvement of the piriform sinus or cervical esophagus.
 - Deep infiltration can involve retropharyngeal space with access to lymphatics in that region and subsequently into the prevertebral fascia.

Other Variants of Squamous Cell Carcinoma of the Pharynx

- Other variants of conventional squamous cell carcinoma that may occur in the oropharynx include:
 - Verrucous carcinoma
 - Papillary squamous cell carcinoma
 - Spindle cell squamous carcinoma
 - Adenosquamous carcinoma
 - Other rare variants
- For a detailed discussion of these histologic variants, see Section 5, Larynx.
- Some of these oropharyngeal SCC variants may be associated with HPV including:
 - Papillary SCC
 - Spindle cell squamous carcinoma
 - Adenosquamous carcinoma (Fig. 10.30)

Neuroendocrine Carcinomas

- Neuroendocrine carcinomas (NEC) represent a heterogeneous group of malignant neoplasms with divergent differentiation along epithelial and neuroendocrine cell lines.
- See Section 5, Larynx, for a more detailed discussion of neuroendocrine carcinomas.
- Of note is the presence of HPV in association with small cell neuroendocrine carcinoma that occurs primarily in the oropharynx.
- Rare tumor type in the pharynx; however, of note is the existence of HPV-associated small cell neuroendocrine carcinoma primarily arising in the oropharynx.

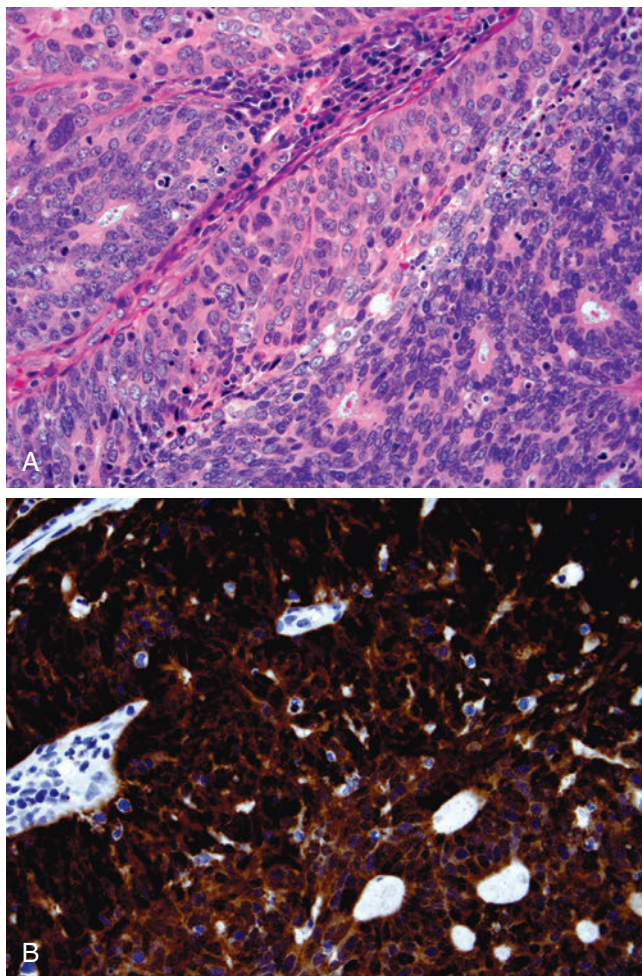


Fig. 10-30. Tonsillar HPV-associated adenosquamous carcinoma.

A, This was a deeply infiltrative tonsillar carcinoma comprised of an admixture of cells with squamous differentiation and glandular differentiation. **B**, Diffuse and strong p16 immunoreactivity in both squamous cell and glandular components. Additional findings seen but not shown included the presence of high-grade intraepithelial dysplasia, diffuse and strong p63 immunoreactivity for cytokeratins (AE1/AE3, CAM5.2, CK5/6) and p63, absence of staining with neuroendocrine markers (e.g., synaptophysin, others), and molecular confirmation for the presence of HPV.

Oropharyngeal HPV-Associated Small Cell Undifferentiated Neuroendocrine Carcinoma (Fig. 10-31)

Definition: Neuroendocrine carcinoma with small cell morphology associated with HPV infection as well as history of tobacco and/or alcohol abuse:

- In contrast to the relatively favorable prognosis associated with HPV-associated squamous cell

carcinomas of the oropharynx, the reported follow-up of patients with oropharyngeal HPV-associated neuroendocrine carcinoma suggests an aggressive behavior despite its association with HPV.

- Also referred to as small cell carcinoma

Clinical

- Uncommon tumor with less than 20 cases reported in the literature
- Much more common in men than women; occur over a wide age range from 35 to 87 years, with a mean age of 59 years
- Symptoms include sore throat, epistaxis, or neck mass.
 - Additional symptoms may include severe headache, hemoptysis, and altered speech.
- Patients often present with advanced clinical stage disease:
 - Initial presentation may include metastatic disease with or without known primary oropharyngeal lesion including to:
 - Cervical lymph nodes
 - Lung
 - Brain
 - Uncommon for primary tumor to be localized to the oropharynx without metastatic disease
- Sites of origin include the palatine tonsil, base of tongue, and lateral pharynx:
 - Tonsillar and base of tongue cancers may extend into the pharynx.
- 64% (9 of 14) of patients reported had known risk factors, including tobacco and/or alcohol abuse.

Pathology

- Histomorphology is that of a poorly differentiated neuroendocrine carcinoma (small cell carcinoma) analogous to that of its pulmonary counterpart, including:
 - Trabecular, nested, organoid, and/or solid growth patterns composed of small to moderately sized cells with increased nuclear-to-cytoplasmic ratio, scant to moderate amounts of pale eosinophilic cytoplasm, and indistinct cell borders
 - Stippled (so-called salt and pepper) nuclear chromatin with absence of nucleoli
 - Nuclear molding may be present.
 - Marked increase in mitotic activity, including atypical forms and necrosis (individual cell and confluent foci)
- Neural rosette-like structures may rarely be present.
- Other histomorphologic tumor types seen in association with the neuroendocrine carcinoma may include:
 - Squamous cell carcinoma, nonkeratinizing and basaloid morphology

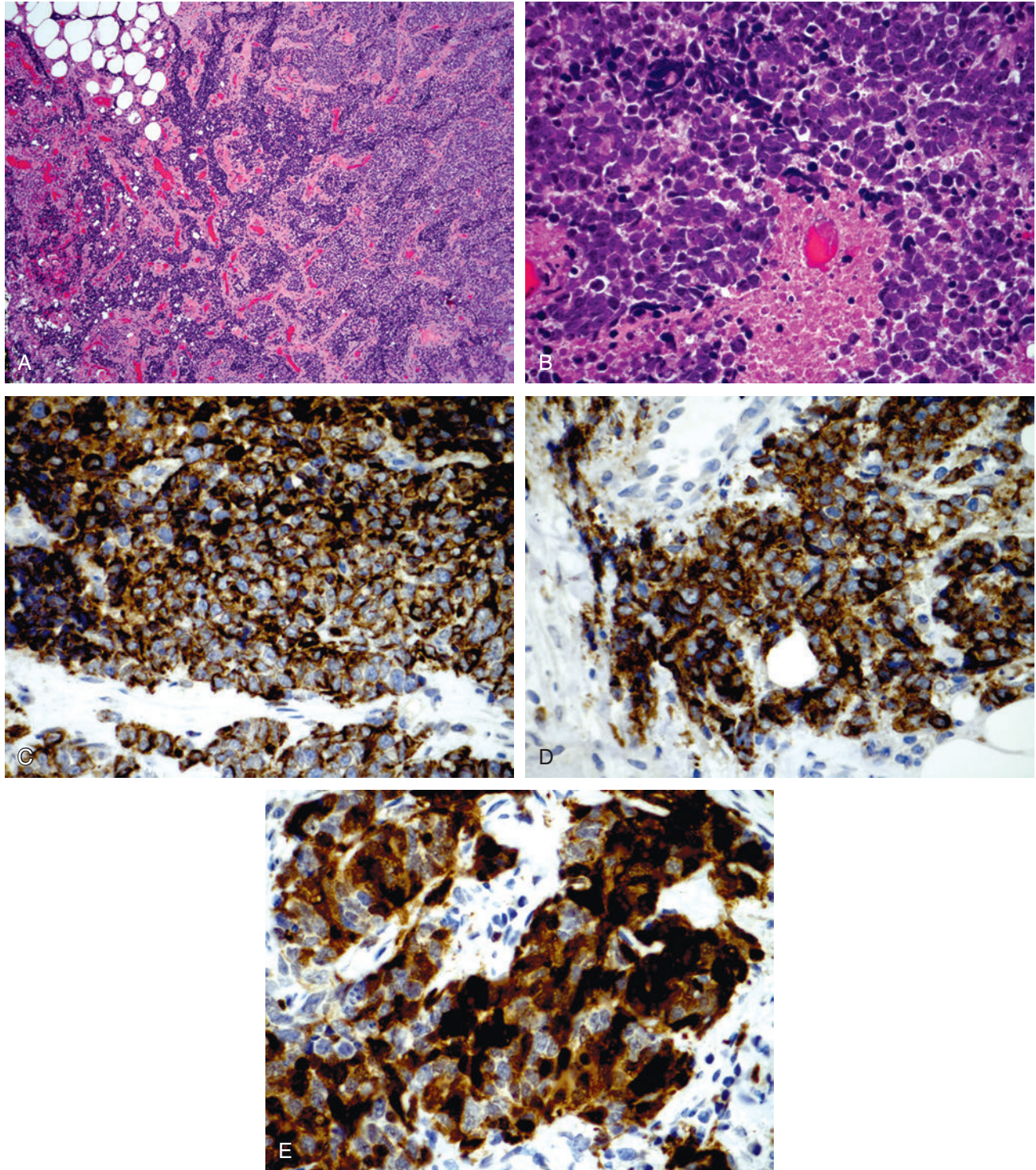


Fig. 10-31. HPV-associated small cell undifferentiated neuroendocrine carcinoma (small cell carcinoma).

A, Hypercellular diffusely infiltrative neoplasm with trabecular and solid growth. **B**, Small to moderate-size cells with stippled nuclear chromatin, absent nucleoli, nuclear molding, increase in mitotic activity, and necrosis (confluent foci and individual cell); immunoreactivity includes **(C)** punctate (dot-like) paranuclear cytokeratin (CAM5.2) staining; **D**, synaptophysin staining; and **(E)** p16 staining. Molecular analysis confirmed the presence of HPV (not shown).

- Immunohistochemistry for small cell component:
 - Immunoreactivity for synaptophysin, chromogranin, CD56, and neuron-specific enolase with variable staining for TTF1
 - Positive for cytokeratins, including punctate paranuclear staining for AE1/AE3 and CAM5.2:
 - CK7 and CK20 may be positive.
 - CK5/6 negative in small cell component
 - Variability of p63 staining reported, including:
 - Reported positivity from focal to diffuse in small cell component in one study
 - Limited positive to squamous cell component and absence in small cell component in another study
 - Two cases analyzed by in situ hybridization (ISH) for Epstein-Barr encoded RNA (EBER) were negative.
- HPV analysis
 - 92% (12 of 13) p16 positive with strong and diffuse staining
 - 80% (8 of 10) in situ hybridization for HPV 16 positive
 - 50% (3 of 6) p16 positive were positive for HPV by PCR

Treatment and Prognosis

- Majority of patients presented with advanced disease, including locoregional nodal metastasis or distant metastases to the lung and brain.
- Treatment includes surgical excision followed by chemotherapy and/or radiation.
- High percentage of patients with local recurrence, locoregional metastasis, and/or distant metastasis:
 - Distant metastatic sites include brain, bone, pleura, lung, pancreas, or adrenal gland.
- One study reported 60% (3 of 5) of patients died of disease with follow-up of 6 to 15 months (mean survival 10 months).
- In contrast to the relatively favorable prognosis associated with HPV-associated squamous cell carcinomas of the oropharynx, the findings of the HPV-associated neuroendocrine carcinoma of the oropharynx suggest an aggressive behavior despite its association with HPV.

Malignant (Minor) Salivary Gland Tumors

- For more detailed discussion see Section 6, Salivary Glands.
- Malignant salivary gland tumors of the oropharynx and nasopharynx are uncommon.
- All subtypes of malignant salivary gland tumors may occur in minor salivary gland sites but the most common types include:

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Some of the more common malignant major salivary gland tumors are uncommon in minor salivary gland locations, including acinic cell adenocarcinoma; a minor salivary gland neoplasm that engenders the diagnostic consideration of an acinic cell adenocarcinoma should raise concern for the likelihood of an alternative diagnosis such as mammary analogue secretory carcinoma (see Section 6, Salivary Glands).
- Select malignant salivary gland carcinomas, including polymorphous low-grade adenocarcinoma and clear cell carcinoma (nonhyalinizing and hyalinizing type), predilect to minor salivary glands, in particular, of the oral cavity.
- All minor salivary gland tumors are unencapsulated; as such, the differentiation of a benign tumor from a malignant tumor is often predicated on the presence or absence of invasion; invasion includes:
 - Into adjacent minor salivary gland parenchyma
 - Into fibroconnective tissues (e.g., fat, skeletal muscle)
 - Peri- and intraneural invasion (i.e., neurotropicism)
 - Lymph-vascular space invasion
 - Extension to and/or into the surface epithelium is not diagnostic of invasion or malignancy.
 - Metastatic disease is essentially diagnostic of a malignant neoplasm.

Low-Grade Nasopharyngeal Papillary Adenocarcinoma

(Fig. 10-32)

Definition: Surface epithelial-derived malignant tumor with adenocarcinomatous differentiation and an indolent biologic behavior.

- Light microscopic findings and the immunohistochemical profile support derivation of this neoplasm from the surface epithelium rather than from the subjacent minor salivary glands.

Synonym: Thyroid-like (low-grade) nasopharyngeal papillary adenocarcinoma

Clinical

- Uncommon primary tumor of the nasopharynx
- No gender predilection; occurs over a wide age range from the second through seventh decades of life (median, 37 years)

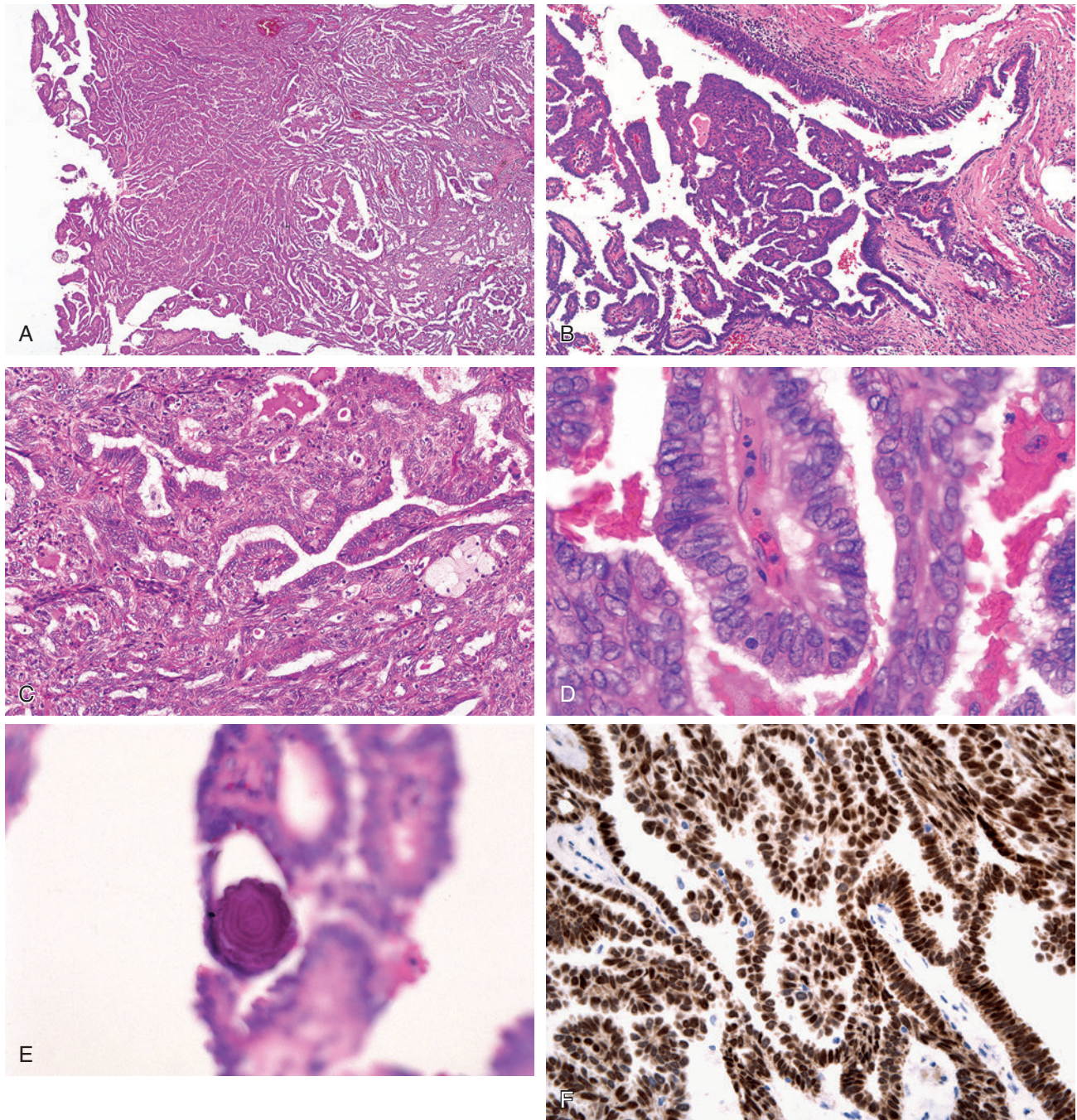


Fig. 10-32. Low-grade nasopharyngeal papillary adenocarcinoma (LGNPPA).

A, Infiltrative neoplasm showing complex papillary growth. **B**, Origin from the nasopharyngeal surface epithelium is seen with transition from normal nasopharyngeal surface epithelium to the neoplastic papillary proliferation. **C**, Complex papillary and glandular growth patterns; scattered cluster of foamy histiocytes is present (*right side of image*). **D**, At high magnification the nuclei show cytomorphologic features similar to those seen in thyroid papillary carcinoma including nuclear irregularities in size and shape, optically clear to dispersed (very fine) appearing nuclear chromatin, and nuclear crowding and overlapping. **E**, Psammoma bodies characterized by the presence of concentric laminations can be present; lesional cells are immunoreactive for **(F)** thyroid transcription factor 1 (TTF-1) (nuclear staining) but **(G)** are negative for thyroglobulin.

Continued

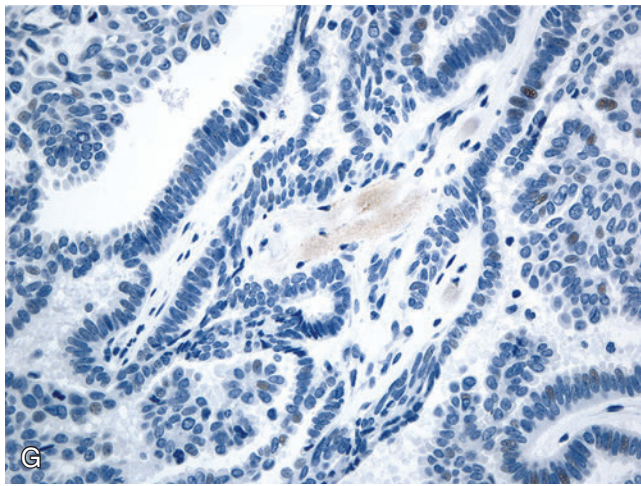


Fig. 10-32, cont'd

- May occur anywhere in the nasopharynx but is most common in the posterior and lateral nasopharyngeal walls and the roof
- Most common symptom is nasal obstruction:
 - Other symptoms may include otitis media with or without associated hearing deficits and postnasal drip.
- No known etiologic factors:
 - A single case reported in association with Turner syndrome
 - No association with EBV or HHV-8

Pathology

Gross

- Exophytic, soft to gritty mass with a papillary, nodular, and cauliflower-like appearance and varying in size from a few millimeters to 3.0 cm

Histology

- Surface epithelial derivation is identified by transition areas from normal nasopharyngeal surface epithelium to neoplastic proliferation:
 - Transitional areas may only be focally identified but may also be absent in any given case.
- Unencapsulated and infiltrative tumor composed of papillary and glandular growth patterns:
 - Papillary structures are complex with arborization and hyalinized fibrovascular cores.
 - Complex glandular pattern characterized by back-to-back and cribriform growth
- Cytomorphology:
 - Cells vary in appearance from pseudostratified columnar to cuboidal.
 - Nuclei are round to oval with vesicular to optically clear-appearing chromatin pattern.
 - Cytoplasm is eosinophilic.

- Nuclear pleomorphism and loss of basal polarity are seen.
- Mitoses and prominent nucleoli are not commonly identified.
- Psammoma bodies and necrosis can be identified.
- Rare examples may show prominent spindle cell component:
 - Spindle cells display nuclear features similar to the epithelial component.
 - Two cell types may merge imperceptibly.
- Histochemistry:
 - Evidence of epithelial mucin as seen by the presence of:
 - Intracytoplasmic diastase-resistant, PAS-positive material
 - Intracytoplasmic and intraluminal mucicarmine material
- Immunohistochemistry:
 - Diffusely positive reactivity with cytokeratins, epithelial membrane antigen (EMA), and thyroid transcription factor 1 (TTF-1) (nuclear)
 - Focal reactivity with carcinoembryonic antigen (CEA)
 - No immunoreactivity with thyroglobulin, S100 protein, calcitonin, p63, or glial fibrillary acidic protein (GFAP)
 - Low proliferation indices by Ki67 of less than 5%
- Cytogenetics and molecular genetics
 - No mutations reported at position 1799 (exon 15) in the *BRAF* gene (*BRAFV600E*) or in exons 9 and 11 of the *KIT* gene

Differential Diagnosis

- Papilloma (surface epithelial or minor salivary gland origin)
- Minor salivary gland neoplasms:
 - Mucoepidermoid carcinoma
 - Acinic cell carcinoma
 - Polymorphous low-grade adenocarcinoma
- Metastatic papillary thyroid carcinoma:
 - Histologic similarities, especially nuclear changes and psammoma bodies, exist between low-grade nasopharyngeal papillary adenocarcinoma and thyroid papillary carcinoma, requiring immunohistochemical stains for differentiation:
 - Thyroglobulin immunoreactivity is present in metastatic papillary thyroid carcinoma and absent in nasopharyngeal low-grade papillary adenocarcinoma.
 - TTF-1 may be present in both tumor types and is not a differentiating stain.

Treatment and Prognosis

- Complete surgical excision via a transpalatal approach is the preferred treatment and is curative.

- Endoscopic resection via combined transnasal and transoral approach may be effective.
- Radiotherapy (preoperative and postoperative) does not appear to be warranted.
- Slow-growing tumor with the potential to recur if incompletely excised
- Metastatic disease does not occur.

HEMATOLYMPHOID MALIGNANT NEOPLASMS

General Considerations

- Classification schemes of lymphomas have varied to include the Rappaport Classification (1966), National Cancer Institute Working Formulation (1982), Lukes-Collins Revised Classification (1992), and Revised European-American Lymphoma (REAL) Classification (1994); currently, the WHO Classification (2007) is a modification of the REAL Classification.
- The fourth edition of the WHO Classification stratifies neoplasms primarily according to lineage to include:
 - Myeloid
 - Lymphoid
 - Histiocytic/dendritic
 - In addition, the fourth edition of the WHO Classification incorporates new information including:
 - New defining criteria for some diseases
 - New entities defined by genetic criteria or by their morphology, immunophenotype, and clinical features.
- Lymphomas are subdivided into non-Hodgkin lymphomas (NHLs) and Hodgkin lymphomas:
 - In the head and neck, NHLs are more common.
- The vast array of clinical and pathologic features of the malignant lymphoproliferative diseases is well beyond the scope of this text; the approach here is to describe the more common types of malignant lymphomas affecting the extranodal lymphoid sites of the head and neck primarily of Waldeyer tonsillar ring; other site-specific malignant lymphomas are discussed in those specific sections to include:
 - NK/T cell in Section 1 on the sinonasal tract
 - Salivary gland malignant lymphomas in Section 6
 - Thyroid gland malignant lymphomas in Section 8
- Majority of malignant lymphomas of Waldeyer tonsillar tissues are B-cell lymphomas, including a wide spectrum of histologic types:
 - Diffuse large cell B-cell lymphoma (DLBCL) is most common.
 - Follicular low-grade lymphomas are uncommon.
- Mucosa-associated lymphoid tissue (MALT) gives rise to a variety of extranodal malignant lymphomas, including head and neck sites (nasopharyngeal, tonsil, salivary glands, and others):
 - Less than 4% of low-grade lymphomas of Waldeyer tonsillar ring are MALT lymphomas.
 - MALT-lymphomas share clinical, histologic, and immunohistochemical features, including:
 - Tendency to remain localized, evolve slowly, and be of B-cell phenotype
- AIDS patients may develop malignant lymphomas originating in head and neck sites or involving this region as part of a systemic process.
- Primary Hodgkin lymphoma occurring in the head and neck is predominantly nodal-based (e.g., cervical lymph nodes):
 - In general, primary Hodgkin lymphoma in mucosal sites and extranodal lymphoid tissues of the head and neck, including Waldeyer tonsillar tissues, are exceedingly uncommon and are not discussed.
- Cause for most lymphomas is unknown:
 - Some cases are associated with immunosuppression, including:
 - Posttransplant lymphoproliferative disorder (PTLD)
 - HIV/AIDS
 - Viruses may play a role in some lymphoma types.

Lymphomas of the Waldeyer Tonsillar Ring (Nasopharynx, Tonsils, and Base of Tongue)

Definition: Primary malignant lymphoid cell neoplasms with the bulk of tumor formed by a ring or group of extranodal lymphoid tissues about the upper end of the pharynx, including the palatine tonsils, pharyngeal tonsils (adenoids) and base of tongue.

Clinical

- Most common primary site for lymphomas that arise in the upper aerodigestive tract accounting for:
 - Approximately 5% to 10% of NHL in Western countries
 - Approximately 20% to 25% of NHL in Asian countries
 - Approximately 16% of all head and neck NHL
 - Approximately 50% of all NHL that are primary in the head and neck
- Majority (approximately 80%) are primary to the site of involvement with a minority representing secondary involvement to an NHL at another site.
- Most common type of NHL of Waldeyer tonsillar ring is diffuse large B-cell lymphoma; less common types of NHLs of these sites include:

- Extranodal marginal zone lymphoma (MALT lymphoma)
- Mantle cell lymphoma
- Follicular lymphoma
- Burkitt lymphoma
- Others
- More common in men than women; occurs over a wide age range but is most common in the sixth to eighth decades of life:
 - Patients with underlying immunodeficiency condition usually are younger.
- Most common sites of occurrence in descending order of frequency are:
 - Tonsils > nasopharynx > base of tongue
- Most common symptoms include dysphagia, odynophagia, swelling or lump in throat, decreased hearing, pain, and sore throat:
 - Majority of masses are unilateral (80% to 90% of cases)
 - Cervical adenopathy is present in approximately 65% of patients.
 - Systemic symptoms (e.g., fever, night sweats, other) not common
 - Multifocality may be present.
- Cause:
 - No known cause in the majority of patients
 - Minority of patients have an underlying/associated immunodeficiency condition that may predispose to NHL, including:
 - Post-transplantation, HIV infection/AIDS
 - Association of NHL, especially diffuse large B-cell lymphoma, with Epstein-Barr virus is considered weak.

Pathology

Gross

- Often large exophytic submucosal mass with or without surface ulceration

Histology

Diffuse Large B-Cell Lymphoma (DLBCL)
(Figs. 10-33 and 10-34)

- Although any NHL type can occur in Waldeyer ring, the most common NHL is DLBCL, representing from 60% to 84% of NHL of these sites.
- Diffuse submucosal dyscohesive cellular infiltrate with:
 - Effacement of normal architecture, including absence/loss of germinal centers, although due to incomplete involvement residual germinal centers may be identified
 - Neoplastic cells are composed of medium to large cells with large round to oval vesicular (non-cleaved) nuclei and several membrane-bound

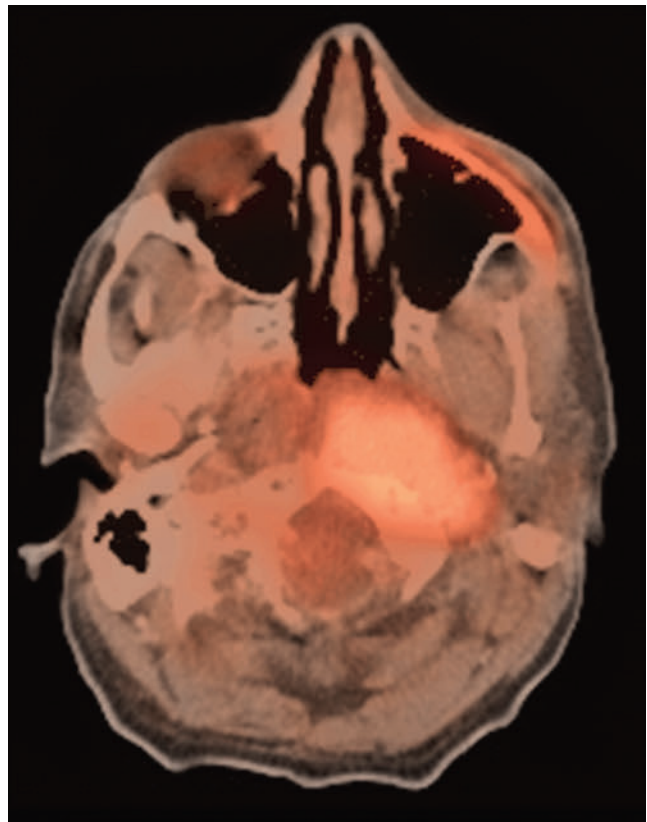


Fig. 10-33. Nasopharyngeal DLBCL.

Left lateral nasopharyngeal diffuse large B-cell lymphoma that demonstrates increased FDG activity on PET/CT examination. A nasopharyngeal carcinoma could have a similar imaging appearance, and tissue specimen examination is the final arbiter for diagnosis, as imaging appearances are often nonspecific. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 29-38, p 1773.)

- small nucleoli or a single centrally located prominent eosinophilic nucleolus
- Nuclear lobulation may be present.
- Mitotic activity, including atypical forms, (coagulative) necrosis, and apoptotic figures can be seen.
- Surface epithelium may be intact or ulcerated; crypt epithelium is usually intact.
- Immunohistochemistry:
 - Positive reactivity with pan-hematolymphoid marker CD45 (leukocyte common antigen [LCA]) and one or more pan-B-cell markers, including CD20, CD79a, PAX5
 - Surface or cytoplasmic immunoglobulin positive (IgM > IgG > IgA)
 - Melanoma-associated antigen (MUM1) expression (nuclear staining):

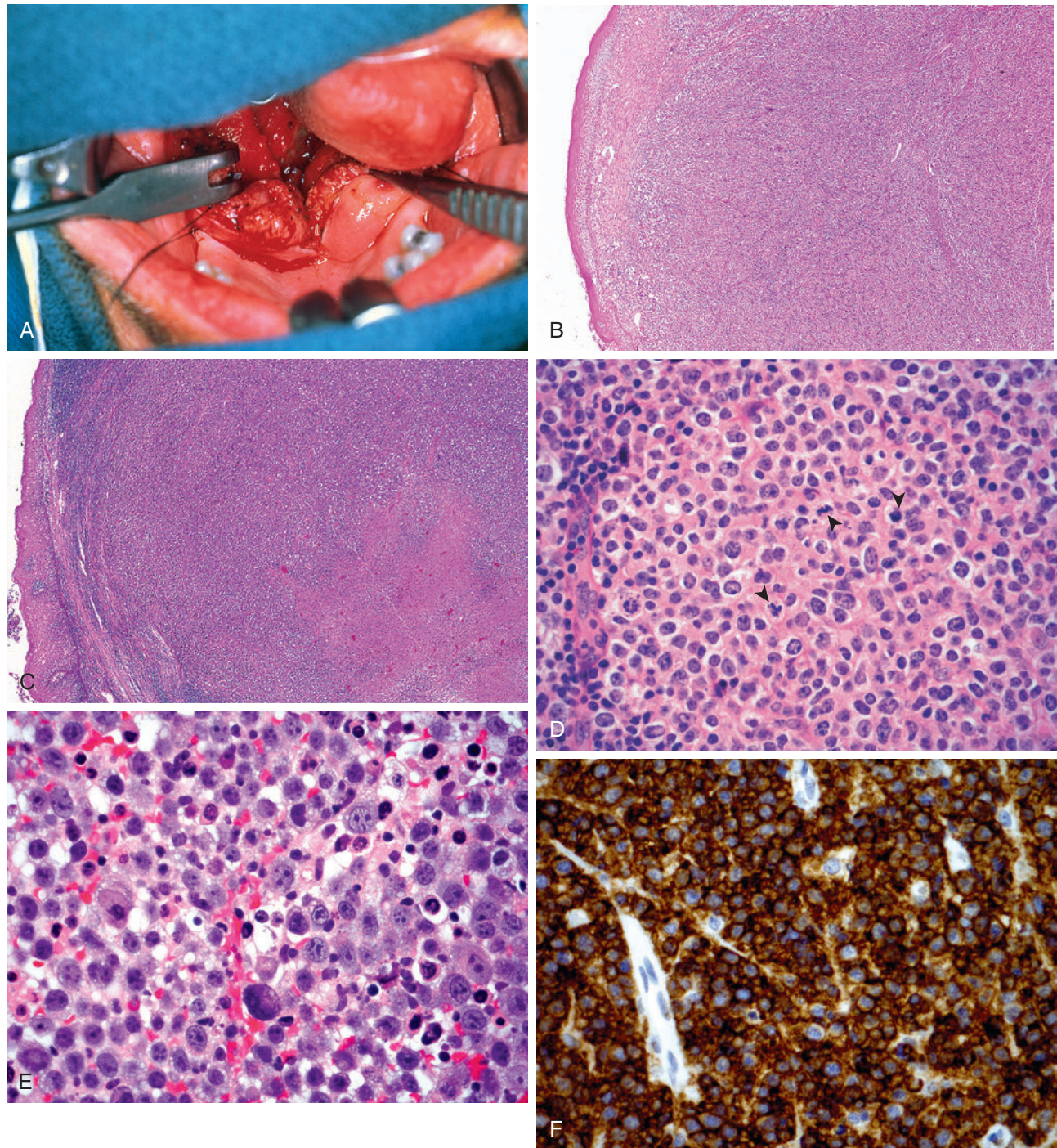


Fig. 10-34. Diffuse large B-cell lymphoma of the tonsil.

A, Unilateral marked tonsillar enlargement. **B**, Effacement of the normal tonsillar architecture by a diffuse cellular proliferation. **C**, Foci of confluent necrosis (*bottom right*). **D** and **E**, Diffuse dyscohesive cellular infiltrate composed of large cells with large round to oval vesicular (noncleaved) nuclei, prominent eosinophilic nucleoli, and increased mitotic activity (*arrowheads* in **D**). Occasionally, cohesive growth suggesting a possible epithelial neoplasm (i.e., carcinoma) can be identified (not shown). Lesional cells are immunoreactive for **(F)** CD45, **(G)** CD20, and **(H)** MUM1 (nuclear). **I**, Lymphomas including DLBCL may show p63 immunoreactivity.

Continued

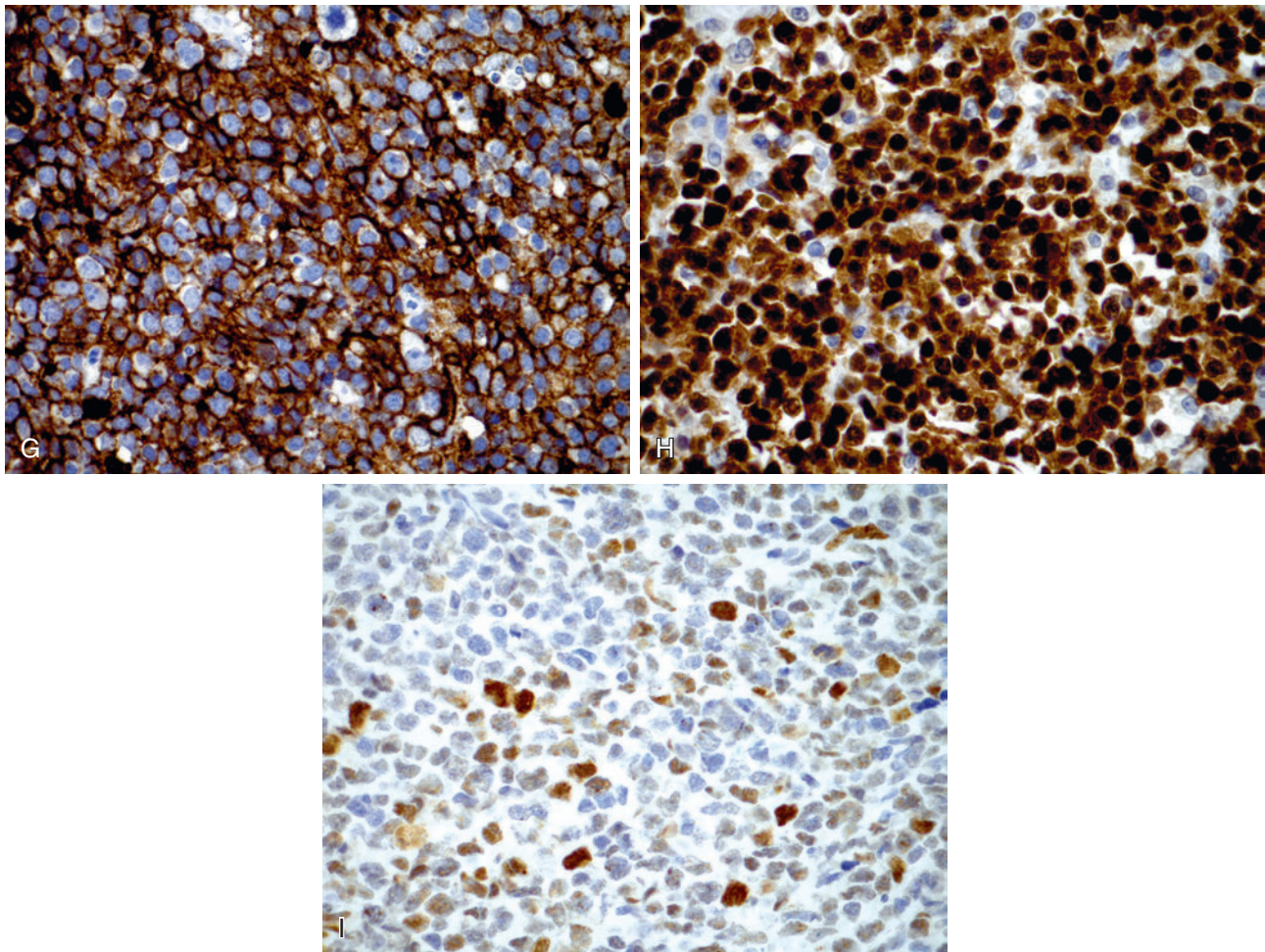


Fig. 10-34, cont'd

- *MUM1* gene encodes a transcription factor responsible for development of B, T, plasma, dendritic, and myeloid cells
- *MUM1* expression originally recognized by upregulation in multiple myeloma; however, not specific for plasmacytic differentiation and can be seen in a variety of neoplasms including:
 - DLBCL
 - Follicular lymphoma
 - Burkitt lymphoma
 - Hodgkin lymphoma
 - Anaplastic large cell lymphoma
 - Lymphoplasmacytic lymphoma
 - Chronic lymphocytic leukemia
 - Marginal zone lymphoma
 - Primary mediastinal large B-cell lymphoma
 - Primary effusion lymphoma
 - Melanoma
- *BCL6* in approximately 60%
- *CD10* expression in 40%
- *CD5* and *CD30* in approximately 10%
- Cyclin D1 (*BCL1*) negative
- High proliferation index by Ki67 of >20% and often >80%
- p53 positive in approximately 40%
- p63 may be positive (usually focal/scattered positive cells)
- Absence of expression for T-cell markers (*CD3*, others)
- Absence of epithelial, melanocytic, neuroendocrine, and myogenic markers
- Hans algorithm subclassifies DLBCL into germinal center B-cell type (GCB) versus non-germinal center B-cell type (non-GCB) with very high concordance with the gene expression profiling (GEP):
 - GCB: *CD10*+, *BCL6*+, *MUM1*–
 - Non-GCB: *CD10*–, *BCL6*+, *MUM1*+
 - GCB DLBCL may have better prognosis than non-GCB DLBCL.

- Cytogenetics and molecular genetics:
 - Clonal rearranged immunoglobulin heavy- and light-chain genes
 - *BCL2* and *BCL6* rearranged in approximately 20% and 30%, respectively
 - *BCL6* mutation in approximately 70%
 - Mutations of *TP53* in approximately 22%
 - *MYC* rearranged in less than 10%:
 - *MYC* rearrangement is a molecular hallmark of Burkitt lymphoma
 - In DLBCL *MYC* rearrangement more frequent in HIV-infected patients and in extranodal lymphomas
 - Usually EBV negative except in setting of immunodeficiency
 - CGH studies show various chromosomal gains and losses.

Differential Diagnosis

- Reactive lymphoid (follicular) hyperplasia
- Infectious-related lymphoid enlargements:
 - Infectious mononucleosis
 - HIV-associated lymphoid lesions
- Nasopharyngeal carcinoma, nonkeratinizing undifferentiated type:
 - Presence of cytokeratins and EBER and absence of CD45 and B-cell marker differentiate carcinoma from lymphoma.
- Mucosal malignant melanoma
- Rhabdomyosarcoma
- Peripheral T-cell lymphomas:
 - Represent less than 15% of Waldeyer ring NHL
 - Most show angiocentric features
 - Uncommonly, anaplastic large cell lymphoma (ALCL) occur (see below).

Treatment and Prognosis

- Treatment primarily includes multiagent chemotherapy and radiotherapy:
 - Multi-agent chemotherapy includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus ant-CD20 (Rituximab).
 - Surgical resection may be needed for symptomatic relief.
- Majority (80%) of NHL of Waldeyer tonsillar ring have localized disease/low clinical stage (i.e., Stage IE, IIE), see [Table 10-8](#) (Ann Arbor Staging System):
 - There is a tendency to spread to cervical lymph nodes.
- For B-cell lymphomas, including DLCL, the prognosis is dependent on the clinical stage:
 - Overall 10-year disease-free survival (for all treatment modalities) is approximately 66%.
 - Overall survival rate of 82%
 - Relapse occurs in 30% to 45% of patients:
 - May be localized to cervical lymph nodes
 - May involve non-head and neck sites, primarily the gastrointestinal tract (GIT), in up to

TABLE 10-8 Ann Arbor Staging System for Lymphomas

Stage	Definition
I	Single lymph node region or
IE	Single extralymphatic organ* or site
II	Two or more lymph node regions on the same side of the diaphragm
IIE	Localized involvement of an extralymphatic organ and one or more lymph node regions on the same side as the diaphragm
III	Lymph node involvement on both sides of the diaphragm
IIIE	Stage III accompanied by localized involvement of an extralymphatic organ
IIIS	Stage III accompanied by involvement the spleen
IIISE	Stage III accompanied by localized involvement of an extralymphatic organ and the spleen
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement
A	Without B symptoms [†]
B	With B symptoms [†]

*Extralymphatic organs defined as those other than lymph node, spleen, thymus, Waldeyer ring, appendix, and Peyer patches.

[†]B symptoms include fever (38°C), drenching night sweats, and loss of more than 10% original weight within 6 months.

20% of patients (GIT involvement may also occur at the initial presentation or even prior to involvement of Waldeyer ring, necessitating clinical evaluation of these sites)

– Less commonly may involve other sites, such as bone marrow, liver, spleen

- Factors associated with adverse prognosis include (International Prognostic Index for Prognostication of Non-Hodgkin Lymphoma, [Box 10-3](#)):
 - Age of patient ≥ 60
 - Advanced clinical stage (III or IV)
 - Number of extranodal sites of involvement (≥ 1)
 - Poor performance status (score of 2 or higher)
 - Abnormal serum LDH level
 - Tumor bulk
 - Presence of B symptoms:
 - B symptoms include fever (38° C), drenching night sweats, and loss of more than 10% original weight within 6 months.

Other Histologic Types of NHLs

- Less common histologic types of NHLs occurring in Waldeyer tonsillar ring include:
 - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma):

BOX 10-3 International Prognostic Index for Prognostication of Non-Hodgkin Lymphoma**Parameters**

- Age: ≥ 60 years
- Stage: Advanced stage (III or IV)
- Number of extranodal sites of involvement: ≥ 1
- Performance status: ≥ 2
- Serum LDH level: Abnormal

International Prognostic Index

- Total number of preceding features that are present

Risk Group Stratification According to the Index

- 0-1: Low risk
- 2: Low intermediate risk
- 3: High intermediate risk
- 4-5: High risk

- In the head and neck, most often involve tonsils; less often other sites (e.g., oral cavity, others)
- Precursor lesions:
 - Unlike MALT lymphomas of other extranodal sites, there is no known association with infectious microorganisms or autoimmune-based chronic inflammatory disorder in the development of MALT lymphoma of Waldeyer tonsillar ring
 - Infectious diseases associated with extranodal MALT lymphomas include:
 - *Helicobacter pylori* with gastric MALT lymphoma
 - *Chlamydia psittaci* with ocular MALT lymphoma
 - *Campylobacter jejuni* and *Borrelia burgdorferi* with cutaneous MALT lymphoma
 - Autoimmune-based chronic inflammatory disorders known to precede development of site-specific MALT lymphoma include:
 - Sjögren syndrome with salivary gland MALT lymphoma
 - Autoimmune thyroiditis with thyroid MALT lymphoma
- Parafollicular, interfollicular, or diffuse proliferation of marginal zone cells
- Most characteristic cell is a small to medium cell with irregular (folded) or elongated nuclei, moderately dense chromatin, inconspicuous nucleoli, and scanty pale to clear-appearing cytoplasm; this appearance is centrocyte-like
- Neoplastic cells may colonize lymphoid follicles.
- Invasion of epithelium (i.e., surface or crypt epithelium, minor salivary glands) forming lymphoepithelial lesions is a distinctive feature

but is not unique to MALT lymphoma and can be present in other lymphomas and in reactive lymphoid proliferations.

- Cells with monocytoid B-cell-like appearance with abundant, clear cytoplasm may be present especially in and around the epithelial structures, resulting in pale collars around the lymphoepithelial lesions:
 - This feature more prominently seen in association with salivary gland (see Section 6)
- Plasma cells may be intermingled with the neoplastic cells:
 - May appear mature (bland appearing) or atypical features including:
 - Enlarged nuclei, distinct nucleoli, Dutcher bodies, crystalline cytoplasmic inclusions
- May be monotypic, representing a part of the neoplasm
- May be so prominent as to suggest a possible diagnosis of extramedullary plasmacytoma
- Increased numbers of large B-cells may be identified in some cases consistent with progression to diffuse large B-cell lymphoma.
- Immunohistochemistry:
 - CD45, CD20, CD79a positive
 - Express IgM > IgA or IgG and show light chain restriction
 - bcl-2 positive in neoplastic cells and in colonizing B-cells but not in residual/reactive germinal centers
 - Co-expression of CD43 may be seen
 - CD5, CD10, CD23, cyclin D1, and bcl6 negative:
 - Infrequently, CD5 may be positive
 - CD21 and CD35 (marginal cell-associated antigens) may be positive:
 - Staining also reveals expanded meshwork of follicular dendritic cells corresponding to colonized follicles
 - Ki67 index is low.
 - EBV negative
- Plasmacytic differentiation may be seen and may predominate in any given tumor simulating a plasmacytoma:
 - In this setting, immunohistochemical stains will be helpful in differentiating a malignant lymphoma with plasmacytic differentiation (CD45 and CD20 positive) from a plasmacytoma (CD45 negative, usually CD20 negative and CD138 positive)
- Cytogenetics and molecular genetics:
 - t(11;18)(q21;q21) occurs in approximately 35% of cases:
 - Seen mainly in pulmonary and gastric tumors

- $t(14;18)(q32;q21)$ occurs in approximately 15% of cases:
 - Found predominantly in salivary gland, eye, skin, and lung tumors
- $t(3;14)(p14.1;q32)$ seen in up to 10% of cases:
 - Found predominantly in thyroid, eye, and skin tumors
- $t(1;14)(p22;q32)$ occurs in 1% to 2% of cases:
 - Appears to be associated with more disseminated or aggressive tumors
- Other genetic changes include:
 - Trisomy 3, 12, and 18
 - Loss of heterozygosity or mutation of TP53
- Indolent neoplasm with tendency to be localized to the involved site for extended periods of time prior to dissemination:
 - High proportion of cases treated by locoregional therapy
- Radiosensitive tumors
- Most patients have early stage disease (stage I/II) at presentation
- In spite of apparent indolent behavior, local or systemic dissemination may occur more frequently than initially believed.
- Involvement of multiple extranodal sites and bone marrow involvement do not appear to portend worse prognosis.
- Prognosis is favorable:
 - 5-year overall survival according to the NHL Classification project is 74%.
 - Relapse rate of 37% with median time to relapse of 47 months
 - Transformation to large cell lymphoma portends worse prognosis.
- Anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK)-positive (Fig. 10-35)
 - ALK+ lymphoma of T-cell lineage characterized by large cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei that by definition shows chromosomal translocation, implicating the *ALK* gene and expression of ALK protein and expression of CD30
 - Male predominance; most frequent in first 3 decades of life
 - Primarily affects lymph nodes, but extranodal disease occurs, including:
 - Most commonly, skin (primary cutaneous ALCL), bone, soft tissue, lung, liver, gastrointestinal tract
 - Less commonly mucosal sites of the head and neck (especially in HIV-positive patients)
- Histology:
 - Hallmark lesional cells are large with pleomorphic nuclei many of which are characterized by eccentric location, kidney- or horseshoe-shaped appearance, perinuclear eosinophilic Golgi zone region, multiple relatively small nucleoli rather than a single large one, and abundant amphophilic to basophilic cytoplasm
 - In addition to the hallmark larger cells, a population of smaller cells with similar cytomorphologic features may be seen aiding in the diagnosis
 - Multinucleated giant cells, some resembling Reed-Sternberg cells, may be prominently identified.
 - Increased mitotic activity is present.
 - Admixture of inflammatory cells including mature lymphocytes, plasma cells, histiocytes, eosinophils, and neutrophils may be present.
- In lymph nodes, malignant cells characteristically infiltrate nodal sinuses simulating sinus histiocytosis or a metastatic neoplasm; cohesive growth of tumor cells may be seen in the paracortical region.
- In cutaneous or mucosal sites, may be associated with pseudoepitheliomatous hyperplasia
- Immunohistochemistry:
 - CD30 (Ki-1) positive in virtually all tumor cells:
 - Staining pattern includes cell membrane and/or in Golgi region
 - ALK-1 (60% to 85%)-cytoplasmic and/or nuclear staining
 - Epithelial membrane antigen (EMA) in a majority (>80%) of cases:
 - Staining pattern similar to the CD30 staining
 - Majority of cases express one or more T-cell markers; however, due to loss of several pan-T-cell antigens often necessary to stain for multiple T-cell markers:
 - CD3 positive in 12%; negative in more than 75% of cases
 - CD2 positive in 45%
 - CD43 in 44%
 - CD4 positive in 40%
 - CD8 in 5%
 - CD5 and CD7 negative
 - CD45RO (UCHL-1) variably positive
 - Some cases may have absence of T-cell (or B-cell) lineage referred to as null cell but show evidence of T-cell lineage at genetic level.

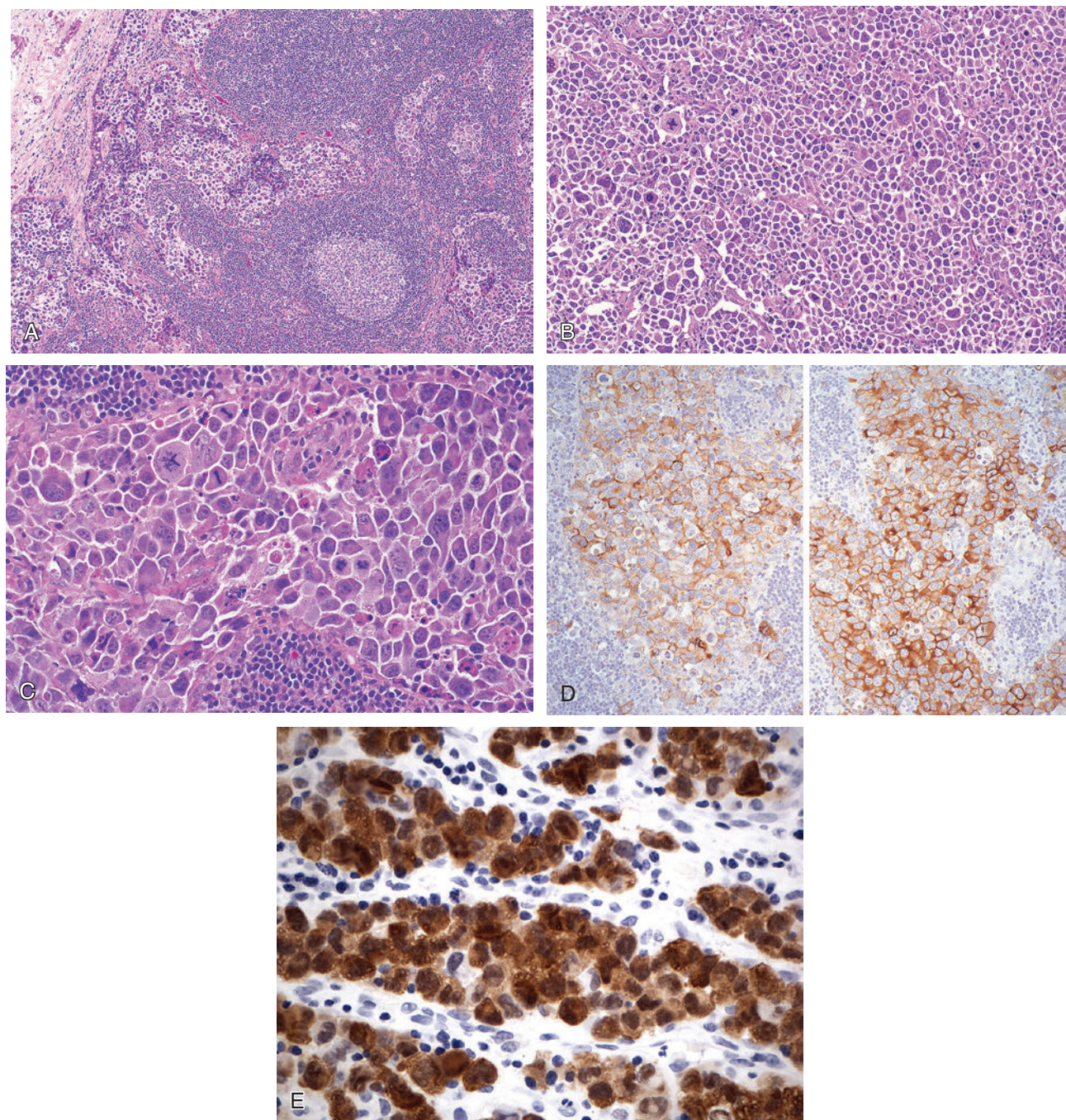


Fig. 10-35. Anaplastic large cell (Ki-1+) lymphoma.

A, Nodal involvement showing characteristic infiltrate in nodal sinuses simulating sinus histiocytosis or metastatic neoplasm. **B**, Tumor cells are large with pleomorphic nuclei with an eccentric location and occasional perinuclear eosinophilic region; numerous mitoses including atypical forms are present. **C**, Occasionally may occur in mucosal sites such as this example in a tonsil; immunoreactivity may include **(D)** (*left panel*) CD30 (Ki-1) and (*right panel*) epithelial membrane antigen; **(E)** ALK-1–positive (nuclear and cytoplasmic staining).

- Cytotoxic associated antigens including TIA-1, granzyme B, and/or perforin expressed in most cases (60% to 88%)
 - Clusterin expressed in majority (>90%) of cases showing Golgi staining pattern
 - Leukocyte common antigen (LCA or CD45) variably positive
 - B-cell markers positive in about 10% of cases
 - CD15 may be positive in a small percentage of cases.
 - CD56 expressed in some cases, associated with worse prognosis
 - Epithelial markers including cytokeratin and p63 may be positive:
 - Cytokeratin rarely positive
 - p63 may be positive in up to 41% of cases.
 - S100 protein, melanoma markers, myogenic markers negative
 - EBV negative
 - Cytogenetics and molecular genetics:
 - Clonal rearrangement of T-cell receptor (TCR) genes in approximately 90% of cases:
 - Presence of TCR genes occurs regardless of whether there is or is not immunoreactivity for T-cell markers
 - Translocation of *ALK* gene on chromosome 2p23:
 - Most common form is t(2;5)(p23;35)
 - *ALK* gene normally not expressed on lymphoid cells and all postnatal normal human tissues except rare cells in the brain so immunohistochemical staining has by and large supplanted molecular tests for *ALK* expression
 - Gene expression profiles have shown distinct molecular signatures between ALCL, ALK-positive and ALCL, ALK-negative cases.
 - Cytomorphologic variants of ALCL, ALK+ include:
 - Common variant (described above) representing approximately 70% of cases
 - Lymphohistiocytic variant representing approximately 10% of cases and characterized by neoplastic cells (see above) admixed with histiocytes
 - Small cell variant representing approximately 5% to 10% of cases and characterized by CD30-negative small T-lymphocytes with irregular nuclei and a minor population of CD30-positive larger cells; the latter tend to concentrate around blood vessels:
 - Signet ring-like cells may be seen.
 - May transform to common variant in approximately one-quarter of cases;
- transformation heralds rapid clinical course with patient dying within 1 year
- Hodgkin-like variant representing approximately 3% of cases and characterized by morphologic features mimicking nodular sclerosis classic Hodgkin disease
 - Monomorphic variant characterized by medium-sized to large cells
 - With uniformity of size and shape (i.e., monotonous appearance), although hallmark lesional cells are usually present
 - Other variants include hypocellular, giant cell, and sarcomatoid variants.
 - Mixed cell or composite variant includes admixture of variants detailed above.
 - Treatment includes multiagent chemotherapy with favorable outcome:
 - Overall 5-year survival of 70% to 77% and failure-free survival (FFS) of 60%
 - In contrast, overall 5-year survival of 48% and FFS of 36% reported for ALCL, ALK-negative cases
 - Relapses commonly occur (approximately 30%) but remain sensitive to chemotherapy.
 - Bone marrow reported from 10% to 17% but increased to near 40% when immunostaining for CD30 is performed:
 - Bone marrow involvement associated with worse prognosis
 - Other types of lymphomas that may rarely occur in Waldeyer ring include (although not limited to):
 - Mantle cell lymphoma (MCL)
 - Follicular lymphoma
 - For more complete discussion on lymphomas, the reader is referred to comprehensive texts on hematolymphoid neoplasms.

Plasma Cell Neoplasms

Definition: Result from expansion of a clone of immunoglobulin (IgG)-secreting heavy chain class-switched terminally differentiated B cells that secrete a single homogeneous monoclonal immunoglobulin referred to as a paraprotein or M-protein; presence of such a protein known as monoclonal gammopathy.

- Plasma cell neoplasms include:
 - Plasma cell myeloma (multiple myeloma):
 - Bone marrow based multifocal plasma cell neoplasm associated with M-protein in serum and/or in urine
 - In most cases there is disseminated bone marrow involvement
 - Clinical spectrum may span from asymptomatic to aggressive and disorders due to deposition of abnormal immunoglobulin chains in tissues

- Plasmacytoma:
 - Solitary plasmacytoma of bone
 - Extramedullary (extraosseous) plasmacytoma
- Immunoglobulin deposition disease:
 - Primary amyloidosis
 - Systemic light chain and heavy chain deposition diseases
- Monoclonal gammopathy of undetermined significance (MGUS)
 - Considered a precursor lesion to plasma cell neoplasm in which there is a low level of paraprotein in peripheral blood below the usual threshold for diagnosis of plasma cell myeloma but may precede development of overt myeloma.

Plasmacytoma

Definition: Neoplasm of plasma cells occurring as a solitary lesion or occurring in the setting of multiple myeloma including:

- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma

Solitary Plasmacytoma of Bone (Osseous Plasmacytoma)

Definition: Localized bone tumor consisting of monoclonal plasma cells.

- Most common sites include vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula

Extramedullary Plasmacytoma (EMP) (Fig. 10-36)

Definition: Localized plasma cell neoplasm arising in tissues other than bone.

- 80% occur in the head and neck:
 - Most cases primarily involve the upper aerodigestive tract, including the sinonasal tract and nasopharynx.

Synonym: Extraosseous plasmacytoma

Clinical

- Comprises approximately 3% to 5% of all plasma cell neoplasms
- 80% are primary (solitary) without evidence of tumor elsewhere; 20% are part of the generalized picture associated with multiple myeloma.
- More common in men than women; occurs over a wide age range but the vast majority of patients are over 40 years of age
- Tends to develop in mucosa-associated sites, including the sinonasal tract, nasopharynx, pharynx (including tonsil), larynx, oral cavity, salivary glands, and thyroid gland

- Clinical presentation dependent on the site of occurrence and may include a soft tissue mass, airway obstruction, epistaxis, pain, proptosis, or cranial nerve involvement
- Serum immunoelectrophoresis may show monoclonal abnormalities in both the systemic and localized forms of the disease:
 - Up to 25% of patients have a monoclonal gammopathy (M component).
 - Disappearance of the M component may be indicative of a cure
- Radiologic features include a soft tissue density; bone destruction may be present; in patients with primary EMP, skeletal survey will be negative.

Pathology

Gross

- May appear as a sessile or pedunculated, mucosa-covered mass measuring from 1 to 7.5 cm in greatest dimension
- Soft to rubbery to firm consistency with a variable color
- Bleed easily on biopsy

Histology

- Typically, submucosal lesion with a diffuse growth pattern and replaces the normal tissue parenchyma
- Composed of plasma cells with varying degrees of maturation including mature, immature, and anaplastic
- Mature plasma cells:
 - Round to oval with an eccentrically situated round nucleus
 - Nucleus has a characteristic clock face chromatin pattern but dispersed nuclear chromatin can be seen
 - Characteristic paranuclear clear zone represents the Golgi apparatus where immunoglobulin is processed and glycosylated for secretion
 - Cytoplasm is abundant and basophilic.
- Immature plasma cells:
 - Larger more irregular appearing nuclei, less condensed chromatin and occasional nucleoli
- Anaplastic variant (See Section 1, Sinonasal Tract) characterized by:
 - Cells with enlarged pleomorphic nuclei, indistinct to prominent eosinophilic nucleoli and a variable amount of eosinophilic cytoplasm
 - Tumor giant cells may be present and there is increased mitotic activity, including atypical forms.
 - In these anaplastic types, the cells may have a plasmacytoid appearance but, by and large, there is loss of the histologic features diagnostic of plasma cell tumor.

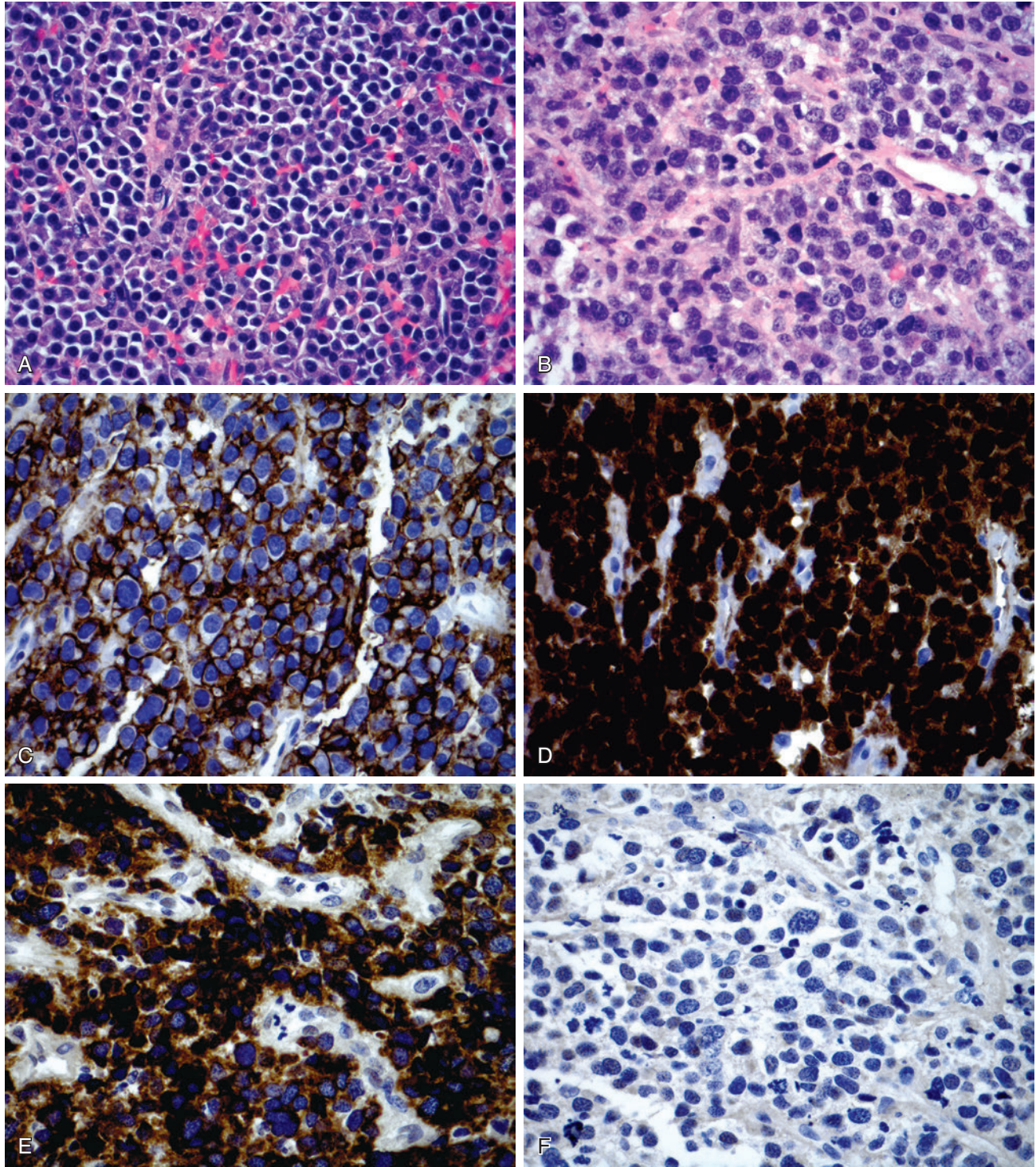


Fig. 10-36. Extramedullary plasmacytoma of the nasopharynx.

A, Diffuse proliferation of mature plasma cells characterized by round to oval cells with eccentrically situated round nuclei with clock face or dispersed nuclear chromatin, abundant basophilic appearing cytoplasm, and the presence of paranuclear clear zones. **B**, Another example predominantly comprised of immature plasma cells comprised of cells with larger more irregular appearing nuclei, less condensed chromatin, occasional nucleoli, and increased mitotic activity. Lesional cells are immunoreactive for **(C)** CD138, **(D)** MUM1 (nuclear). Neoplastic plasma cells typically show light chain restriction as seen by in situ hybridization showing the **(E)** presence of lambda light chain staining and **(F)** absence of kappa light chain staining.

- Amyloid deposits may be present in association with the plasma cell infiltrate and stain with Congo red or crystal violet
- Immunohistochemistry:
 - Monotypic cytoplasmic immunoglobulin (IgG or IgM type) heavy and/or light chain restriction (by immunohistochemistry or in situ hybridization)
 - Is present plasma cell malignancies generally are:
 - CD79a, CD138, CD38, MUM1, OCT2 and BOB.1 often positive
 - Leukocyte common antigen (CD45) often but not always negative
 - CD20 and PAX 5 negative
 - Variable EMA staining
 - Some cases may be cytokeratin positive
 - CD31 may be positive
 - May express CD56 in majority of cases

Differential Diagnosis

- Reactive plasmacytosis
- IgG4-related disease
- Diffuse large B cell lymphoma:
 - CD45 and CD20 positive in contrast to plasma cell neoplasm that are typically CD45 and CD20 negative and CD138 positive
- Plasmablastic lymphoma:
 - Distinctive aggressive variant of diffuse large B-cell lymphoma often occurring in HIV patients and arising in the oral cavity
 - Share similar histologic features and immunophenotype as plasma cell neoplasms including CD138, MUM1, CD38 positive and CD20 negative
 - Majority of cases associated with Epstein-Barr virus (EBER positive) but not associated with human herpes virus 8 (HHV8)
- Carcinoma:
 - Presence of cytokeratins and/or EMA and absence of CD45 and CD20 may lead to an erroneous diagnosis of an epithelial malignancy

Treatment and Prognosis

- Diagnosis of EMP warrants complete skeletal examination and clinical staging to determine the extent of disease and thus predict the outcome:
 - Staging is required prior to the initiation of therapy and may necessitate a bone marrow biopsy.
- Treatment is dependent on the extent of disease and may include radiotherapy alone or, for large tumors, local resection followed by radiotherapy.
- Many cases of EMP remain localized, and surgical resection with postoperative radiotherapy (30-50 Gy) is curative.
- 70% of patients with EMP are alive at 10 years, with a median survival of 7 to 9 years

- Involvement of a head and neck site may represent dissemination from multiple myeloma, or dissemination may occur to other sites from the primary head and neck involvement.
- Prognosis is drastically affected by the presence of disseminated disease—median survival after dissemination is less than 2 years.

Mucosal Malignant Melanoma

Definition: Neural crest-derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation.

- For a more complete discussion see Section 1, Sinonasal Tract.

Sarcomas

- In general, sarcomas of the pharynx are uncommon.
- Although uncommon, virtually all types of sarcomas may occur in these sites.
- Among the more common sarcomas of the pharynx, in particular the nasopharynx, is rhabdomyosarcoma and synovial sarcoma.

Rhabdomyosarcoma (RMS)

(Figs. 10-37 through 10-42)

Definition: Malignant neoplasm showing skeletal muscle differentiation.

Clinical

- Most common soft tissue sarcoma in children under 15 years of age:
 - Accounts for approximately 3% to 4% of all childhood sarcomas of adolescents and young adults
 - Occurs predominantly in infants and children; less frequent occurrence in adolescents and young adults
 - Approximately 2% occur at birth
 - Annual incidence of 4.5 cases per million per year
- Rare in people older than 45 years:
 - Accounts for approximately 2% to 5% of all adult sarcomas
- Anatomic distribution of RMS includes:
 - Head and neck is the most common site of origin with approximately 35% of all cases.
 - Of these approximately 25% to 33% involve the upper aerodigestive tract.
 - Genitourinary tract second most common site with approximately 24% of all cases
 - Following the head and neck and genitourinary tract, the next most common sites of occurrence

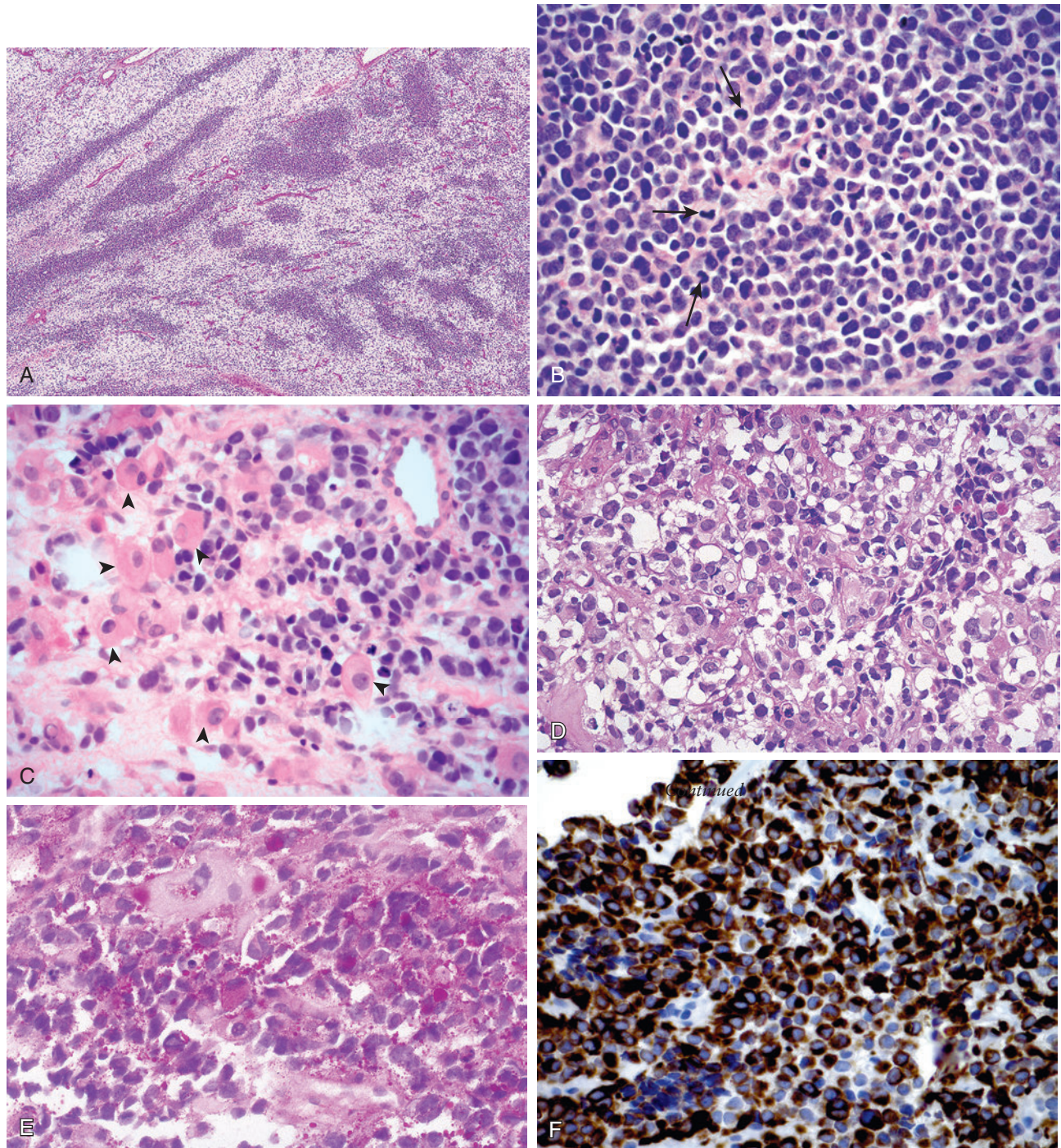


Fig. 10-37. Embryonal rhabdomyosarcoma.

A, At low magnification there is variability in cellularity, including alternating hyper- and hypocellular (myxoid) areas. **B**, The neoplastic infiltrate is composed of small undifferentiated (primitive-appearing) round cells with hyperchromatic nuclei and indistinct cytoplasm; mild nuclear pleomorphism, increased mitotic activity (*arrows*), and individual cell necrosis are present. **C**, Scattered within the malignant small round cell infiltrate are rhabdomyoblasts appearing as large round to oval cells with prominent eosinophilic cytoplasm (*arrowheads*). **D**, The neoplastic infiltrate may include cells with clear-appearing cytoplasm. **E**, PAS staining showing the presence of intracytoplasmic-positive material indicative of glycogen deposition (removed with diastase, not shown); lesional cells are diffusely immunoreactive for (**F**) desmin and (**G**) myogenin (myf-4, nuclear staining).

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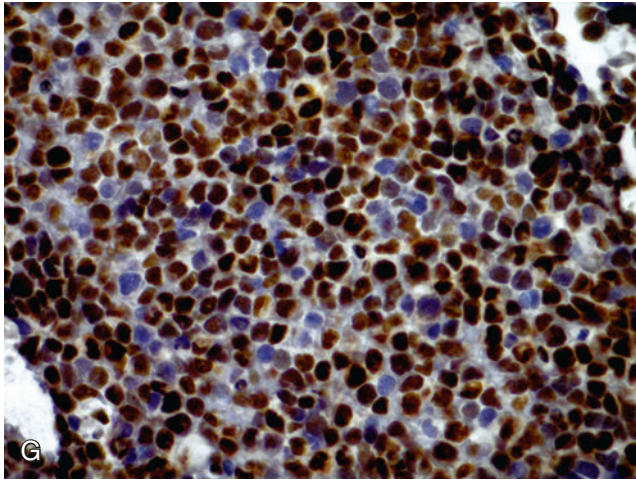


Fig. 10-37, cont'd

in decreasing order include extremities (19%), parameningeal (16%), and orbit (9%).

- Approximately 32% occur in “miscellaneous” or “other” sites.
- Histologic type (see below) correlates to patient age:
 - Embryonal RMS, including botryoid and spindle cell subtypes, affect primarily young children between birth and 15 years but is not limited to this age group.
 - Alveolar RMS tends to affect older patients with peak ages of 10 to 25 years, although it may also occur in older adults.
 - In adult populations over 40 years of age, embryonal RMS is the most common histologic type; in addition, spindle cell RMS occurs in a significant percentage of adult RMS.

Head and Neck RMS

- In the head and neck, RMS is primarily but not exclusively a disease of the pediatric population:

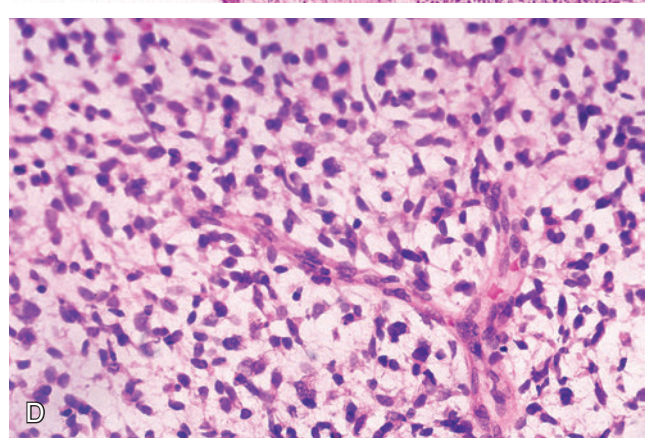
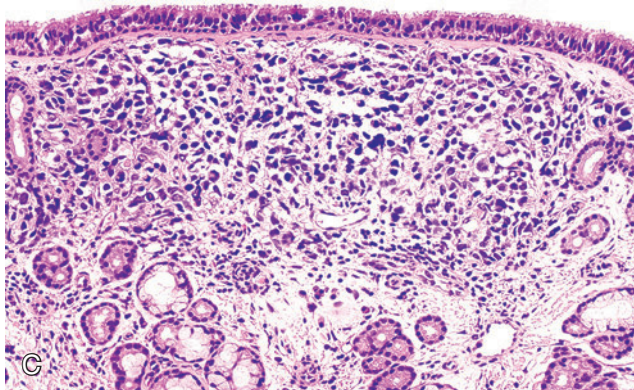
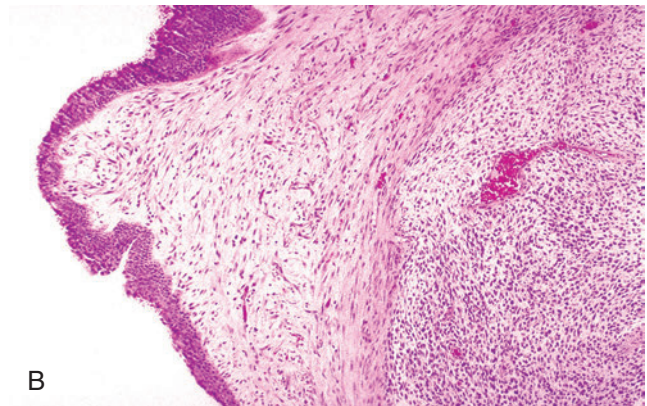
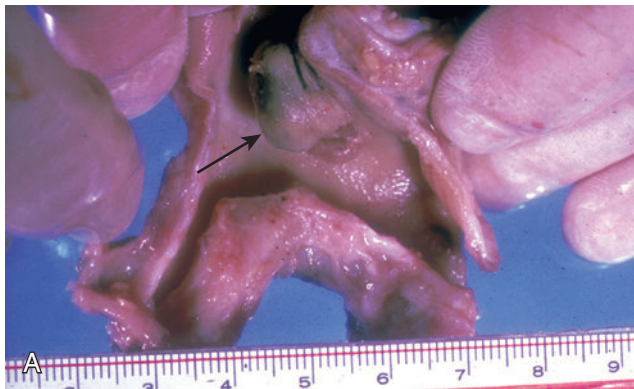


Fig. 10-38. Embryonal rhabdomyosarcoma, botryoid type.

A, Polypoid mass protruding into the lumen of the trachea at the carina (*arrow*). **B**, Polypoid nodule with loose myxoid stroma separating the submucosal tumor cells from intact surface epithelium. **C**, Another example showing subepithelial condensation of tumor cells separated from intact surface ciliated respiratory epithelium by a thin layer of hyalinized-appearing stroma. **D**, Neoplastic cells include primitive (undifferentiated) small cells as well as cells with stellate cytoplasmic processes set in a myxoid stroma; Y-shaped plexiform capillary blood vessel is present.

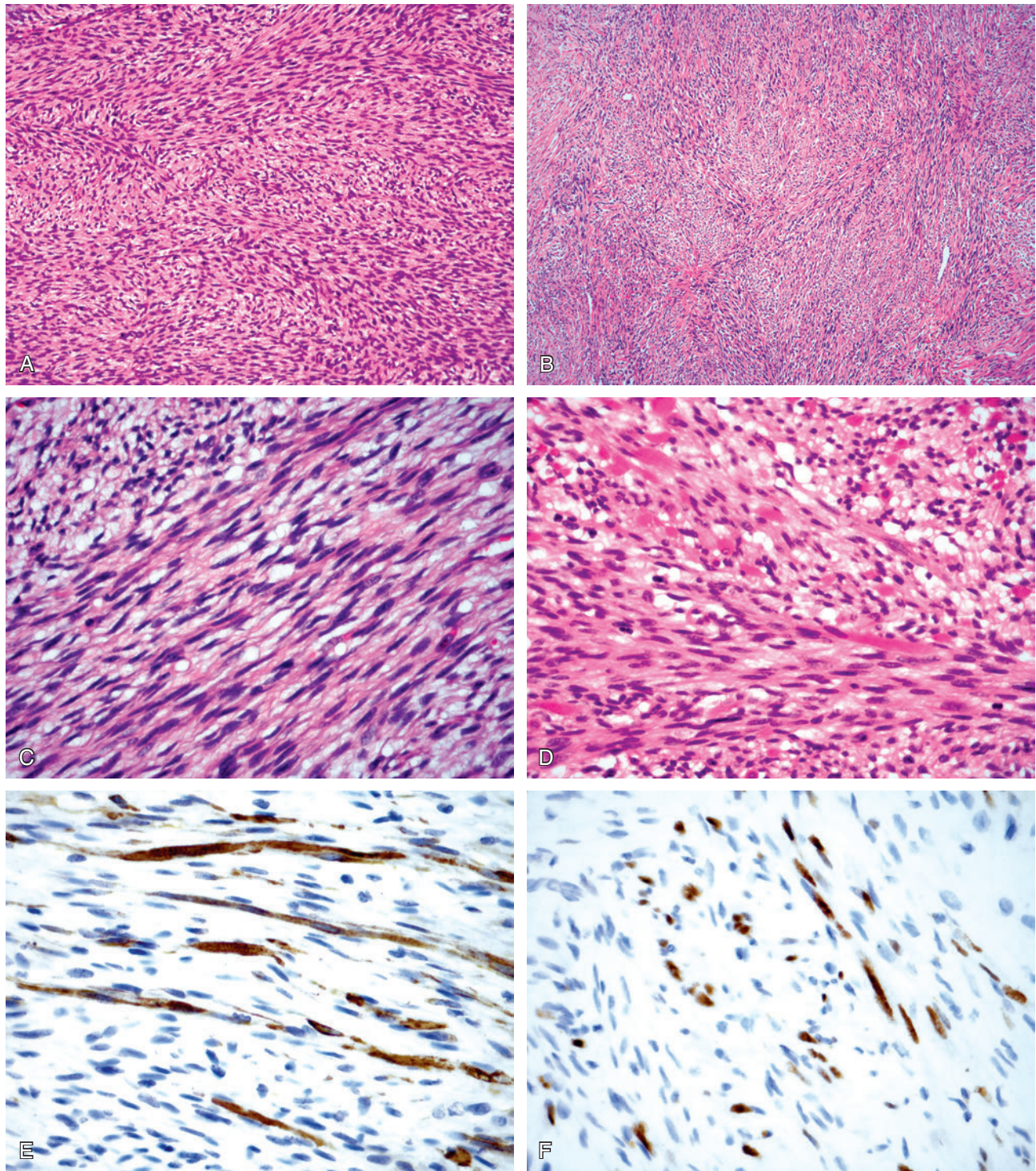


Fig. 10-39. Embryonal rhabdomyosarcoma, spindle cell variant.

A, Spindle cell proliferation arranged in fascicular and storiform growth pattern. **B**, Collagen-rich type characterized by spindle cells separated by abundant collagenized stroma arranged in storiform to whorled growth pattern. **C**, Relatively uniform-appearing spindle-shaped cells. **D**, Scattered rhabdomyoblasts are present. The spindle cells are immunoreactive for **(E)** desmin and **(F)** myogenin (myf-4, nuclear staining).

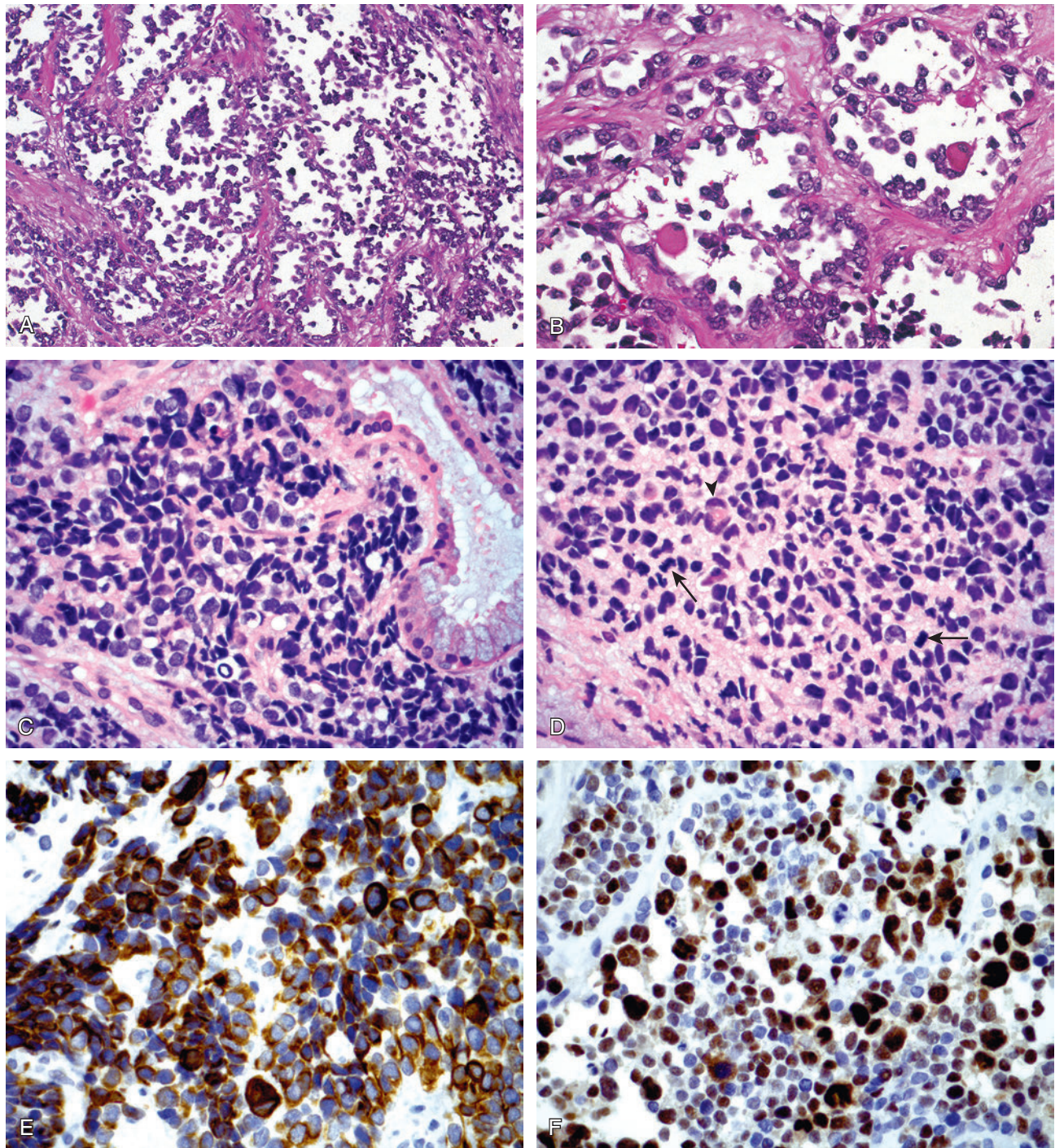


Fig. 10-40. Alveolar rhabdomyosarcoma.

A, Alveolar rhabdomyosarcoma is characterized by neoplastic aggregates separated by a hyalinized fibroconnective tissue. **B**, In alveolar rhabdomyosarcoma there is often loss of cellular cohesion resulting in “alveolar” spaces; scattered rhabdomyoblasts are present. **C**, Solid form of alveolar rhabdomyosarcoma characterized by densely packed clusters of tumor cells resembling round cell areas of embryonal RMS but an absence of an alveolar growth pattern; lesional cells about a residual submucosal mucoserous gland (*right*). **D**, Multinucleated giant cell with peripherally situated nuclei (*arrowhead*) represent a diagnostically important finding in alveolar rhabdomyosarcoma; in contrast, multinucleated giant cells are not commonly found in embryonal RMS; scattered mitotic figures are present (*arrows*). Lesional cells are immunoreactive for **(E)** desmin and **(F)** myogenin (myf-4, nuclear staining).

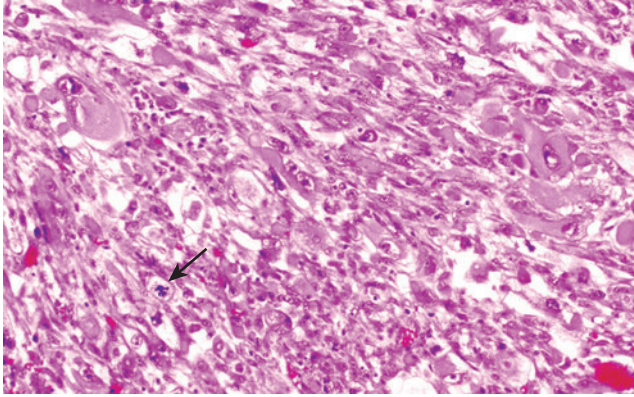


Fig. 10-41. Pleomorphic rhabdomyosarcoma.

Pleomorphic rhabdomyosarcoma characterized by large round or pleomorphic tumor cells with hyperchromatic nuclei, prominent nucleoli, and eosinophilic cytoplasm; spindle-shaped or racket-shaped cells (rhabdomyoblasts) with irregular contours are present; an atypical mitotic figure can be seen (*arrow*).

- 43% of patients are under 5 years of age
- 78% of patients are under 12 years of age
- In the head and neck, parameningeal tumors are the most common and include:
 - Nasopharynx, sinonasal tract, middle ear and mastoid, pterygopalatine-infratemporal fossa
- Most frequent sites in the head in neck include:
 - Nasopharynx > middle ear and mastoid > sinonasal tract > soft tissues of the neck > oral cavity (tongue, lip, palate)
- In children and adolescents, RMS represents the most common aural-related malignant neoplasm.
- No gender predilection, although some reports show a slight male predominance
- Symptoms depend on the site of occurrence but due to destructive growth include:
 - Pain, facial swelling, bleeding, proptosis, airway obstruction, and difficulty breathing
 - At diagnosis approximately one third of patients have associated neurologic findings, the most common of which are facial nerve deficits; neuropathies of cranial nerves III, V, VI-XII may also occur.
 - Middle ear and mastoid may present with painless unilateral otitis media unresponsive to antibiotic therapy associated with a serosanguineous discharge.
- Cause:
 - Majority of RMS occurs with no known etiologic factors.
 - Small subset occurs with syndromes caused by germline mutations:
 - Embryonal RMS associated with syndromes caused by mutations in the RAS signaling

BOX 10-4 Modified Conventional Classification of RMS*

- Embryonal
- Botryoid
- Alveolar
- Pleomorphic
- Sarcoma not classified
- Small round cell sarcoma, type indeterminate
- Extrasosseous Ewing sarcoma

*Horn and Enterline Classification.
RMS, Rhabdomyosarcoma.

BOX 10-5 National Cancer Institute Classification of RMS

Embryonal RMS (Favorable)

- Conventional
- Botryoid
- Leiomyomatous
- Aggressive histologic features

Alveolar RMS (Unfavorable)

- Conventional
- Solid

Pleomorphic RMS

RMS (other)

RMS, Rhabdomyosarcoma.

pathway including Costello syndrome (*HRAS* gene mutations), neurofibromatosis 1 (*NF1* gene mutations), and Noonan syndrome

- Some embryonal RMSs are associated with Beckwith-Weidemann syndrome (dysregulation of imprinted genes in 11p15.5 region).
- RMS of unclassified histology occurs in Li-Fraumeni syndrome (caused by *TP53* mutations) and infrequently (as well as embryonal RMS) in Gorlin syndrome (*PTCH1* mutations in active hedgehog signaling pathway)

Pathology

Gross

- RMS of mucosal sites of the upper aerodigestive tract appears as submucosal, well-circumscribed, multinodular, or polypoid lesions that on cut section has a glistening, gelatinous, gray-white surface; hemorrhage and cyst formation may be seen.
- RMS of the middle ear and mastoid most often appears as an aural (external or middle ear) polypoid lesion similar in appearance to an aural polyp.

Histology

- Histologic classification of RMS has evolved over time (Boxes 10-4 through 10-6); at present the

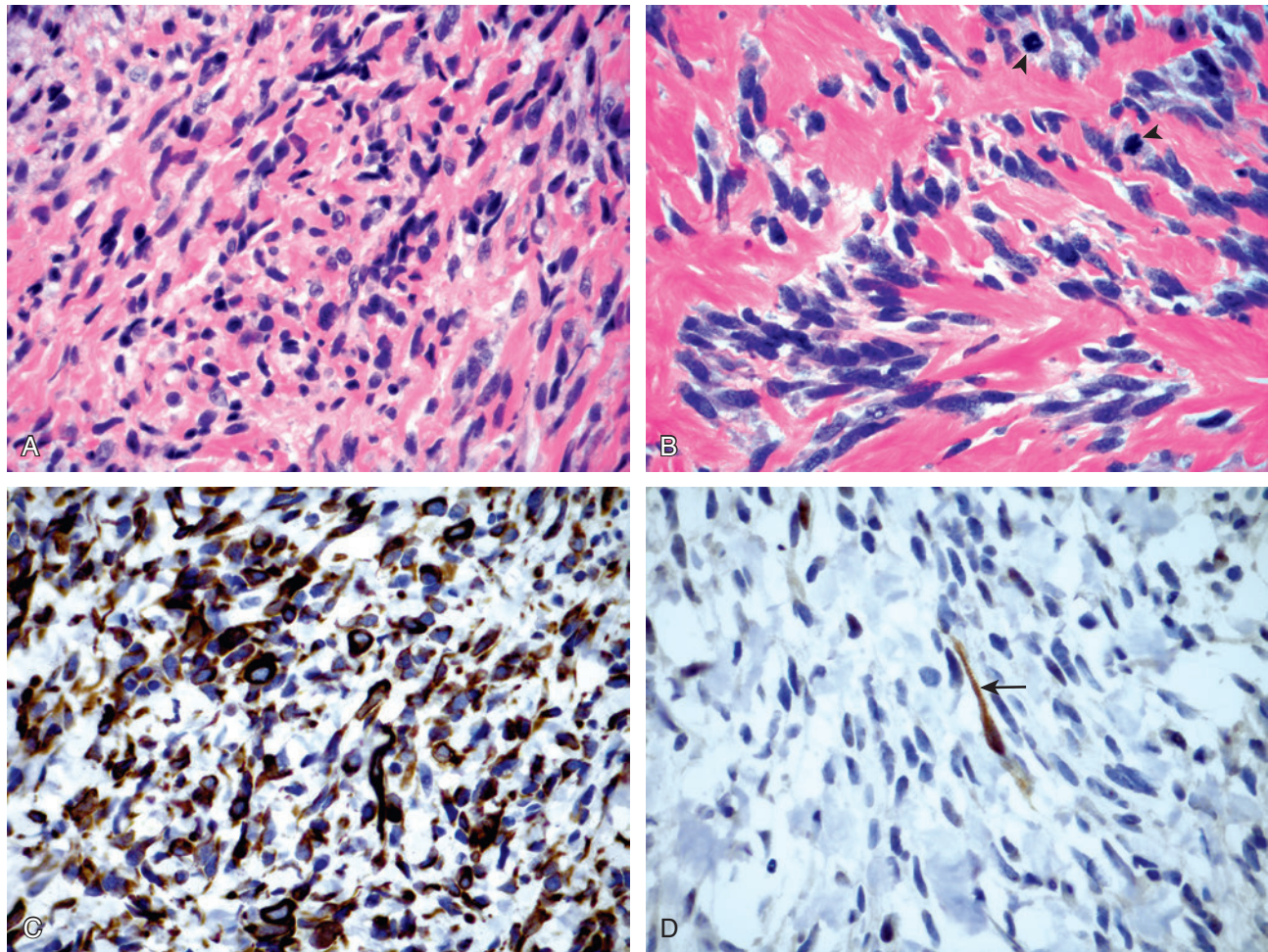


Fig. 10-42. Sclerosing rhabdomyosarcoma.

A, Neoplastic cells with associated abundant eosinophilic hyalinized stroma are composed of primitive-appearing nuclei with coarse nuclear chromatin and irregular nuclear contours. **B,** Eosinophilic hyalinized stroma is a dominant feature; increased mitotic activity is present (*arrowheads*). **C,** Strong desmin reactivity. **D,** Very focal myogenin (*myf-4*) staining including one positive cell with identifiable cross-striations (*arrow*).

BOX 10-6 International Classification of RMS

Superior Prognosis

- Botryoid RMS
- Spindle RMS

Intermediate Prognosis

- Embryonal RMS

Poor Prognosis

- Alveolar RMS
- Undifferentiated RMS

Subtypes Whose Prognosis Is Not Presently Evaluable

- RMS with rhabdoid features

RMS, Rhabdomyosarcoma.

International Classification of RMS, a modification of the conventional scheme, is advocated given its reproducibility and prognostic significance (see [Box 10-6](#)).

- Majority of head and neck RMS of all ages and all sites is embryonal type that includes botryoid and spindle cell subtypes.
- Next most common histologic type is alveolar RMS; alveolar RMS tend to occur in older aged individuals as compared with embryonal RMS, including botryoid and spindle subtypes.
- Other histologic types of RMSs may occur in the head and neck but are considered uncommon.
- Rhabdomyoblasts, the cell of origin for this sarcoma, take on numerous appearances, including small round cells to ribbon- or strap-shaped to large and pleomorphic:

- Rhabdomyoblasts with cross-striations are not always identified, and their absence does not exclude the diagnosis of rhabdomyosarcoma.

Embryonal RMS (see Fig. 10-37)

- Typically, at low magnification there is a variation in the cellularity of these tumors with alternating hyper- and hypocellular areas; the latter often is associated with a loosely textured myxoid stroma.
- Composed of primitive mesenchymal cells in various stages of embryogenesis of normal skeletal muscle (myogenesis), ranging from well-differentiated neoplasms resembling skeletal muscle to poorly differentiated neoplasms requiring immunohistochemical staining to confirm myogenic differentiation
- Cellular components consist of an admixture of cell types, including:
 - Small undifferentiated (primitive-appearing) round or spindle-shaped cells with hyperchromatic nuclei and indistinct cytoplasm; mild nuclear pleomorphism, increased mitotic activity, and necrosis are present
 - Differentiated large round to oval cells with eosinophilic cytoplasm characteristic of rhabdomyoblasts
 - Matrix with little collagen and varying amounts of myxoid stroma
- Cells with cross-striations are rare in round cells but are more apparent neoplasms with more prominent spindle cell component and can be seen in 50% to 60% of cases:
 - Rhabdomyoblasts range from slender spindle-shaped cells with peripherally placed myofibrils to large eosinophilic cells with strap, tadpole, ribbon, or racket shapes and one or two centrally positioned nuclei and prominent nucleoli with or without cross-striations.
 - As compared with the cross-striations of normal skeletal muscle, the cross-striations in rhabdomyoblasts are more irregular in distribution and traverse only part of the cell.
- Uncommonly, embryonal RMS with foci of prominent cellular pleomorphism may occur; these tumors are still recognized as embryonal RMS given:
 - Presence of areas of more typical embryonal RMS
 - Frequent identification of cross-striations
 - Prognosis not altered except if the cellular pleomorphism is diffuse, at which point differentiation from pleomorphic RMS is difficult.
- Heterologous elements, including (immature) cartilage and/or bone may be identified:
 - These findings are more often seen in RMS of the genitourinary tract and in retroperitoneal RMS.

Botryoid Variant of Embryonal RMS (Sarcoma Botryoides) (see Fig. 10-38)

- Terminology derived from Greek term *botryos*, meaning bunch of grapes
- Gross appearance in a hollow viscus or body cavity is as a polypoid mass:
 - Characteristic gross appearance not required for diagnosis
- Histologically, subepithelial condensation of tumor cells separated from intact surface epithelium by a zone of loose stroma referred to as a cambium layer:
 - Cambium layer represents required criteria for diagnosis of botryoid type
 - Surface epithelium may show reactive hyperplasia or metaplasia (e.g., squamous cells).
- Polypoid nodules often with loose myxoid stroma
- Cells range from primitive (undifferentiated) small cells to cells with rhabdomyoblastic differentiation:
 - Cells with stellate cytoplasmic processes are often prominent.
- Stroma typically loosely cellular with myxoid appearance

Spindle Cell RMS (see Fig. 10-39)

- Rare subtype that tends to occur in young patients (less than 7 years of age) with a male predilection
- Most frequently found in the paratesticular region but second most common site of occurrence includes mucosal sites of the head and neck, including nasopharynx and sinonasal tract.
- Grossly, appears well circumscribed but unencapsulated with a nodular, whorled appearance on cut section and measuring from 4 to 6 cm in greatest diameter
- Histology:
 - Composed almost exclusively of elongated fusiform or spindle cells with cigar-shaped or blunted central nuclei and tapered ends (similar to smooth muscle cells) and prominent nucleoli
 - Cells have eosinophilic fibrillar cytoplasm with distinct cell borders with or without identifiable cross-striations (pointing to skeletal muscle differentiation).
 - Collagen-rich type characterized by spindle cells separated by abundant collagenized stroma arranged in storiform to whorled growth pattern
 - Collagen form type more cellular proliferation with cells arranged in bundles or fascicles (resembling fibrosarcoma)

Alveolar RMS (see Fig. 10-40)

- Composed of ill-defined aggregates of poorly differentiated small round to oval neoplastic cells with

central loss of cellular cohesion resulting in formation of irregular alveolar spaces

- Dense, hyalinized fibroconnective and/or fibrovascular septa surround and separate the neoplastic aggregates.
- Tumor cells have round to oval hyperchromatic nuclei with a scant amount of indistinct cytoplasm:
 - Cells at the center of the alveolar spaces are more loosely arranged and often show degenerative changes as well as necrosis.
 - Cells at the periphery of the alveolar spaces are better preserved and often adhere to the fibrous septa.
 - Mitotic figures are readily identified.

Solid Form of Alveolar RMS

(see Fig. 10-40)

- Absence of an alveolar pattern and the neoplasm is composed of densely packed clusters of tumor cells resembling round cell areas of embryonal RMS but with more uniform cellularity with little to no fibrosis
- Solid areas more commonly seen at periphery of the tumor
- Often incipient alveolar spaces are present.
- Similar to examples with alveolar pattern, in the solid form there is:
 - Regular arrangement of fibrous septa surrounding primitive round cells
 - Tumor cells with round to oval hyperchromatic nuclei with a scant amount of indistinct cytoplasm
 - Increased mitotic activity
- Neoplastic rhabdomyoblasts with prominent granular eosinophilic cytoplasm are less common in the alveolar type than in the embryonal type:
 - Rhabdomyoblasts in alveolar RMS located or attached to fibrous septa tend to be strap- or spindle-shaped.
 - Cross-striations are not commonly identified and, if present, are found in spindle-shaped or strap cells.
- Multinucleated giant cells are often found in alveolar RMS and represent a diagnostically important finding:
 - In contrast, multinucleated giant cells are not commonly found in embryonal RMS.
 - Giant cells typically have multiple peripherally situated nuclei with weakly eosinophilic cytoplasm and absence of cross-striations.
- Lymph node metastasis may precede identification of primary tumor:
 - When alveolar RMS metastasizes, the alveolar pattern may be retained in the metastatic site.

Pleomorphic RMS (see Fig. 10-41)

- Rare high-grade variant of RMS occurring almost exclusively in adults older than 45 years (mean of 56 years), although may occur in younger patients (second and third decades of life)
- Predilection to males
- Most common site of occurrence is the deep soft tissues of extremities, in particular the thigh; less common sites of occurrence include the chest wall, abdomen/retroperitoneum, chest/abdominal wall, spermatic cord/testes, upper extremity, and head and neck.
- Typically present as rapidly enlarging, painless mass growing over months; metastatic disease (to lungs) may occur at presentation
- Tumors are usually large, measuring over 10 cm in size.
- Histology is characterized by the presence of loosely arranged, large round or pleomorphic tumor cells with hyperchromatic nuclei and deeply eosinophilic cytoplasm:
 - Pleomorphic, bizarre cells with deeply eosinophilic cytoplasm and some cell-to-cell molding represent the most helpful light microscopic feature in suggesting a diagnosis of RMS.
 - Spindle-shaped, tadpole-shaped, or racket-shaped rhabdomyoblasts similar to those seen in embryonal RMS are present but tend to be larger with more irregular contours.
 - Cells with cross-striations are rare.
 - Cellular proliferation usually is haphazardly arrayed, but storiform and fascicular growth patterns can be present.
- Rarely, cells with rhabdoid morphology can be seen characterized by cells with peripherally placed vesicular nuclei, prominent nucleoli, and intracytoplasmic hyaline inclusions.
- In the presence of primitive round cells, a diagnosis of pleomorphic RMS is questionable and more likely represents alveolar RMS.

Sclerosing RMS (see Fig. 10-42)

- Uncommon variant of RMS characterized by presence of hyalinizing, matrix-rich stroma
- Exact relationship between sclerosing RMS and embryonal RMS or alveolar RMS remains to be determined:
 - Some authors classify sclerosing RMS with spindle RMS, suggesting it is a variant of embryonal RMS.
 - Alternatively, it could be a new subtype of RMS.
- Sclerosing RMS shares some overlapping features with alveolar RMS but does not harbor *PAX 3* fusions as seen in alveolar RMS except for rare single case with a *PAX3-FOXO1A* fusion.

- May occur in children or adults
- Histology:
 - Neoplastic cells divided into lobules, small nests, microalveoli, and single-files with associated abundant hyalinized, eosinophilic to basophilic matrix resembling osteoid or chondroid material
 - Hyalinized stroma is dominant feature that makes up 50% of the entire neoplasm.
 - Moderately cellular lesions composed of primitive-appearing nuclei with coarse nuclear chromatin, irregular nuclear contours, small and occasionally multiple nucleoli, and limited amount of eosinophilic cytoplasm
 - Strap cells may be seen but rhabdomyoblasts are uncommon.
 - High mitotic rate

Epithelioid RMS

- Rare and unusual type of RMS composed of sheets of epithelioid cells with abundant amphophilic to eosinophilic cytoplasm
- Tendency to:
 - Occur in elderly patients (median age of 70 years), male predilection
 - Arise in deep soft tissues of upper and lower extremities, head and neck, and trunk
 - Mimics carcinoma or melanoma
 - Aggressive clinical course
- Histology:
 - Epithelioid cells with large vesicular nuclei, prominent nucleoli, abundant densely eosinophilic cytoplasm
 - High mitotic rate with atypical mitoses

Special Studies

- In the presence of a poorly differentiated neoplasm lacking evidence of cross-striations, special stains are invaluable in confirming the diagnosis of rhabdomyosarcoma and differentiating it from other lesions.
- Histochemistry:
 - Cells contain glycogen as demonstrated by periodic acid-Schiff (PAS) positivity cleared by diastase digestion
 - Intracellular myofibrils can be seen by Masson trichrome and phosphotungstic acid hematoxylin (PTAH) stains.
- Immunohistochemistry:
 - Desmin, myoglobin, myogenic transcription factors (MyoD1, myogenin [myf-4]), and muscle-specific actin positive:
 - Desmin not entirely specific but is reasonably sensitive marker for RMS:
 - Can be seen in a wide variety of lesions including although not limited to leiomyosarcoma, epithelial neoplasms, others

- Cytoplasmic staining
- In sclerosing RMS shows dot-like staining which is unique and different staining pattern as seen in other types of RMSs
- Myoglobin is a specific although not sensitive marker for skeletal muscle tumors:
 - Tends to be restricted to more differentiated cells
 - Can be detected in non-muscle cells due to diffusion
 - Cytoplasmic staining
- Myogenic transcription factors (MyoD1, myogenin [myf-4]):
 - Expressed in more than 90% of RMSs of all subtypes
 - Excellent specificity but may be seen in other rare tumor types with rhabdomyoblastic differentiation
 - Nuclear staining
 - MyoD1 and myogenin expressed in >95% of embryonal cells including spindle cell RMS and alveolar RMS including solid variant
 - Embryonal RMS expresses very high levels of MyoD1 and comparatively less MyoD1 or equal expression of both
 - Alveolar RMS expresses very high levels of myogenin and comparatively less MyoD1
 - Sclerosing RMS typically shows strong expression of MyoD1 but very little myogenin (myf-4).
 - Pleomorphic RMS less frequently MyoD1 and myogenin positive, and may only show small percentage of positive tumor cells
- Muscle-specific actin-sensitive marker for RMS but:
 - Can be seen in a wide variety of lesions including although not limited to leiomyosarcoma, epithelial neoplasms, others
 - May be absent in poorly differentiated RMS
 - Cytoplasmic staining
- Cytokeratins, S100 protein, leukocyte common antigen, neuroendocrine markers (chromogranin, synaptophysin, CD56), and melanocytic markers are typically negative:
 - Cytokeratins including wide spectrum and CAM5.2 may be identified in alveolar RMS in up to 50% of cases
 - Neuroendocrine markers may be positive in alveolar RMS, including CD56 (present in majority of cells), synaptophysin (up to about one third of cases), and chromogranin (up to about 22% of cases)
 - CD99 may be present in alveolar RMS.

- Ultrastructural findings:
 - Bundles of thick (myosin) filaments with attached ribosomes (ribosome and myosin complex) and thin (actin) fibrils
 - Admixture of alternating thin (actin) and thick (myosin) filaments in parallel (longitudinal) arrangement with hexagonally appearing (on cross section) Z banding
 - Golgi apparatus, mitochondria, glycogen droplets can be present.
 - Cytogenetic and molecular genetics:
 - Embryonal RMS:
 - Consistent loss of heterozygosity (LOH) at chromosome 11p15.5, which may result in activation of tumor suppressor gene(s) GOK
 - Botryoid type:
 - Deletion of short arm of chromosome 1
 - Trisomies of chromosomes 13 and 18
 - Hyperdiploid clone with complex karyotype including numerous chromosomal gains
 - Case with trisomy 8
 - Spindle cell RMS:
 - Very few reports on cytogenetics, including:
 - Absence of PAX3-FOXO1 or PAX7-FOXO1 gene fusion:
 - ◻ Genetically more closely related to embryonal RMS than alveolar RMS
 - Der(2)t(2;7) with involvement of 2q36-37
 - Structural rearrangements of chromosomes 8, 12, 21, 22
 - NCOA2 rearrangements found in pediatric but not adult cases, suggesting:
 - ◻ Spindle cell RMS is a heterogeneous disease genetically as well as clinically
 - ◻ A relationship between NCOA2-rearranged spindle cell RMS occurring in young childhood and congenital RMS, which often displays rearrangements at 8q13 locus (NCOA2)
 - Alveolar RMS characterized by distinctive cytogenetic abnormalities distinct from other types of RMSs and other round cell tumors:
 - t(2;13)(q36;q14) translocation 60% of cases:
 - Above translocation results in shortening of chromosome 13 and elongation of chromosome 2:
 - ◻ Breakpoints occur in PAX3 gene at chromosome 2 and FOXO1A gene (formerly FKHR) on chromosome 13 results in a PAX3-FOXO1A fusion gene on chromosome 13 and a FOXO1A-PAX3 fusion gene on chromosome 2.
 - ◻ PAX3-FOXO1A fusion appears to be more sensitive and specific than FOXO1A-PAX3 in detecting RMS.
 - t(1;13)(p36;q14) translocation in 20% of cases
 - Juxtaposes PAX7 gene on 1p36 with FOXO1A gene on 13q14
 - Approximately 80% of alveolar RMS have PAX3-FOXO1A fusion or PAX7-FOXO1A fusion; therefore approximately 20% lack either of these fusions:
 - About half of the fusion-negative cases had solid growth pattern.
 - None of the PAX3-FOXO1A fusion had solid growth pattern.
 - Rare examples with PAX7-FOXO1A fusion had solid growth pattern.
 - Gene expression microarray data indicate that several genes discriminate between fusion-positive and fusion-negative RMS with high specificity:
 - A panel of immunohistochemical markers, including myogenin, AP2β, NOS-1, and HMGA2 can be used as surrogate markers of fusion status in RMS:
 - ◻ Provide an alternative to molecular methods for identification of fusion-positive RMS
 - ◻ Useful in cases with scant or poor-quality material; useful in fusion-negative alveolar RMS as an indicator that a variant gene fusion may be present
 - Fibroblast growth factor receptor genes FGFR4 and FGFR1 recently implicated in pathogenesis of alveolar RMS
- Sclerosing RMS:
 - Do not harbor PAX 3 fusions as seen in alveolar RMS, except for rare single case with a PAX3-FOXO1A fusion.

Differential Diagnosis

- Aural polyp:
 - Embryonal RMS of the middle ear is frequently polypoid and may be confused with an aural polyp
 - Prominent inflammatory cell infiltrate including mature plasma cells and lymphocytes seen in aural polyps may overrun and obscure diagnostic rhabdomyoblasts.
 - Cellular components of RMS including spindle-shaped cells with brightly eosinophilic cytoplasm, cross-striations, and immunohistochemical evidence of myogenic marker reactivity contrast with the mixed acute and chronic inflammatory cell infiltrate, including mature plasma cells with Russell bodies seen in aural polyps.
- Poorly differentiated and spindle cell malignant neoplasms, including malignant melanoma, Ewing family of tumors, non-Hodgkin malignant lymphoma, synovial sarcoma, others:

- Differentiation can be accomplished by histochemical, immunohistochemical, and cytogenetic analysis.
- Fetal (juvenile) rhabdomyoma, intermediate type:
 - May be difficult to differentiate from spindle cell RMS
 - Features that may assist in this differential diagnosis include:
 - Greater uniformity and less cellular pleomorphism in fetal rhabdomyoma than in spindle RMS
 - Absence of invasive growth, necrosis, and absent to few mitoses in fetal rhabdomyoma
 - Tendency of fetal rhabdomyoma to occur in older aged individuals as compared with spindle RMS, which often occurs in very young patients (5 years and younger)
- Undifferentiated pleomorphic sarcoma and pleomorphic leiomyosarcoma:
 - May be difficult to differentiate from pleomorphic RMS
 - Differentiation is best accomplished by immunohistochemical staining for myoglobin, MyoD1, or myogenin and by ultrastructural analysis
 - Undifferentiated pleomorphic sarcoma and pleomorphic leiomyosarcoma may show immunoreactivity for actin and desmin.

Treatment and Prognosis

- For all histologic types of RMSs, treatment includes a combination of surgery and multiagent chemotherapy with or without radiotherapy.
- Following biopsy diagnosis, recommendations for treatment depend on several factors including site of the disease, clinical group of the disease, and stage of the disease.
- Tumor staging is an important element in the overall approach to treating the disease; since there is a tendency to bone marrow metastasis, a bone marrow aspiration/biopsy is part of the staging process.
- Clinical staging of patients determined by IRS-II study for patients younger than 21 years with confirmed diagnosis of RMS—[Box 10-7](#)
- TNM classification, [Table 10-9](#); this classification relies on pretreatment assessment of the extent of tumor.
- Favorable and unfavorable factors are detailed in [Box 10-8](#):
 - Low-risk patients include those with localized disease with embryonal histology:
 - Most of these patients have resected Group I and II tumors as well as Group III tumors arising in favorable sites.
 - Intermediate-risk patients include those with embryonal RMS that are Group III, stage II or

BOX 10-7 RMS: Clinical Staging*

Group 1

Localized disease, completely resected (regional nodes not involved)

- A. Confined to muscle or site/organ of origin, completely resected
- B. Contiguous involvement with infiltration outside the muscle or organ of origin. As through fascial planes, completely resected.

Group 2

- A. Gross resection with evidence of microscopic local residual disease
- B. Regional disease with involved lymph nodes, completely resected with no microscopic residual disease
- C. Regional disease with involved nodes, grossly resected, but with evidence of microscopic local and/or nodal residual disease

Group 3

Incomplete resection or biopsy with gross residual disease

Group 4

Distant metastatic disease at presentation

*Intergroup Rhabdomyosarcoma Studies Classification. RMS, Rhabdomyosarcoma.

BOX 10-8 RMS: Favorable and Unfavorable Factors

Prognostically Favorable

- Infants and children
- Orbital or genitourinary (non-bladder or prostate) location
- Small size (<5 cm)
- Botryoid or spindle cell type
- Localized noninvasive tumor without regional lymph node involvement or distant metastasis
- Complete initial resection

Prognostically Unfavorable

- Adults
- Location in head and neck (nonorbital), paraspinal region, abdomen, biliary tract, retroperitoneum, perineum, or extremities
- Large size (greater than 5 cm)
- Alveolar (especially *PAX3/FOXO1A* fusion transcript positive) or pleomorphic type
- Diploid DNA content
- Local tumor invasion, especially parameningeal or paraspinal region, paranasal sinuses, or skeleton
- Local recurrence whether during or not during therapy
- Regional lymph node involvement or distant metastasis
- Incomplete initial excision or unresectability
- Diffuse myogenin expression

RMS, Rhabdomyosarcoma.

III, and all patients with nonmetastatic alveolar RMS.

- High-risk patients include all those with metastatic disease.
- Prognostic gene-expression signature reported with reproducible and significant effects:
 - Among nonmetastatic patients, patients who were *PAX3/FOXO1* positive had significantly

TABLE 10-9 Rhabdomyosarcoma: TNM Staging*

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T1a	Superficial tumor*
T1b	Deep tumor*
T2	Tumor >5 cm in greatest dimension
T2a	Superficial tumor*
T2b	Deep tumor*
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1 [†]	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Anatomic Stage/Prognostic Groups	
Stage IA	T1a N0 M0 G1,GX T1b N0 M0 G1,GX
Stage IB	T2a N0 M0 G1,GX T2b N0 M0 G1,GX
Stage IIA	T1a N0 M0 G2,G3 T1b N0 M0 G2,G3
Stage IIB	T2a N0 M0 G2 T2b N0 M0 G2
Stage III	T2a,2b N0 M0 G3 Any T N1 M0 Any G
Stage IV	Any T Any N M1 Any G
Histologic Grade (G) (FNCLCC System preferred)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

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*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

[†]Presence of positive nodes (N1) in M0 tumors is considered Stage III.

Grade is determined by differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as: differentiation 1-3; mitotic activity 1-3; necrosis 0-2. Scores are summed to designate grade including: G1 = 2 or 3; G2 = 4 or 5; G3 = 6-8.

Differentiation: Score 1 = sarcoma resembling normal, mature mesenchymal tissue; Score 2 = sarcomas of definite histologic type; Score 3 = synovial sarcomas, embryonal sarcomas, undifferentiated sarcomas, sarcomas of unknown/doubtful tumor type.

Mitotic account: Score 1 = 0-9 mitoses per 10 high power fields (HPFs); Score 2 = 10-19 mitoses per 10 HPFs; Score 3 = > 20 mitoses per 10 HPFs.

Necrosis: Score 1 = no tumor necrosis; Score 2 = ≤ 50% tumor necrosis; Score 3 = >50% tumor necrosis.

poorer outcome compared with alveolar-negative and PAX7/FOXO1-positive patients.

- Overall survival rates based on data from IRS-IV includes:
 - 95% for low-risk patients
 - 75% for intermediate-risk patients
 - 27% for high-risk patients
- Prognosis is best for orbital RMS followed by head and neck and genitourinary (nonbladder/prostate) RMS:
 - 5-year survival rates include:
 - Orbit: 92%
 - Head and neck, nonprostate/bladder RMS: 80%
 - Parameningeal, bladder, prostate, extremities: 70%
- Poorest prognosis seen in association with RMS of retroperitoneum, biliary tract, and peritoneum
- Adverse outcomes accounting for prognostic differences related to anatomic sites have been linked to:
 - Late detection of tumor
 - Large tumor size
 - Difficulties during surgical excision
 - Meningeal involvement with or without spinal fluid spread
 - Metastatic disease
- Diffuse immunohistochemical reactivity for myogenin correlated with decreased recurrence-free intervals and overall survival independent of histologic subtype, translocation status, tumor site, or stage
- A problem specifically related to middle ear and mastoid RMS is the delay in diagnosis due to misinterpretation of the biopsy specimen as inflammatory polyps or as granulation tissue; this delay in diagnosis may result in more advanced stage disease, placing patients at greater risk for treatment failure due to uncontrollable local disease.
- Therapy-induced cytodifferentiation more often seen in embryonal RMS, including botryoid subtypes as compared with other subtypes:
 - In botryoid RMS, cytodifferentiation and decreased proliferative activity are associated with favorable clinical course.
- High recurrence rate seen in association with inadequately resected tumors:
 - Recurrent tumor may herald metastatic disease.
 - Histology of recurrent RMS may be less differentiated than primary RMS, although some may show greater degree of differentiation (e.g., rhabdomyoblasts with cross-striations) than primary RMS.
- Metastatic disease occurs in up to 20% of cases; metastatic sites include:
 - Regional lymph nodes: depend on tumor location with greater incidence of nodal metastasis in

patients with RMS of the prostate, paratesticular region, and extremities as compared with RMS of the orbit, head, and neck

- Distant hematogenous metastasis to the lungs, bone marrow > other viscera (brain, meninges, liver, kidney, pancreas, and heart)
- In alveolar RMS, lymph node metastasis may precede identification of primary tumor.
- There may be a high incidence of cardiac metastasis.
- In some examples, cutaneous metastatic disease may be the initial presentation.
- Histology of metastatic RMS may be less differentiated than primary RMS, although some may show greater degree of differentiation (e.g., rhabdomyoblasts with cross-striations) than primary RMS.

Synovial Sarcoma

(Figs. 10-43 through 10-45)

Definition: Malignant soft tissue neoplasm of uncertain histogenesis primarily arising in para-articular regions in close association with tendon sheaths, bursa, and joint capsules but uncommonly occurs within joint spaces displaying a variable degree of epithelial differentiation and specific chromosomal translocation $t(x;18)(p11;q11)$ leading to formation of a *SS18-SSX* fusion gene.

NOTE:

- Despite its designation, origin from synovial tissues has never been confirmed.
- Felt to arise from a pluripotential mesenchymal cell, accounting for its occurrence in unusual locations and expression of epithelial and mesenchymal markers.



Fig. 10-43. Hypopharyngeal synovial sarcoma.

The resected tumor is circumscribed and multinodular with a gray to tan-white appearance.

Synonyms: Synovioma; tenosynovial sarcoma; synovial cell sarcoma; synoviosarcoma; malignant synovioma; synovioblastic sarcoma; soft tissue carcinoma

Clinical

Synovial Sarcoma of Soft Tissues

- Synovial sarcoma represents approximately 5% to 10% of all soft tissue sarcomas.
- Slight male predilection; most often occurs adolescents and young adults in the second through fourth decades of life
- Presentation is that of a palpable, deep-seated swelling or mass often (50% of cases) associated with tenderness and/or pain.
- Predominantly (85% to 95%) occur in the deep soft tissue of the extremities, especially in the vicinity of large joints such as the knee:
 - Intimately related to tendons, tendon sheaths, and bursal structures outside the confines of the joint space
 - Less frequently attached to fascial structures, ligaments, aponeuroses, and interosseous membranes
 - Rarely (less than 5%) are intraarticular; intraarticular involvement more often occurs secondarily by direct extension from an extraarticular lesion
 - Approximately 5% to 10% arise in the head and neck.
 - Approximately 5% arise in the trunk.
 - Remainder occur in a wide variety of unusual sites throughout the body
- Although a specific cause is not known, some cases may have:
 - Antecedent history of trauma to the affected site
 - Prior history of radiation to the affected site

Head and Neck Synovial Sarcoma

- Less than 10% of all synovial sarcomas occur in the head and neck region.
- Equal to slight male predilection; may occur over a wide age range but tends to occur in the adolescent and young adult population with an average age of 25 at the time of presentation.
- Most common sites of occurrence in the head and neck include the neck and the pharyngeal region (hypopharynx and retropharynx):
 - In the neck, synovial sarcoma typically (but not always) localizes to the level of the bifurcation of the carotid artery intimately associated with the prevertebral fascia.
 - Less common site of the occurrence includes the larynx:
 - Laryngeal and hypopharyngeal involvement may occur by direct extension from a neck primary tumor.

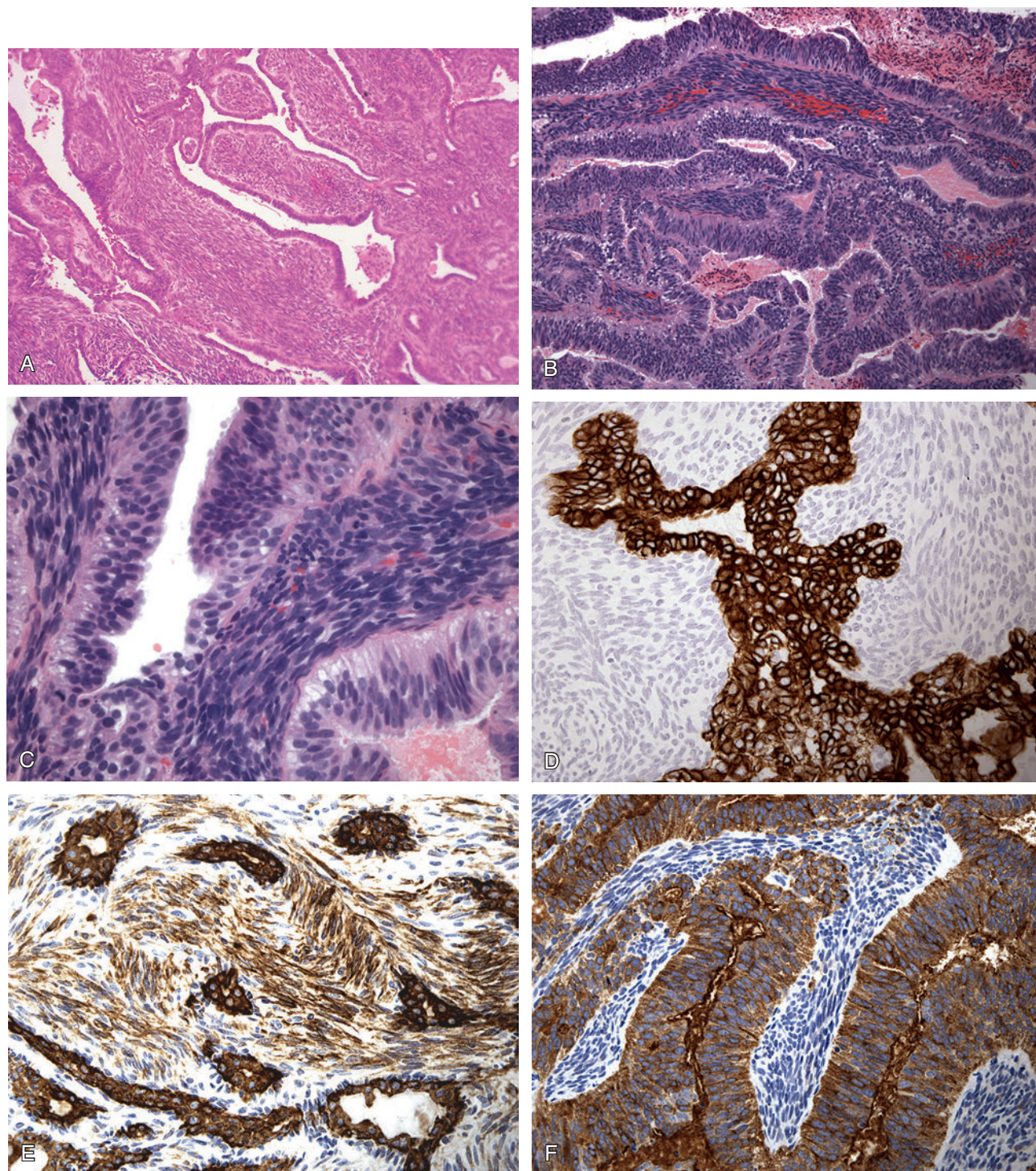


Fig. 10-44. Pharyngeal synovial sarcoma.

A through **C**, Biphasic synovial sarcoma comprised of a combination of epithelioid cells and spindle cells with the epithelioid cells lining the gland-like spaces appearing columnar and the spindle-shaped cells arrayed in fascicular to storiform growth pattern. Immunoreactivity in biphasic synovial sarcomas may include (**D**) cytokeratin (AE1/AE3) in the epithelioid cells; (**E**) CK7 in both epithelioid and spindle cells; (**F**) epithelial membrane antigen (EMA) in epithelioid and spindle cells;

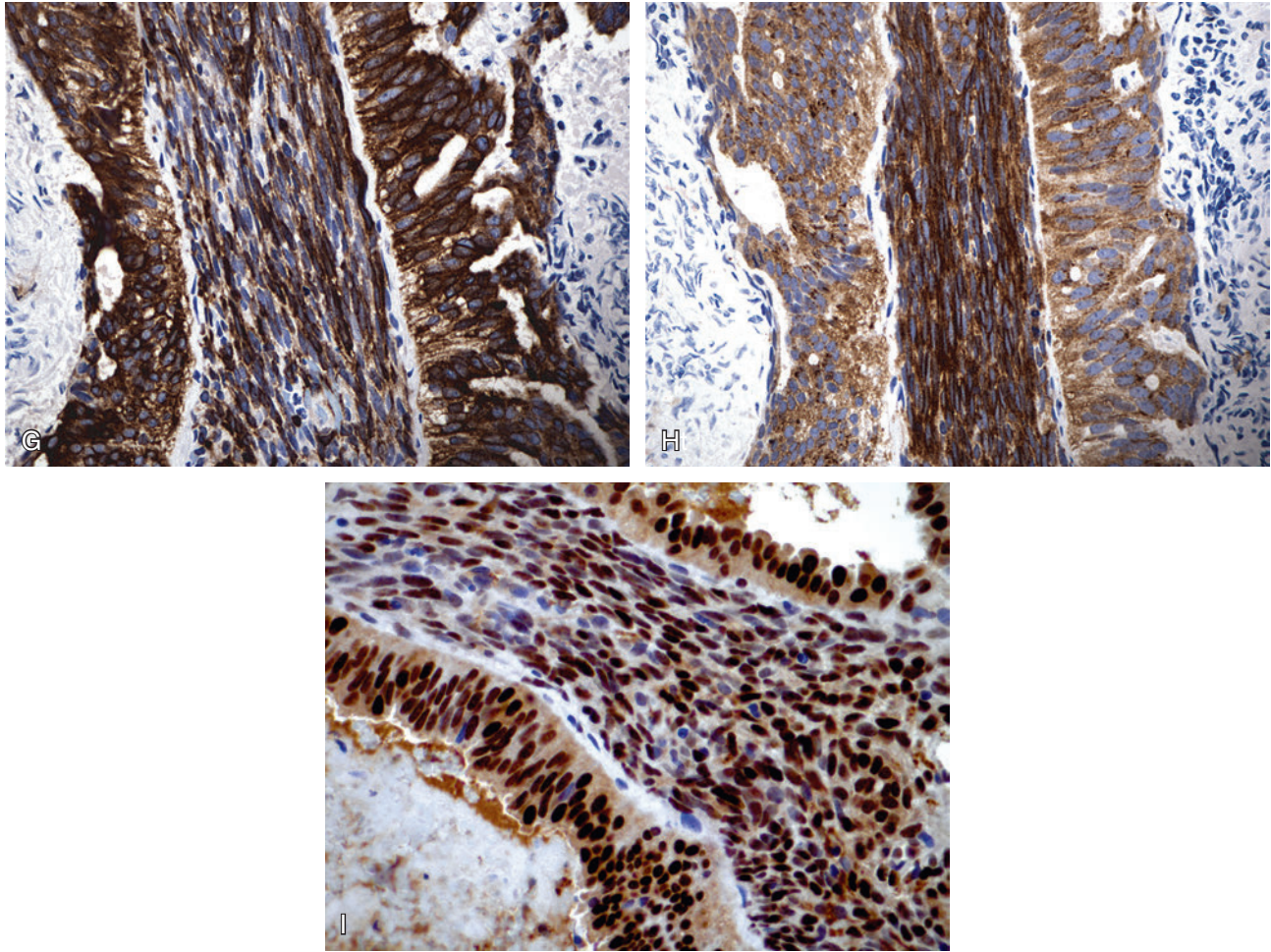


Fig. 10-44, cont'd

(**G**) bcl2 in epithelioid and spindle cells; (**H**) CD99 (Ewing's marker) in epithelioid and spindle cells; and (**I**) TLE1 (nuclear staining) in epithelioid and spindle cells, representing an extremely useful marker for synovial sarcoma and serving as a discriminating stain from other sarcomas.

- Rare head and neck sites of occurrence include the oral cavity (tongue, soft palate), tonsil, parotid gland, and trachea.
- Symptoms vary according to site of occurrence:
 - Neck: palpable mass with or without associated pain, weight loss
 - Pharynx (retropharynx, hypopharynx): dysphagia, dyspnea, hemoptysis, otalgia, foreign body sensation in throat, pain, weight loss
 - Larynx: hoarseness, dysphagia, dyspnea, sore throat, foreign body sensation in throat, pain
- Radiology
 - CT and MRI:
 - Heterogeneous soft tissue mass with enhancement
 - Multiple spotty opacifications more pronounced at the periphery than the center of

the lesion in an otherwise undistinguished soft tissue mass is a characteristic finding in about one third of cases; these opacifications represent focal calcifications and, although not limited to synovial sarcoma, may assist in the radiographic differential diagnosis.

- There are no known risk factors.

Pathology

Gross

- Circumscribed or pseudoencapsulated spherical, lobulated, or multinodular mass ranging in size from 1 to 10 cm
- Variation in color (yellow, gray, or white), consistency (soft, rubbery, firm, gritty), and appearance of the cut surface (fibrous, whorled, cystic, mucoid)

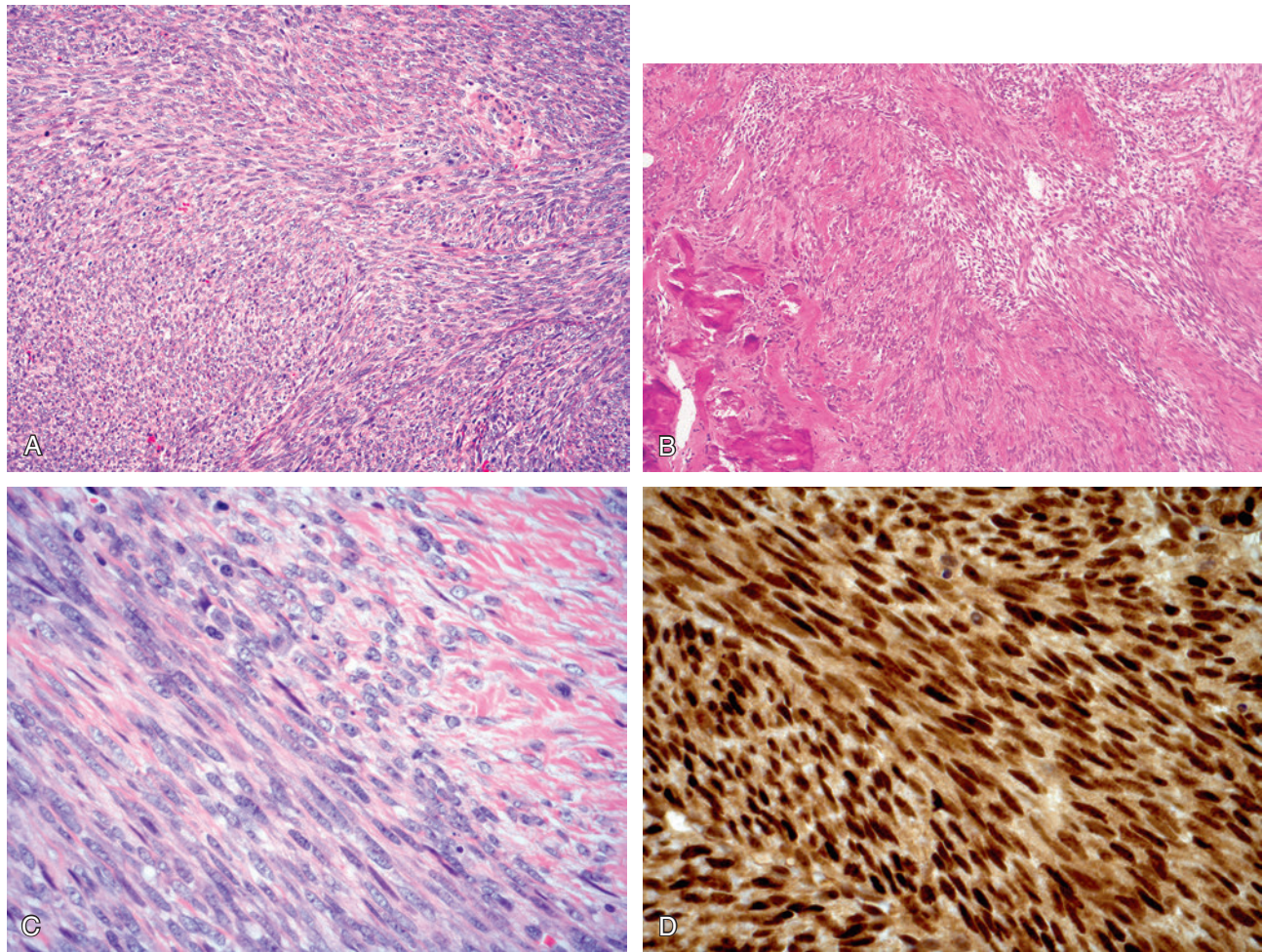


Fig. 10-45. Hypopharyngeal monophasic (fibrous) synovial sarcoma.

A, Fascicular to storiform growth. **B**, Stromal calcifications are present (*left lower*). **C**, Fibroblast-like cells composed of well-oriented, plump spindle-shaped cells with oval to spindle-shaped, hyperchromatic to vesicular nuclei and scant, indistinct cytoplasm; stromal hyalinization characterized by thick collagen bands is present (*upper right*). **D**, Diffuse and strong TLE1 (nuclear staining).

Histology

NOTE: Regardless of its site of occurrence, the histologic findings are essentially similar.

- Two major categories of synovial sarcomas including biphasic and monophasic types that are composed of epithelial cells and/or spindle cells:
 - Depending on the relative prominence of cell type and differentiation, synovial sarcomas can be classified into four types:
 - Biphasic: admixture of epithelioid and spindle (fibrous) cells
 - Monophasic fibrous: most common histologic subtype
 - Monophasic epithelioid
 - Poorly differentiated

Biphasic Synovial Sarcoma (Fig. 10-44)

- Classic type consisting of a combination of epithelial cells and spindle cells
- Epithelial cells:
 - Columnar, cuboidal, or polygonal cells
 - Large, round to oval, vesicular nuclei, abundant pale-staining cytoplasm with distinct cell borders
 - Arranged in solid cords, nests, whorls, and glandular structures, the latter containing granular or homogeneous eosinophilic secretions:
 - Squamous metaplasia including keratin pearls and keratohyaline granules may be present and should not be mistaken for squamous cell carcinoma.

- Spindle cells:
 - Generally represent the more prominent component
 - Fibroblast-like composed of well-oriented, plump spindle-shaped cells with oval to spindle-shaped, hyperchromatic to vesicular nuclei and scant, indistinct cytoplasm
 - Form solid sheets resembling fibrosarcoma but typically lack herringbone pattern or long sweeping fascicles seen in fibrosarcoma
- Mitoses in the epithelioid and spindle cell areas can be seen but generally are not abundant.
- Nuclear palisading may occasionally be present; papillary epithelial foci may be present.
- Alternating cellular and less cellular areas are a common finding:
 - Less cellular areas display hyalinization, calcification, or myxoid change.
 - Collagen in hyalinized areas may be diffusely distributed as thick collagen bands separating malignant spindle cells or extensively distributed compressing neoplastic cells to areas with limited hyalinization appearing as narrow bands or plaque-like masses.
 - Myxoid foci tend to be limited but occasionally may be predominantly myxoid.
- Calcification is a characteristic feature:
 - Present in approximately 20% of cases
 - Varies in any given case from focal and irregular in distribution to extensive and readily identified
 - More pronounced at the periphery of tumor than at its center
 - May or may not be associated with ossification; chondroid foci are rare
- Some examples may show prominent cystic change.
- Mast cells often are present and tend to be more numerous in the spindle cell areas:
 - Other inflammatory cells, as well as multinucleated giant cells, are uncommonly present.
- Vascularity varies from a few scattered vascular structures to prominent dilated vascular spaces with a hemangiopericytomatous pattern.

Monophasic Fibrous Synovial Sarcoma (Fig. 10-45)

- Relatively common tumor in soft tissue sites; uncommon in the head and neck
- Similar histologic features to the spindle cell (fibrous) component of the classic biphasic synovial sarcoma
- Extensive sampling may reveal an epithelioid cell component:
 - Even in the absence of a definitive epithelioid cell component, cells with a more epithelioid cell appearance, including more eosinophilic-appearing cytoplasm and greater cohesive growth

than surrounding spindle cell components, are present.

- More epithelioid-appearing cells show epithelial differentiation by immunohistochemical staining (see below).

Monophasic Epithelioid Synovial Sarcoma

- Rare tumor type of all locations
- Diagnosis and differential diagnosis predicated on cytogenetic and molecular genetic findings (see below)

Poorly Differentiated Synovial Sarcoma

- Uncommon tumor type of all locations
- Associated with three types or patterns:
 - Large cell or epithelioid pattern:
 - Composed of variably sized round nuclei with prominent nucleoli
 - Small cell pattern:
 - Nuclear features similar to other small round cell tumors
 - May form rosette-like structures
 - Spindle cell pattern:
 - Composed of spindle-shaped cells with high-grade nuclear features, marked increase in mitotic activity and necrosis
 - Often richly vascularized with thin-walled, dilated vascular spaces
 - May have cells with a rhabdoid appearance characterized by intracytoplasmic hyaline inclusions

Special Stains

- Histochemistry:
 - Stains for epithelial mucin including PAS (with and without diastase), mucicarmine, alcian blue and colloidal iron show positive material within epithelial cells, pseudoglandular spaces, and intracellular areas:
 - Positive staining remains despite treatment with diastase and hyaluronidase
 - In contrast to adenocarcinoma, the positive material is more conspicuous in pseudoglandular spaces and intracellular clefts than in the epithelial cells
 - Stains for mesenchymal or stromal mucin including colloidal iron and alcian blue show positive material in relation to the spindle cell component and myxoid areas:
 - Material is rich in hyaluronic acid and is removed by prior treatment with hyaluronidase
 - Present in the interstices of the spindle cell areas and myxoid areas
 - Weakly mucicarminophilic and is negative with PAS staining

- Mast cells stain with PAS, alcian blue, and toluidine blue
- Immunohistochemistry:
 - Epithelial cells and spindle cells:
 - Cytokeratins and epithelial membrane antigen (EMA) positive:
 - Intensity of staining is greater in epithelial cells
 - Staining may be present with cytokeratin but not EMA or EMA but not cytokeratin, so both markers should be performed.
 - Immunoreactivity seen for cytokeratins 7, 19, 8/18 (CAM5.2), and 14 in epithelial cells of biphasic tumors:
 - More limited cytokeratin expression in monophasic synovial sarcoma, including CK7 (79%), CK 19 (60%), CK8/18 (45%)
 - Even more limited expression in poorly differentiated synovial sarcoma, including CK7 (50%), CK 19 (61%)
 - Vimentin positive
 - S100 protein is present in up to 30% of cases:
 - Usually present in cases showing expression of epithelial markers
 - May be present in cases lacking expression of epithelial markers
 - CD99 (O13 or Ewing marker) product of *MIC2* gene present in a majority (60% to 70%) of synovial sarcomas:
 - Cytoplasmic and membranous staining
 - bcl-2 positive (75% to 100%) of synovial sarcomas:
 - Diffuse and intense reactivity
 - CD34, endothelial cell markers, melanocytic markers, myogenic markers, and hematolymphoid markers are usually negative.
 - Transducin-like enhancer of split 1 (TLE1) positive (nuclear):
 - Member of groucho/TLE family of genes that encodes transcriptional corepressor implicated in epithelial and neuronal differentiation, body patterning, and hematopoiesis
 - Extremely useful marker for synovial sarcoma serving as a discriminating stain from other sarcomas:
 - Positive in high percentage of molecularly confirmed cases
 - Very rarely expressed in other sarcomas
 - Particularly useful in cytokeratin-negative cases
 - SMARCB1/INI1 protein expression
 - Reduced expression reported in synovial sarcoma with preservation retained in most cases and complete loss of SMARCB1/INI1 protein expression not reported (see epithelioid sarcoma below).
- Electron microscopy:
 - Epithelial cells:
 - Junctional complexes, zonula adherens, or desmosome-like structures seen interconnecting cells:
 - Findings supported by expression of tight junction-related proteins including ZO-1, claudin-1, and occludin
 - Not present in normal synovium
 - Luminal microvilli or villous filopodia can be seen in cells lining or forming gland-like spaces.
 - Spindle cells:
 - Continuous basal lamina separating spindle-shaped cells from epithelioid cells and gland-like structures
- Cytogenetic and molecular genetics:
 - Balanced reciprocal translocation t(X;18) (p11.2;q11.2) found in more than 90% of synovial sarcomas regardless of subtype:
 - Involves fusion of *SS18* (also known as *SYT*) gene on chromosome 18 and either the *SSX1* or *SSX2* gene on the X chromosome (both at Xp11) or rarely with *SSX4* gene (also at Xp11):
 - Two thirds harbor *SS18-SSX1* fusion:
 - Almost all are biphasic synovial sarcomas.
 - One third harbors *SS18-SSX2* fusion:
 - Majority are monophasic synovial sarcomas.
 - Can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) or fluorescent in situ hybridization (FISH), including a break-apart *SS18* probe
 - Detection can be performed on material from a fine-needle aspiration biopsy, on frozen tissue, or paraffin-embedded tissue.
 - Translocation is sensitive and specific for a diagnosis of synovial sarcoma.

Differential Diagnosis

Biphasic Synovial Sarcoma

- Carcinosarcoma
- Glandular malignant peripheral nerve sheath tumor
- Malignant mesothelioma
- Malignant melanoma
- Papillary thyroid carcinoma:
 - Rare examples of synovial sarcoma may show papillary epithelial cell features that in certain clinical settings of the head and neck may raise concern for a diagnosis of thyroid papillary carcinoma.
 - Presence in papillary thyroid carcinoma of characteristic cytomorphologic (i.e., nuclear) features, true psammoma bodies and immunoreactivity for thyroglobulin and thyroid transcription factor 1

(TTF-1) as well as the absence of a biphasic cell pattern will allow for differentiation.

Monophasic Fibrous Synovial Sarcoma

- Fibrosarcoma
- Leiomyosarcoma
- Hemangiopericytoma
- Spindle cell squamous carcinoma
- Malignant peripheral nerve sheath tumor
- Malignant melanoma

Monophasic Epithelioid Synovial Sarcoma

- Carcinoma (primary or metastatic)
- Epithelioid sarcoma (ES):
 - Rare malignancy of the head and neck:
 - Approximately 4% of all ESs occur in the head and neck.
 - Malignancy of unknown cell of origin showing predominantly epithelioid cytomorphology
 - More common in men than in women; primarily occurs in adolescents and young adults
 - Predilection to flexor surfaces of fingers and hand > wrist and forearm > knee and lower leg (pretibial region) > buttocks, thigh > shoulder, arm, ankle, foot, and toes:
 - Given predilection for the above sites, also referred to as classic, conventional, or distal form of epithelioid sarcoma
 - Histologic features include:
 - Nodular growth with central necrosis and peripheral palisading of tumor cells that at low magnification suggests a granulomatous process (pseudogranulomatous appearance)
 - Admixture of epithelioid and spindle-shaped cells
 - Transitions between the two cell types can be seen
 - Slight nuclear pleomorphism is present
 - Cells have round to oval vesicular nuclei, identifiable central nucleoli, eosinophilic cytoplasm, and ill-defined cell borders
 - Neurotropism and perivascular invasion commonly present
 - Mitotic activity is usually low (typically less than 5 mitoses per 10 high-power fields).
 - Immunoreactive for vimentin, epithelial markers, and CD34:
 - Vimentin (100%)
 - Epithelial membrane antigen (96%), CK8 (94%), and CK19 (72%)
 - More pronounced in epithelioid areas than spindle areas
 - CD34 is positive in >50% of cases.
 - ERG expression (uniform nuclear staining) reported in a significant percentage (38%) of epithelioid sarcomas:
 - Similar staining to that seen in angiosarcomas
 - Negative for ERG gene rearrangement, indicating that ERG expression is not likely related to ERG-involving translocations in epithelioid sarcoma
 - Other endothelial markers (e.g., CD31, others) absent
- Variable immunoreactivity identified for actins (smooth muscle and muscle specific), S100 protein, and neuron-specific enolase
- Loss of nuclear expression of SMARCB1 protein (also known as *INI1*) a tumor-suppressor gene located on long arm of chromosome 22:
 - Expression lost in distal and proximal types of ESs
 - Homozygous deletions or mutations of this gene characteristic of malignant rhabdoid tumor of infancy and their CNS counterpart atypical teratoid/rhabdoid tumor
- Ultrastructural findings include presence of epithelial differentiation (i.e., desmosome-like intercellular junctions, tonofilaments, surface microvilli), and uncommitted fibroblast-like mesenchymal cells
- Cytogenetic and molecular genetics findings reported include:
 - Aberration of the long arm of chromosome 22 (22q11) in proximal and distal types of ESs
 - A variety of chromosomal gains and losses, none specific for epithelioid sarcoma
- Complete surgical resection is the preferred treatment.
- Multiple recurrences often resulting from incomplete resection is characteristic.
- 5-year survival rates range between 50% and 85%.
- 10-year survival rates range between 42% and 55%.
- Recurrence rate of approximately 77% at 10 years
- Metastases occur in approximately 45% of patients:
 - Primarily to the lung followed by regional lymph nodes; less frequently to skin (scalp), bone, brain, liver, CNS, and soft tissue
- Approximately one third of patients die of disease.
- Adverse prognostic features include:
 - Male gender
 - Advanced age at presentation
 - Large tumor size (measuring ≥ 5 cm)
 - Nondistal extremity location
 - High mitotic rate
 - Presence of angioinvasion

- Presence of hemorrhage and necrosis
- Inadequate initial excision
- Multiple recurrences
- Metastatic disease at presentation
- Proximal type of epithelioid sarcoma (ES):
 - Propensity to arise in axial locations including pelvis, perineum, and genital tract
 - Tendency to occur in older adults
 - Histologic findings include:
 - Multinodularity
 - Presence of large epithelioid (carcinoma-like) cells with vesicular nuclei, marked cytologic atypia, and prominent nucleoli
 - Rhabdoid cellular features are commonly present and in any given case may predominate, making differentiation from an extra-renal rhabdoid tumor difficult.
 - Tumor necrosis is commonly seen but does not result in pseudogranulomatous appearance classic or distal epithelioid sarcoma.
 - Rarely, hybrid tumors composed of histologic features of distal ES and proximal ES occur.
 - Immunohistochemical and ultrastructural features similar to those of the distal ES
 - More aggressive biologic course:
 - Tends to be resistant to all forms of therapy
 - Higher (and earlier) rates of tumor-related deaths as compared with distal ES
- SYT-SSX fusion protein that results from the X,18 translocation is an appealing target, as are the proteins overexpressed in synovial sarcoma including bcl-2 and EGFR.
- In the setting of advanced disease improved survival reported in patients:
 - Age less than 35 years of age
 - Response to first-line chemotherapy:
 - The response rate to doxorubicin plus ifosfamide reported to be superior to either agent when given singly
 - Metastasectomy is not associated with improved prognosis.
- Overall prognosis for head and neck synovial sarcoma is not good with tendency to local recurrence as well as for metastatic disease (lung, lymph nodes, and bone):
 - Approximately 20% to 44% develop recurrent tumor.
 - Approximately 24% to 48% develop distant metastases.
 - Overall 5-year survival is 47% to 58%.
 - Mean survival following distant metastasis is less than 2 years.
- Recurrent and/or metastatic synovial sarcoma may demonstrate histologic variation from the primary neoplasm:
 - Biphasic synovial sarcoma may recur or metastasize as a predominantly or exclusively monophasic (epithelioid or spindle cell) synovial sarcoma.
- Favorable prognostic factors include:
 - Childhood patients (15 years or younger)
 - Smaller tumors (less than 5 cm)
 - Distal extremity location
 - Low tumor stage
 - Extensively calcified synovial sarcomas reported to have better long-term prognosis
 - Complete (local) surgical eradication
 - Patients with SYT/SSX2 fusion transcript reported to have longer disease-free survival than patients with SYT/SSX1 fusion transcript:
 - Not universally accepted as an independent prognostic indicator
- Adverse prognostic factors include:
 - Increasing age (>40 years)
 - Larger tumors (≥5 cm)
 - Tumors with poorly differentiated areas
 - Other histologic features reported to have adverse prognostic impact include:
 - Increased mitotic activity (>10 mitoses per 10 high-power fields)
 - Presence of extensive tumor necrosis
 - Histologically higher grade tumors
 - Presence of rhabdoid cells
 - Local recurrence
 - Distant metastasis

Poorly Differentiated Synovial Sarcoma

- Ewing family of tumors
- Rhabdomyosarcoma
- Hemangiopericytoma
- Malignant lymphoma
- Mesenchymal chondrosarcoma
- Carcinoma (primary or metastatic)
- Epithelioid sarcoma
- Neuroblastoma
- Extrarenal rhabdoid tumor

Treatment and Prognosis

- Complete surgical resection is the preferred treatment.
- Nodal metastasis is rare and a neck dissection is not indicated.
- Adjuvant therapy (preoperative and postoperative radiotherapy and chemotherapy) may be beneficial:
 - Improved disease-free and overall survival
 - Chemosensitive regimens that include ifosfamide and doxorubicin or epirubicin result in partial or complete response in approximately 50% of patients.
- Novel therapies such as targeted therapy show promise in the treatment of synovial sarcoma:

Chordoma of the Craniocervical (Base of Skull) Region

(Figs. 10-46 and 10-47)

Definition: Low- to intermediate-grade malignant tumor that arises from and recapitulates the embryonic remnants of the notochord.

- Notochord and chordoma development:
 - Notochord functions as a primitive axial skeleton in humans.
 - From the time of its development in the third to fourth week of gestation, the notochord extends from the sphenoid bone at the junction of the occipital bone, exits its bony confines to run in close apposition to the primitive pharynx,

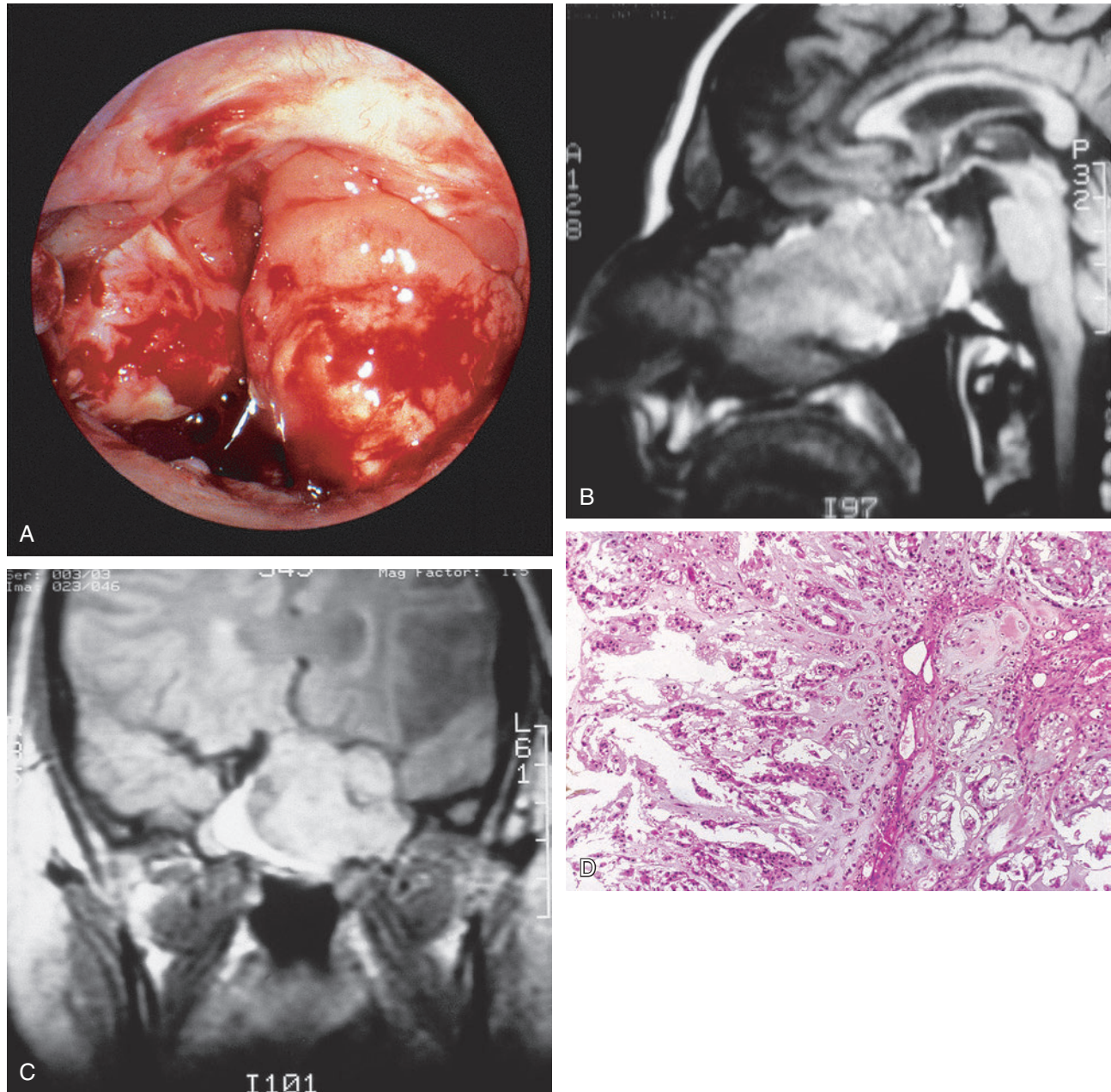
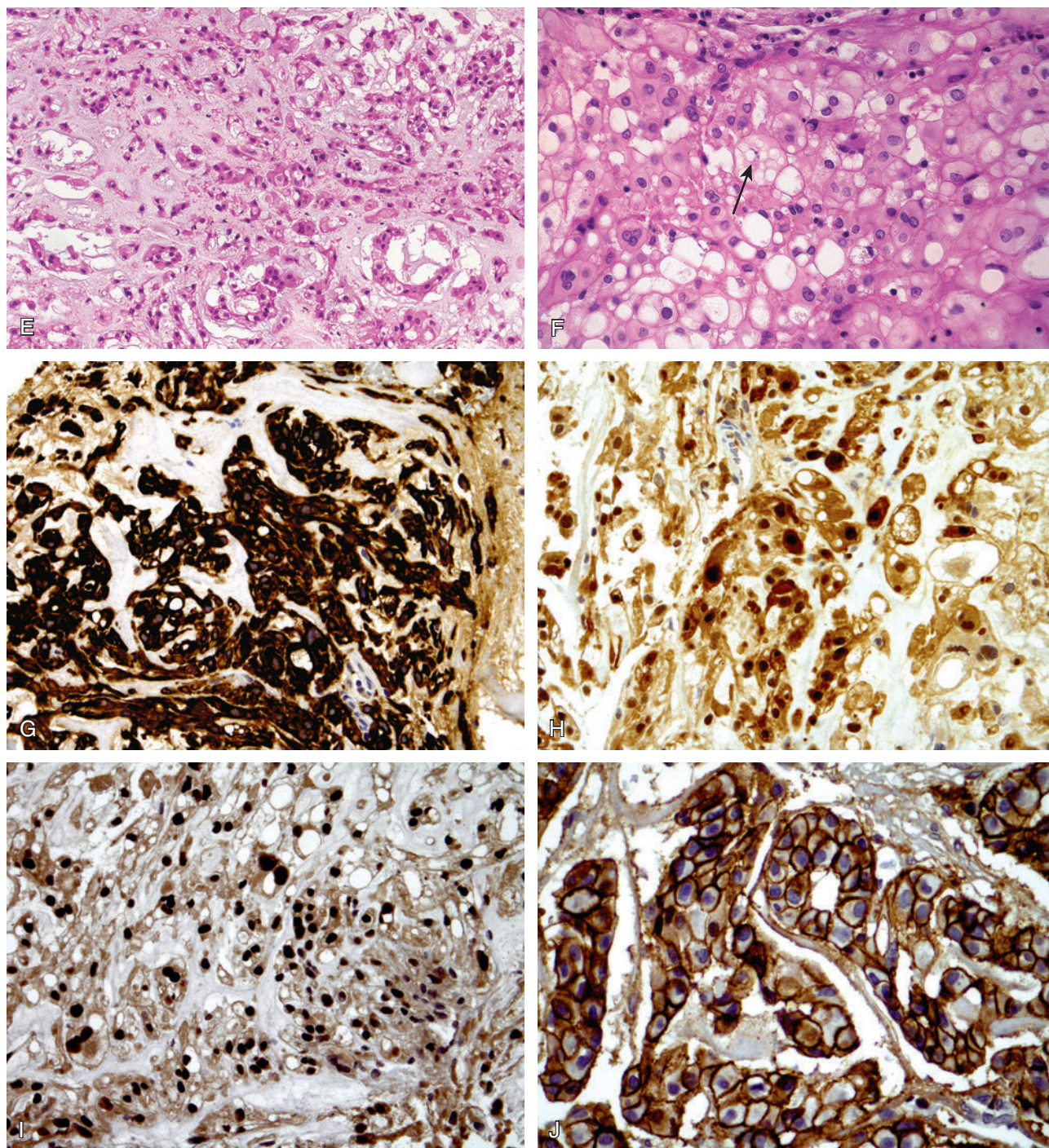


Fig. 10-46. Nasopharyngeal chordoma.

A, Endoscopic appearance is that of a tan-pink to fleshy mucoid or gelatinous mass. **B** and **C**, MRI sagittal and coronal views showing a large nasopharyngeal soft tissue density eroding into and destroying the bone at the base of the skull. **D**, Characteristic histologic appearance consisting of a lobular neoplastic growth associated with a copious extracellular mucinous matrix.

Continued

**Fig. 10-46, cont'd**

E, Cords, pseudoacini, and trabecular growth. **F**, Epithelioid cells with vesicular to hyperchromatic nuclei and abundant granular to vacuolated-appearing cytoplasm; vacuolization represents glycogen or mucous accumulation that, when extensive, can create cells with a “soap-bubble” appearance referred to as physaliferous cells. Lesional cells are immunoreactive for **(G)** cytokeratin (AE1/AE3), **(H)** S100 protein, **(I)** brachyury (nuclear), and **(J)** E-cadherin (membranous).

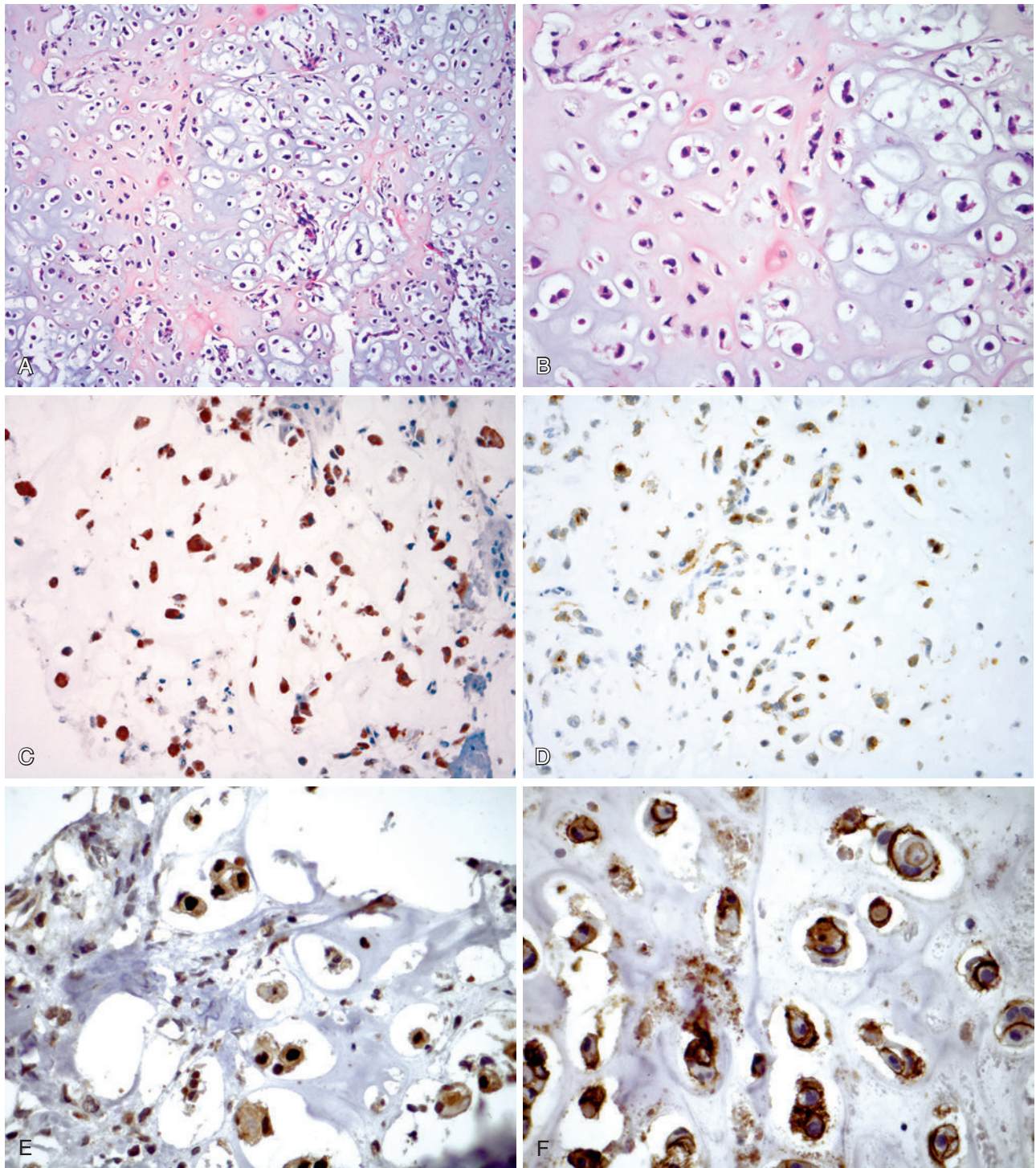


Fig. 10-47. Chondroid chordoma.

A and **B**, In addition to histologic foci of conventional chordoma (see [Fig. 10-46](#)), a cartilaginous component is present, including a hypercellular cartilaginous-appearing infiltrate including binucleate cells. Lesional cells are immunoreactive for **(C)** S100 protein, **(D)** EMA, **(E)** brachyury (nuclear), and **(F)** E-cadherin (membranous).

reenters the bone in the basiocciput, and then courses via the apical odontoid ligament through the center of the vertebral bodies to end at the coccyx.

- In the vertebral column, the notochord is divided into segments and disappears by the seventh week of gestation.
- Persistence of notochordal tissue is seen within the nucleus pulposus of the intervertebral disks.
- Chordomas do not arise from the intervertebral body remnants but rather from incomplete regression of notochordal tissue along the notochordal tract during development with common sites of occurrence, including:
 - Sacrococcygeal region, bones of the skull and the vertebra (cervical > lumbar > thoracic)
 - Craniocervical chordomas are identified most frequently in the dorsum sellae, clivus, and nasopharyngeal regions.
- Represent approximately 1% to 4% of all malignant bone tumors
- Most common in the sacrococcygeal region (approximately 50%) followed by the craniocervical/base of skull including the clivus (approximately 35%) and vertebral column (approximately 15%)
- Conventional, chondroid, and dedifferentiated variants recognized
- Myoepithelioma of soft tissue is synonymous with parachordoma; histologically distinct from chordoma; for a more complete discussion see Section 4, Neck, and Section 6, Salivary Glands.

Conventional Chordoma

(see Fig. 10-46)

Clinical

- More common in men than women; can occur in any age but is generally not common before the fourth decade of life
- Most frequent site of involvement in the head and neck is the base of skull, including dorsum sellae, clivus, and nasopharyngeal regions:
 - *Clivus* in Latin means slope.
 - The clivus is a sloping surface (slopes obliquely) formed successively by the basilar part of the occipital bone, the posterior part of the body and then the dorsum sellae of the sphenoid bone that lies anterior to the foramen magnum
 - On axial planes, the clivus sits just posterior to the sphenoid sinuses.
 - Just lateral to the clivus bilaterally is the foramen lacerum, which contains the internal carotid artery proximal to its anastomosis with the circle of Willis
 - Posterior to the clivus is the basilar artery.
 - The pons sits on the clivus.

- Symptoms vary according to the site of occurrence and extension of tumor and include:
 - Diplopia, visual field defects, headaches, pain, nasal obstruction, epistaxis, nasal discharge, soft tissue mass, and endocrinopathies (secondary to destruction of the sella turcica, resulting in loss of pituitary function)
- Radiology:
 - Expansile and destructive osteolytic lesions often associated with a soft tissue mass
 - Nodular and/or cystic deposits of calcification are often seen:
 - Calcifications seen in association with chordomas occur as a result of bone sequestration following its destruction or as dystrophic calcification
 - Destruction of the sella turcica may be seen.
 - Nasopharyngeal chordomas appear as a soft tissue density.

Pathology

Gross

- In comparison with chordomas of other sites (e.g., sacrococcygeal), which can be removed in toto and are well demarcated or encapsulated, those of the base of skull, given the anatomic constraints, often are removed in fragments and are soft, mucoid, or gelatinous with a pink to gray color and a variegated appearance with solid and cystic areas.

Histology

- Pseudoencapsulated tumor separated into a lobular growth by fibrous connective tissue associated with a copious extracellular mucinous matrix
- Neoplastic cells are arranged in cords, sheets, pseudoglands, or clusters.
- Neoplastic cells include:
 - Many appearing epithelioid with vesicular nuclei and abundant, granular to vacuolated-appearing cytoplasm:
 - Vacuolization represents glycogen or mucus and when extensive can appear with a signet ring or a soap bubble appearance compressing the nucleus peripherally and creating the characteristic physaliferous cells.
 - Other cells are small with round to oval hyperchromatic to vesicular nuclei and eosinophilic cytoplasm.
- Nuclear pleomorphism and mitoses are infrequently identified; necrosis and dystrophic calcification can be identified.
- Glandular differentiation, including tubules and acini not present, but pseudoglandular and pseudoacinar foci may be present
- Histochemistry:
 - Diastase-sensitive, periodic acid Schiff–positive, and mucin-positive intracytoplasmic material

TABLE 10-10 Immunohistochemistry of Chordomas: Differential Diagnosis

	CK	EMA	S100	Brachy	E-cad	D2-40	RCC/Pax8	GFAP	CK20/CDX2	MGB
Chord	+	+	+	+	+	–	–	–	–	–
CC	+	+	+	+	+	–	–	–	–	–
DC, SC	–	–	–	–	–	–	–	–	–	–
CS	–	–	+	–	–	+	–	–	–	–
ME	–*	–*	+	–	–	–	–	+	–	–
Mets RCC	+	+	–	–	–	–	+	–	–	–
Mets GIT	+	+	–	–	–	–	–	–	+	–
Mets MDC	+	+	–	–	+	–	–	–	–	+
Mets LCB	+	+	–	–	–	–	–	–	–	+

CC, Chondroid chordoma; *Chord*, conventional chordoma; CK, cytokeratins; CS, chondrosarcoma; D2-40, podoplanin; DC, SC, dedifferentiated chordoma, sarcomatous component; E-cad, E-cadherin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; ME, myxopapillary ependymoma; *Mets RCC*, metastatic renal cell carcinoma; *Mets GIT*, metastatic gastrointestinal tract adenocarcinoma; *Mets MDC*, metastatic mammary duct carcinoma; *Mets LCB*, metastatic lobular carcinoma of the breast; MGB, mammaglobin; RCC, renal cell carcinoma marker; S100, S100 protein.

*Rare ependymomas may have sparse CK or EMA immunoreactivity.

- Immunohistochemistry (Table 10-10):
 - Cytokeratin, epithelial membrane antigen (EMA), S100 protein, and vimentin positive:
 - Cytokeratin and vimentin consistently positive
 - EMA positive in 90% or more
 - S100 protein positive in 50% to 75%
 - Brachyury positive (nuclear):
 - Transcription factor involved in notochord development
 - Expressed in virtually all cases of chordoma
 - Sensitive and specific marker for chordoma
 - Expression may be lost following decalcification in formic and nitric acid.
 - E-cadherin (membranous):
 - Cadherins are calcium-dependent transmembranous intercellular adhesion molecules that are divided into three classes—E-, P-, and N-cadherin—with distinctive immunologic specificities and tissue distributions.
 - E-cadherin and N-cadherin detected in most chordoma cells irrespective of histologic subtype
 - Reported inverse relationship in tumor aggressiveness based on E-cadherin and N-cadherin:
 - Decreased expression of E-cadherin and increased expression of N-cadherin may underlie the transition from a less to a more aggressive tumor phenotype.
 - Carcinoembryonic antigen may occasionally be positive.
 - Podoplanin (D2-40) negative:
 - Podoplanin considered a sensitive marker in cartilaginous neoplasms (e.g., chondrosarcoma)
 - Glial fibrillary acidic protein and myoepithelial markers (e.g., p63, calponin) negative
- Cytogenetics and molecular genetics:
 - Complex karyotype with loss of chromosomes 3 (especially 3p), 4, 10, and 13
 - Candidate region for sporadic and inherited chordoma development mapped to 1p36.13
 - By comparative genomic hybridization most frequent changes include:
 - Gains of chromosomes 5q, 7q, 12q, and 20
 - Losses of chromosomes 1p, 3p

Differential Diagnosis

- Chondrosarcoma:
 - Usual type
 - Extraskelatal myxoid type
- Liposarcoma, myxoid
- Mucinous adenocarcinoma
- Pleomorphic adenoma
- Myxopapillary ependymoma
- Soft tissue chordoma:
 - Arise in soft tissue locations unrelated to bone, including:
 - Buttock, wrist, leg, toe, thumb, ankle, shoulder, and chest wall
 - Histologically identical to osseous ones
 - Immunoreactive for brachyury
 - Differ from osseous-related chordomas in their greater tendency to occur in distal locations where small size and surgical resectability result in better disease control
 - Existence of soft tissue chordoma implies that notochordal remnants are not a prerequisite for chordoma development.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - Due to location in base of skull often impossible to surgically eradicate
 - High-dose radiotherapy is utilized in advanced disease where complete resection is impossible.
 - Chemotherapy has no proven efficacy.
- Rarely cured after surgery alone or combined with conventional radiotherapy and more recent evidence suggests that optimal treatment may include stereotactic (gamma knife) radiation therapy or proton beam therapy alone or, when possible, combined with a gross total resection.
- Despite their slow growth, chordomas are relentless neoplasms associated with extensive local infiltration and destruction of adjacent, often vital, structures:
 - Death often due to uncontrollable local disease
 - Metastases are generally a late complication and involve the lungs, bone, liver, and lymph nodes.
- 5-year survival rate for patients under 40 years is 100% as compared with 22% for patients over 40 years of age:
 - Mean survival rates for sacrococcygeal chordomas are slightly better than for cervicofacial chordomas.

Chondroid Chordoma

(see Fig. 10-47)

- Controversial tumor type considered a histologic variant of conventional chordoma with cartilaginous differentiation in association with conventional chordoma:
- Alternative considerations relative to the origin of this tumor include:
 - It is a low-grade or well-differentiated chondrosarcoma.
 - It is a hybrid tumor with chordomatous and cartilaginous differentiation.
- Represent from 5% to 15% of all chordomas and up to 35% of craniocervical (spheno-occipital) chordomas
- Characterized by:
 - More frequent occurrence in women and younger patients than nonchondroid chordoma
 - Virtual exclusive occurrence at the base of skull; rarely may occur elsewhere (e.g., sacrococcygeal)
 - In addition to histologic foci of conventional chordoma, a cartilaginous component is also present:
 - Cartilage can be either benign or malignant.
 - In any given tumor the percentage of each component may vary, representing the dominant

component, the minor component, or approximately equal components.

- Immunohistochemistry (see Table 10-10):
 - S100 protein:
 - Identified in cartilaginous and conventional chordomatous elements
 - Cytokeratin and EMA immunoreactivity:
 - Identified in cartilaginous and conventional chordomatous elements although expression less prominent in cartilaginous foci
 - Brachyury positive (nuclear):
 - Identified in cartilaginous and conventional chordomatous elements
 - E-cadherin positive (membranous):
 - Identified in cartilaginous and conventional chordomatous elements
 - Podoplanin (D2-40) negative
- Purported better prognosis than typical chordomas:
 - Average survival rate for the chondroid chordoma reported to be 15.8 years as compared with 4.1 years for the nonchondroid chordoma
 - Some studies have found no statistical differences in the survival of patients with chondroid chordoma as compared with conventional chordoma, and current opinion is that the conventional chordoma and chondroid chordoma have similar survival rates.
- Existence of chondroid chordoma distinct from low-grade chondrosarcoma has been questioned.
- Separation as a distinct variant of chordoma has been based on immunohistochemical differences between chordoma (S100 protein, epithelial markers, brachyury positive, and D2-40 negative) and chondrosarcoma (S100 protein and D2-40 positive and epithelial markers and brachyury negative)
- Expected immunohistochemical reactive pattern not consistently identified in all cases
- Diagnostic approach may include:
 - Chondroid chordoma for those tumors, showing admixture of conventional chordoma and chondrosarcoma *with* immunoreactivity for epithelial markers anywhere in the tumor
 - Chondrosarcoma for those tumors showing admixture of conventional chordoma and chondrosarcoma *without* immunoreactivity for epithelial markers anywhere in the tumor.

Dedifferentiated Chordoma

- Defined as the presence of conventional or chondroid chordoma with associated sarcomatous component:

- Sarcomatous component most often includes features of undifferentiated pleomorphic sarcoma, but may rarely be fibrosarcoma, osteosarcoma, chondrosarcoma, and rhabdomyosarcoma.
- Rare malignancy; represent less than 6% of all chordomas
- May occur:
 - As a de novo neoplasm
 - Years following radiotherapy for a conventional chordoma (may be considered as postradiation sarcoma)
 - In the absence of prior treatment (i.e., radiotherapy) years after diagnosis and surgical management only of a conventional chordoma
 - Based on the above, theories proposed for the development of dedifferentiated chordomas include spontaneous transformation, radiation induction, and collision tumors.
- Immunohistochemistry (see [Table 10-10](#)):
 - Conventional and chondroid chordoma elements:
 - S100 protein, cytokeratin, EMA, brachyury, E-cadherin positive
 - Podoplanin (D2-40) negative
 - Dedifferentiated (sarcomatous) component:
 - Absence of S100 protein, cytokeratin, EMA, brachyury, E-cadherin
 - Vimentin positive
- Aggressive tumor type:
 - Lethal over relatively short time periods with death often occurring within 1 year of diagnosis
 - Local recurrence and distant metastases, the latter including to the lungs:
 - Metastatic disease may include only conventional chordoma, only sarcomatous component, or both components.

Follicular Dendritic Cell Sarcoma/Tumor (FDCS) ([Fig. 10-48](#))

Definition: Neoplasm of spindled to ovoid cells showing morphologic and phenotypic features of follicular dendritic cells.

Clinical

- Rare tumor
- No gender predilection; typically a tumor of adults:
 - Marked female predominance for inflammatory pseudotumor-like variant
- Usually presents with painless lymphadenopathy most often in the cervical neck region and, less often, in the axillary region
- Extranodal sites of occurrence include:
 - Mucosal sites of the upper aerodigestive tract:
 - Most frequently involves the tonsil and pharynx
 - Other less common sites of occurrence include the palate, soft tissue, and thyroid gland.

- Intra-abdominal sites
- Skin, intestines, soft tissues, mediastinum, lung, and breast
- Clinical presentation of head and neck sites includes enlarging, painless mass that may be associated with dysphagia or other obstructive phenomenon.
- Occur in association with Castleman disease in about 10% to 20% of patients:
 - Most often it is Castleman disease of the hyaline vascular type, and less frequently, the plasma cell type
 - Castleman disease may precede FDCS or the two lesions occur simultaneously.
 - Presence HMGIC rearrangement, a member of the high mobility group protein family, by combined immunocytologic-cytogenetic approach in anti-CD21 reactive follicular dendritic cells has confirmed that a clonal proliferation of follicular dendritic cells occurs in the hyaline vascular variant of Castleman disease and also provides a possible molecular pathway explaining stromal overgrowths and stromal neoplasms developing from this disorder
 - An increased incidence in patients who have been treated for long-standing schizophrenia has been reported.
- Inflammatory pseudotumor-like variant of FDCS:
 - Purportedly a distinctive variant
 - Differs from conventional FDCS by its:
 - Marked female predominance
 - Selective localization in intra-abdominal sites, especially the liver and spleen
 - Frequent presence of systemic symptoms
 - Indolent behavior despite an intra-abdominal location
 - Dispersed distribution of tumor cells and prominent lymphoplasmacytic infiltration and consistent association with EBV
 - Unclear whether these tumors represent a true FDCS or a variant of inflammatory pseudotumor
 - FDCS in other organs are consistently EBV negative and HHV-8 negative.

Pathology

Gross

- Usually well circumscribed and solid
- In the mucosa of the upper aerodigestive tract are usually polypoid with an intact surface epithelium; medium size of about 5 cm but may range widely in size from a few centimeters to as large as 20 cm as might occur in retroperitoneum

Histology

- In lymph nodes, there is partial or complete effacement of the nodal architecture.

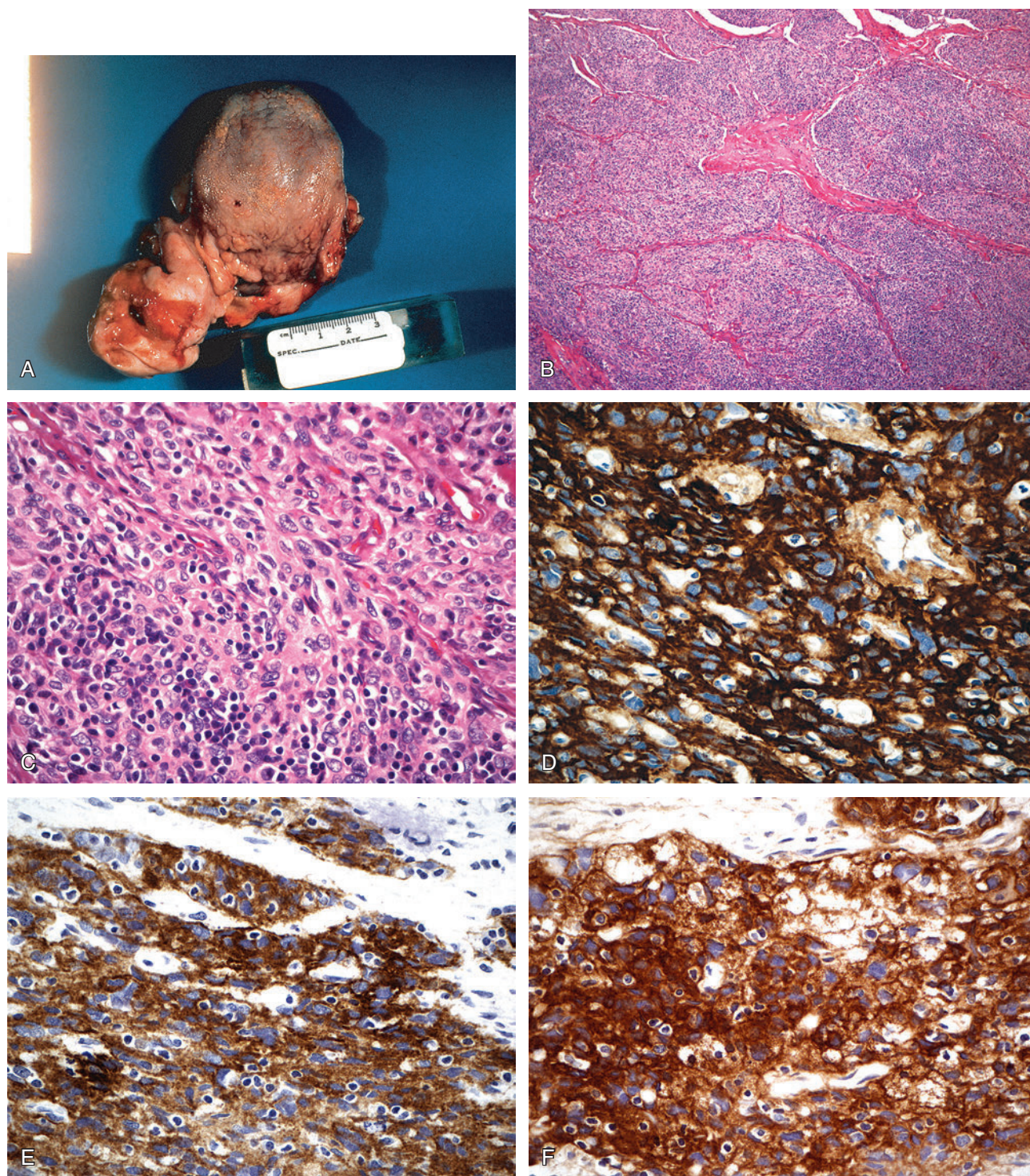


Fig. 10-48. Follicular dendritic cell sarcoma.

A, Postmortem specimen of a large submucosal that originated in the palatine tonsil. **B**, Submucosal cellular proliferation with diffuse to focally fascicular and whorled growth. **C**, Cellular proliferation composed of round to oval to elongated (spindle-shaped) nuclei with vesicular or granular-appearing chromatin and indistinct cell borders; immunoreactivity is present for **(D)** CD21, **(E)** CD23, and **(F)** CD35.

- In mucosal sites of the upper aerodigestive tract there is usually a submucosal cellular proliferation.
- Growth characteristics include diffuse, storiform, fascicular, and whorled.
 - Uncommonly there may be fluid-filled cystic spaces, some in a perivascular location resembling thymoma or amyloid change.
- Cellular proliferation includes oval to spindle-shaped cells with round to oval, uniform-appearing, elongated nuclei with vesicular or granular-appearing chromatin, inconspicuous nucleoli, and pale to slightly eosinophilic cytoplasm with indistinct borders.
- Scattered multinucleated giant cells may be identified; pseudonuclear inclusions may be present.
- Absent to scattered mitotic figures (0 to 10 mitoses per high-power fields) can be found but atypical mitoses, significant pleomorphism, and necrosis are usually absent; however, in some cases marked nuclear pleomorphism with increased mitoses, atypical mitotic figures and necrosis (confluent foci) may be identified.
- A background lymphocytic infiltrate either as individual cells or in clusters can be identified throughout the tumor, and often in a perivascular (cuffing) location; occasional germinal centers can be identified.
- Immunohistochemistry:
 - Positive for one or more follicular dendritic markers including CD21, CD35, CD23
 - In addition, consistent expression is present for follicular dendritic cell-specific markers (e.g., Ki-M4P, CAN.42)
 - Diffuse strong staining for clusterin identified in 100% of cases, including cases that were negative for traditional markers (CD21, CD23, CD35), but classified based on characteristic ultrastructural features (see below):
 - Staining for clusterin is useful in classification of dendritic cell tumors, particularly when the more common markers of follicular dendritic cells are not expressed.
 - Usually reactive for vimentin, fascin, desmoplakin, HLA-DR, and epidermal growth factor receptor (EGFR)
 - Variably reactive for epithelial membrane antigen (EMA)
 - EMA reactivity is present despite the fact that normal follicular dendritic cells are EMA negative.
 - Variable reactivity for S100 protein, CD68
 - Typically negative for cytokeratins, CD45, CD20, although exceptionally these markers may be present
- Consistently negative for CD1a, CD3, CD34, CD79a, CD30, melanocytic markers, desmin, and vascular markers
- EBV negative (except in the inflammatory pseudotumor-like variant) and human herpesvirus-8 negative
- Proliferation indices by Ki67 range from 1% to 25%.
- Electron microscopy:
 - Presence of complex interdigitating (villous) cytoplasmic processes or extensions, often joined through numerous cell junctions, including well-formed desmosomes
- Cytogenetics and molecular genetics:
 - Gene rearrangement studies have revealed germline configuration for the immunoglobulin heavy chain and T-cell receptor β , δ , and γ genes.

Differential Diagnosis

- Wide variety of tumor types, including (but not necessarily limited to) carcinoma, melanoma, sarcoma, lymphoma, and other dendritic cell tumors (e.g., Langerhans cell granulomatosis, interdigitating dendritic cell tumor):
 - Interdigitating dendritic cell tumor/sarcoma (IDCT) consistently expresses S100 protein and vimentin, shows variably weak reactivity for CD 68, lysozyme, and CD45, and is negative for CD21, CD23, CD35, CD1a, Langerin, cytokeratins, EMA, CD30, and CD34.
 - Rare examples showing mixed morphology of FDCS and interdigitating dendritic cell sarcoma
 - In general, an extensive immunohistochemical work-up is indicated to exclude the other tumor types and in establishing the diagnosis of FDCS.

Treatment and Prognosis

- Treatment includes surgical excision with or without adjunctive therapy (i.e., radiotherapy, chemotherapy).
- Overall behavior is rather indolent and has been likened to low-grade sarcomas:
 - From 40% to 50% of patients develop local recurrence after a latency period of several years
 - Distant metastasis may occur but is considered uncommon:
 - Common sites of metastasis include lymph nodes, lung, and liver.
- Death due to local recurrence and/or distant metastasis may occur.
- At least 10% to 20% of patients ultimately die of disease, often after a long period of time.
- Poorer prognosis associated with:
 - Intra-abdominal presentation
 - Significant cytologic atypia (high-grade features)

- Extensive coagulative necrosis
- High proliferative index
- Larger size (greater than 6 cm)
- Lack of adjuvant therapy has a poorer prognosis

- Rare malignancy
- More commonly occurs in the sinonasal tract (see Section 1)
- Histologic and immunohistochemical similar to that seen in sinonasal counterparts

Leiomyosarcoma (LMS)

Definition: Malignant neoplasm with smooth muscle differentiation.

- LMS is covered in greater detail in the section on the sinonasal tract.
- For more complete discussion see Section 1, Sinonasal Tract.

Liposarcoma

Definition: Malignant neoplasm with adipocyte cell differentiation.

- For more complete discussion see Section 6, Larynx.

Malignant Peripheral Nerve Sheath Tumors (MPNST)

Definition: Malignant tumor of peripheral nerves or having differentiation along the lines of various elements of the nerve sheath.

Synonyms: Malignant schwannoma; neurogenic sarcoma; neurofibrosarcoma

- For more complete discussion see Section 4, Neck.

Angiosarcoma

Definition: Malignant neoplasm with endothelial cell differentiation.

- For more complete discussion see Section 1, Sinonasal Tract.

Teratocarcinosarcoma (Malignant Teratoma) of the Pharynx

Definition: Malignant neoplasm composed of cells from all three germ layers.

SECONDARY NEOPLASMS TO THE PHARYNX

- Metastatic tumors to the pharynx occur via hematogenous spread and may occur in the setting of a known primary neoplasm outside the head and neck or may represent the initial manifestation of disease (i.e., occult metastasis):
 - More often, metastasis to the upper aerodigestive tract is part of widely metastatic disease from a known index malignant tumor.
 - Metastatic disease to these sites may occur at presentation of the primary tumor or may occur years following treatment for the primary tumor.
- Virtually every conceivable malignancy may metastasize to the upper aerodigestive tract:
 - For gnathic metastases, the most common primary malignant tumors are (in descending order): breast, kidney, lung, prostate, thyroid, colon, other
 - For soft tissue metastases:
 - Females: breast, other
 - Males: lung > kidney, skin, other

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Anatomy of the Neck

ANATOMY OF THE NECK

- Prominent landmarks in the neck are the hyoid bone, thyroid cartilage, trachea, and sternocleidomastoid muscles.
- The neck is divided into the anterior and posterior triangles by the sternocleidomastoid muscles (Fig. 11-1):
 - Anterior triangle:
 - Lateral limit: anterior border of the sternocleidomastoid muscle
 - Medial limit: anatomic midline of the neck
 - Above: lower border of the mandible
 - Subdivisions of the anterior triangle include:
 - Carotid triangle
 - Submandibular (submaxillary) triangle
 - Inferior carotid (muscular) triangle
 - Submental or suprahyoid triangle
 - Contents of the anterior triangle include:
 - Common carotid artery with its internal and external branches
- Cranial nerves IX through XII
- Internal jugular vein
- Superficial and deep cervical lymph nodes
- Posterior triangle:
 - Anteromedial: posterior border of the sternocleidomastoid muscle
 - Posteriolateral: anterior border of the trapezius muscle
 - Below: the clavicle
- Contents of the posterior triangle include:
 - Subclavian artery
 - External jugular vein
 - Branches of the cervical plexus
 - Cranial nerve XI (accessory)
 - Numerous lymph nodes, including the posterior cervical and supraclavicular lymph nodes

FURTHER READING

References may be accessed online at ExpertConsult.com.

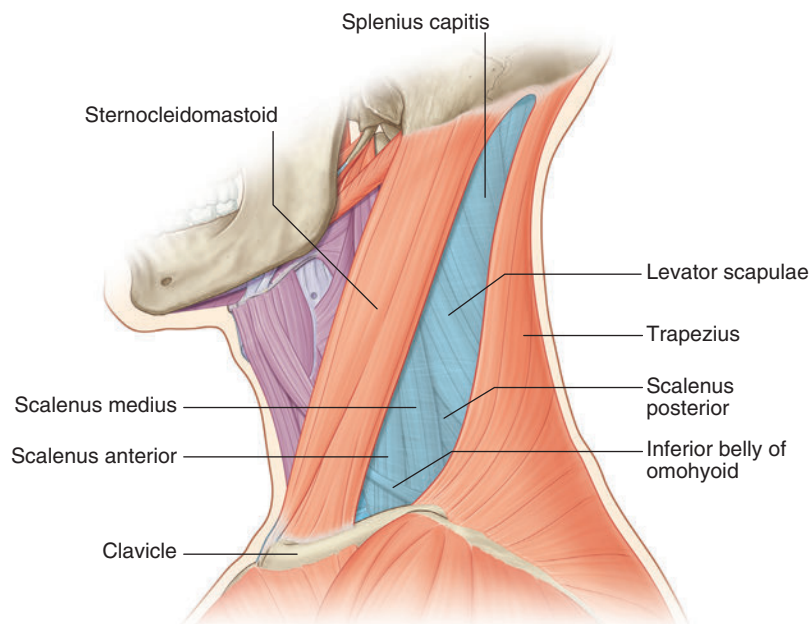


Fig. 11-1. The triangles of the neck.

(From *Standring S: Gray's anatomy*, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone.)

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Non-Neoplastic Lesions of the Neck

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE NECK (Box 12-1)

BOX 12-1 Classification of Non-neoplastic Lesions of the Neck

Developmental Cystic Anomalies

- Branchial cleft anomalies
- Thyroglossal duct cyst
- Cervical thymic cyst
- Bronchogenic cyst
- Dermoid cyst
- Others

Infectious and Related Diseases/Lesions

- Bacterial and mycobacterial
- Fungal

- Viral
- Protozoal
- Sarcoidosis
- Others

Reactive, Inflammatory, and Tumor-like Lesions

- Mesenchymal lesions
- Others

BENIGN CYSTIC LESIONS OF THE CERVICAL NECK

- Cystic lesions of the neck represent a diverse group of lesions listed in [Box 12-2](#).

BRANCHIAL ANOMALIES (BA)

Definition: Congenital malformations related to the branchial apparatus.

Embryology

- Branchial apparatus appears around the fourth week of gestation and consists of a paired series of six arches, five pouches, and five clefts or grooves.
- Embryologic development of the head and neck structures can be classified through the development of the branchial apparatus, including arches (mesoderm), clefts (ectoderm), and pharyngeal pouches (endoderm) ([Table 12-1](#)).

BOX 12-2 Non-Neoplastic Cystic Lesions of the Neck

Cystic Lesions of the Cervical Neck

Developmental Cysts

- Branchial cleft cyst
- Thyroglossal duct cyst
- Cervical thymic cyst
- Bronchogenic cyst
- Parathyroid cyst
- Others

- Branchial apparatus gives rise to most of the important structures of the head and neck, including the face, oral cavity, ears, and neck.

Clinical

- No gender predilection; occur at any age, but most commonly become evident in young adults
- Predominantly occur in the lateral neck along the anterior portion of the sternocleidomastoid muscle:
 - Also seen in the area around the external ear, in the external auditory canal, and in the parotid gland
- Generally, occur as an isolated phenomenon but may be familial or may rarely be associated with other congenital defects, including:
 - Malformed auricles
 - Hearing abnormalities
 - Patent ductus arteriosus
 - Tear duct atresia

Branchial Cysts, Sinuses, and Fistulas

- Branchial cleft anomalies are divided according to the branchial apparatus involved and are further divided into cysts, sinuses, or fistulas:
 - *Cysts* are epithelial-lined structures that may occur as an isolated lesion or may occur in association with a sinus or fistula.

TABLE 12-1 Branchial Apparatus and Derivatives

	Arches (Mesoderm)	Pharyngeal Pouches (Endoderm)	Clefts (Ectoderm)
First	<i>Cartilage bar (Meckel cartilage):</i> Ramus and body of mandible Maxilla Incus (body) Malleus (head and neck) Part of pinna of ear <i>Muscles and ligaments:</i> Temporalis Masseter Pterygoids (medial and lateral) Digastric (anterior belly) Mylohyoid Tensor tympani Tensor veli palatini Anterior two thirds of tongue Sphenomandibular lig. Anterior malleolar lig. <i>Innervation:</i> Trigeminal (maxillary and mandibular divisions) <i>Vasculature:</i> Facial artery	Epithelial lining of the middle ear cavity, inner part of the tympanic membrane, eustachian tube, mastoid air cells	Epithelial lining of the external auditory canal, and outer part of the tympanic membrane
Second	<i>Cartilage bar (Reichert cartilage):</i> Incus (long process) Malleus (manubrium) Stapes (long process) Styloid process Hyoid (lesser horn and upper body) Part of pinna of ear <i>Muscles and ligaments:</i> Facial (auricularis, buccinator, frontalis, occipitalis, orbicularis oculi, oris platysma) Digastric (posterior belly) Stapedius Stylohyoid Stylohyoid lig. <i>Innervation:</i> Facial <i>Vasculature:</i> Lingual branch of ext. carotid artery	Epithelial lining of the tonsillar fossa and palatine tonsil	None
Third	<i>Cartilage bar:</i> Hyoid (lower body and greater horn) <i>Muscles and ligaments:</i> Stylopharyngeus Palatopharyngeus Posterior third (base or root) of tongue <i>Innervation:</i> Glossopharyngeal <i>Vasculature:</i> Internal carotid artery	Inferior parathyroid glands, thymus, pyriform sinus	None
Fourth	<i>Cartilage bar:</i> Thyroid <i>Muscles and ligaments:</i> Cricothyroid Levator palatini Posterior third (base) of tongue <i>Innervation:</i> Vagus (superior laryngeal branch) <i>Vasculature:</i> Arch of aorta Right subclavian artery	Superior parathyroid glands C-cells of ultimobranchial body	None
Fifth and sixth	<i>Cartilage bar:</i> Cricoid Arytenoids <i>Muscles and ligaments:</i> Intrinsic muscles of larynx Upper esophageal muscles <i>Innervation:</i> Vagus (recurrent laryngeal) <i>Vasculature:</i> Pulmonary arteries Ductus arteriosus	C-cells of ultimobranchial body (5th pharyngeal pouch) 6th pharyngeal pouch: none	None

- *Sinuses* are tracts with a single opening; the opening may be to skin, representing a branchial cleft or ectodermally derived sinus tract (cutaneous sinus tract), or to mucosa, representing a branchial pouch or endodermally derived sinus tract (mucosal sinus tract).
- *Fistulas* are tracts with two openings, which can be cutaneous or mucosal.

Clinical

- Cysts present as nontender, fluctuant masses in appropriate locations; cysts may become inflamed and abscesses may develop, potentially associated with dysphagia, dyspnea, or stridor.
- Sinuses and fistulas are associated with discharge of mucoid and/or purulent secretions from the tract opening.
- Up to 10% of cases may be bilateral.
- Histogenesis of branchial cleft anomalies is controversial:
 - Among the structures proposed as the origins for these anomalies include the branchial apparatus (considered to represent the origin for these abnormalities), salivary gland inclusions, and thymic duct.

First Branchial Anomalies (Fig. 12-1)

Clinical

- In comparison to second branchial anomalies, first branchial anomalies are uncommon, representing from 1% to 8% of all branchial apparatus defects.
- Typically occur in the area of the external ear and may include cysts, sinuses, and fistulas.
- First branchial anomalies may be identified in a variety of locations, including pre-, post-, or infra-auricular, at the angle of the jaw, associated with the earlobe, and in the external auditory canal or involving the parotid gland.
- Involvement of the external auditory canal may result in otalgia or otorrhea.
- Parotid involvement may result in an intra- or periparotid mass that may be mistaken for a parotid gland tumor.

Pathology

Gross

- Majority of first BA are cysts, representing more than two thirds (68%) of these anomalies:
 - Appear as solitary cystic lesions without an associated sinus tract
- Sinuses and fistulas equally make up the remainder of these lesions:
 - Fistula tract in first branchial anomalies may extend from the skin over or through the parotid and open in the external auditory canal.

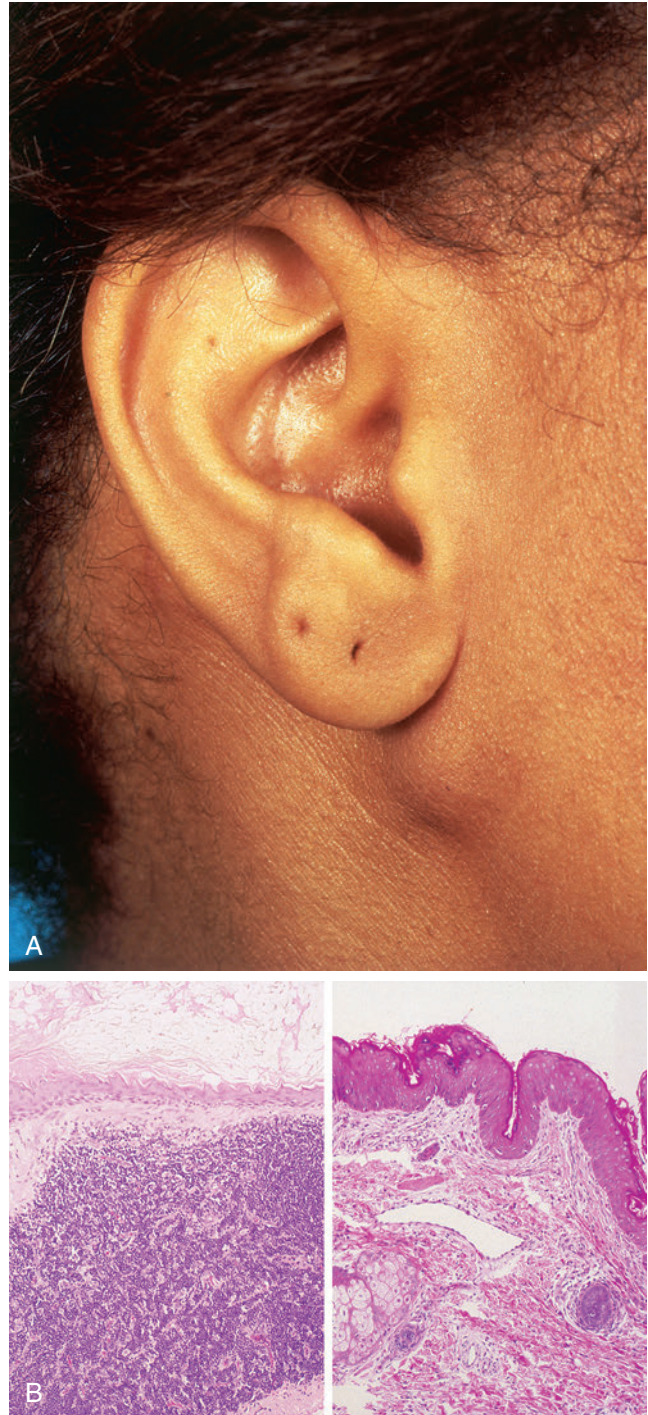


Fig. 12-1. First branchial cleft cyst.

A, Infra-auricular, freely movable, and fluctuant mass.

B, Left, First branchial cleft cyst (Work type I) is composed of keratinizing squamous epithelial lining devoid of adnexal structures; a dense lymphoid infiltrate is seen in the cyst wall; **Right,** first branchial cleft cyst (Work type II) is composed of keratinizing squamous epithelial lining with associated adnexal structures.

Microscopic

- First branchial lesions can be divided into two types as defined by Work, which are referred to as type I and type II lesions:
 - Type I:
 - Contains only ectodermal elements, including keratinizing squamous epithelium without adnexal structures (i.e., hair follicles, sebaceous glands, sweat glands) or cartilage, thereby duplicating the membranous external auditory canal
 - Represents a first cleft anomaly only
 - Typically are located medial, inferior, or posterior to the concha and pinna
 - Sinuses parallel the external auditory canal and end in a blind sac at the level of the mesotympanum.
 - External auditory canal is intact and hearing is normal.
 - Type II:
 - Have ectodermal and mesodermal elements, including keratinized squamous epithelium, cutaneous adnexa, and cartilage, thereby duplicating the external auditory canal and pinna
 - Typically localize to a point just below the angle of the mandible
 - Sinus or fistula tracts extend upward over the angle of the mandible through the parotid gland toward the external auditory canal.
- Type II anomalies are more intimately associated with the parotid gland than type I anomalies, although parotid tissue may be found in association with type I sinus or fistula tracts.
- Tracts associated with type II defects may terminate short of the external auditory canal or may open up in the external auditory canal near the junction of the cartilaginous portion and osseous portion of the canal; communication with the middle ear is uncommon.
- For either type I or type II defects, an associated prominent lymphoid component is not usually present, contrasting with second BA; only when inflamed or infected will there be an associated lymphoid component.
- Some authorities recommend that, due to the overlapping histology between Work types I and II, all first branchial cleft anomalies be classified only as cysts, sinuses, or fistulas.
- Unless inflamed, a prominent lymphoid component is not seen, contrasting to the findings that can be seen in second branchial cysts.

Differential Diagnosis

- Epidermoid cyst
- Dermoid cyst

Treatment and Prognosis

- Regardless of the histology, complete surgical excision is the preferred treatment:
 - Inadequate excision results in recurrence and increased risk of infection.
 - Incision and drainage are indicated in cases in which abscesses have developed, and in this situation complete surgical excision must wait until resolution of the infection.
 - Type II anomalies are often intimately associated with the parotid gland, necessitating a superficial parotidectomy to ensure complete excision.
 - Although there is no consistent relationship between the tract and the facial nerve as it courses through the parotid gland, exposure and dissection of the nerve and its branches are required in Work type II anomalies.

Second Branchial Anomalies

(Figs. 12-2 through 12-4)

Synonym: Second branchial cysts also referred to as (cervical) lymphoepithelial cyst

Clinical

- Accounts for the majority of the branchial apparatus anomalies, representing from 92% to 99% of all cases
- Equal gender predilection; typically occurs in the third through fifth decades of life:
 - Uncommon in patients older than 50 years of age:
 - Less than 3% of cysts present after the age of 50
 - Lateral neck cysts in patients 50 years of age and older should prompt diagnostic consideration for a metastatic cystic squamous cell carcinoma (see Chapter 13).
- Occur along the anterior border of the sternocleidomastoid muscle; most common at the level of the angle of the mandible
- Present as a painless, fluctuant neck mass that may increase in size in the face of an upper respiratory tract infection, at which time they may become painful
- Cysts are much more common than fistulas.
- Sinuses and fistulas are most often identified at birth or in early childhood, presenting as a small opening above the clavicle through which mucoid secretions may be expressed; these are divided into three types:
 - Incomplete external, with an external (cutaneous) but no internal (pharyngeal) opening
 - Incomplete internal, with a pharyngeal but no cutaneous opening

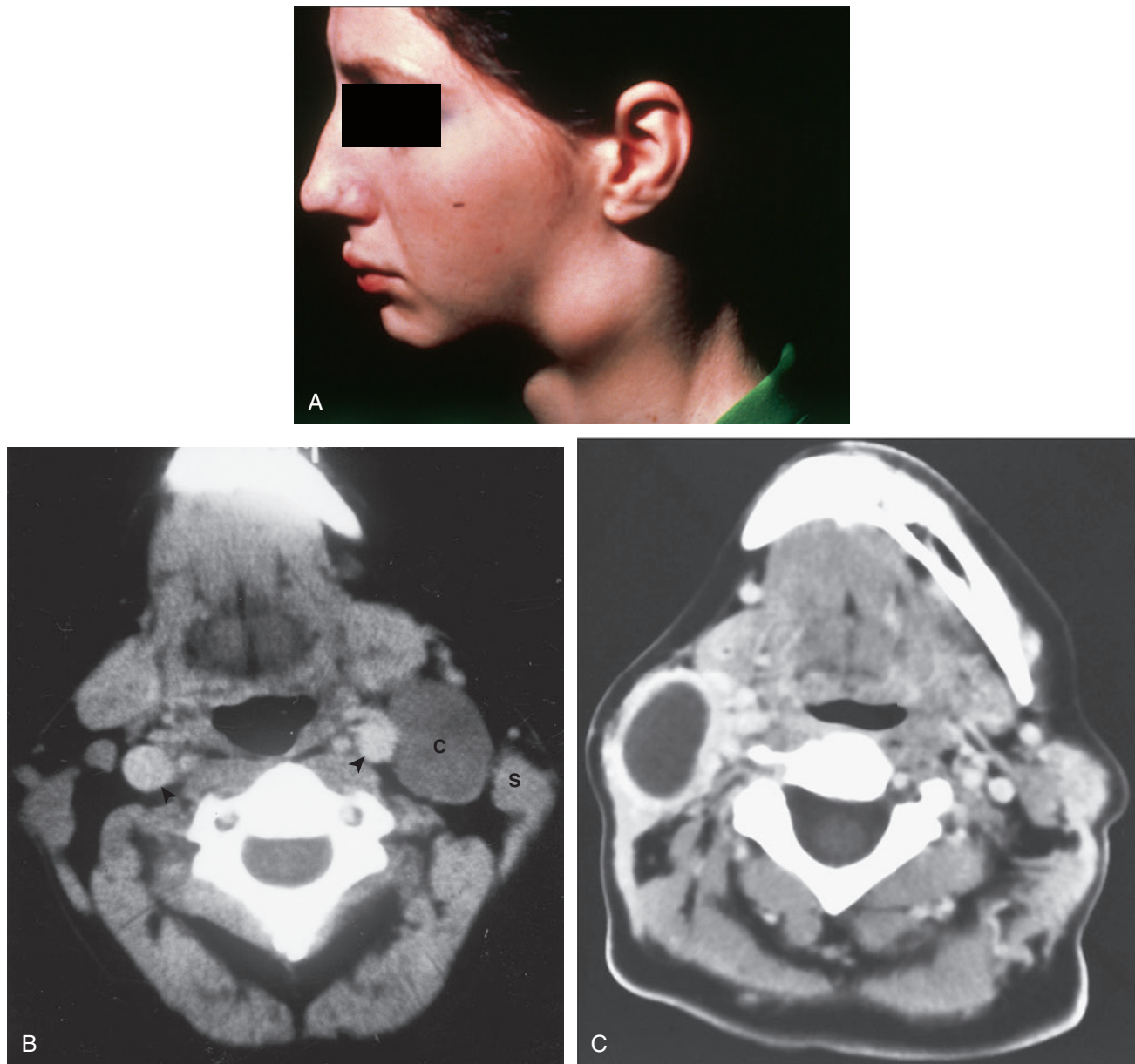


Fig. 12-2. Second branchial cleft cyst.

A, Second branchial cleft cyst occurring along the anterior border of the sternocleidomastoid muscle as painless, fluctuant neck mass. **B**, Axial CT, enhanced: fluid-filled cyst (c) anterior to the left sternocleidomastoid muscle (s). The thin-walled cyst does not enhance after administration of intravenous contrast. Jugular veins (arrowheads). **C**, Axial contrast-enhanced CT shows a cyst in the right neck with a fairly thick, enhancing rim. The cyst is behind the submandibular gland, lateral to the carotid sheath structures, and along the anterior margin of the sternocleidomastoid muscle. This was an infected second branchial cleft cyst. (**B**, **C**, from Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 2244, Fig. 37-14, D.)

- Complete, with pharyngeal and cutaneous openings:
 - The cutaneous opening is seen anywhere along the anterior border of the sternocleidomastoid muscle from the hyoid bone to the sternum, with the epithelial tract coursing cephalad,

between the internal and external carotid arteries, over cranial nerves IX and XII, deep to the posterior belly of the digastric muscle and terminating close to the middle constrictor muscle or with an internal opening in the pharyngeal wall and/or tonsillar region.

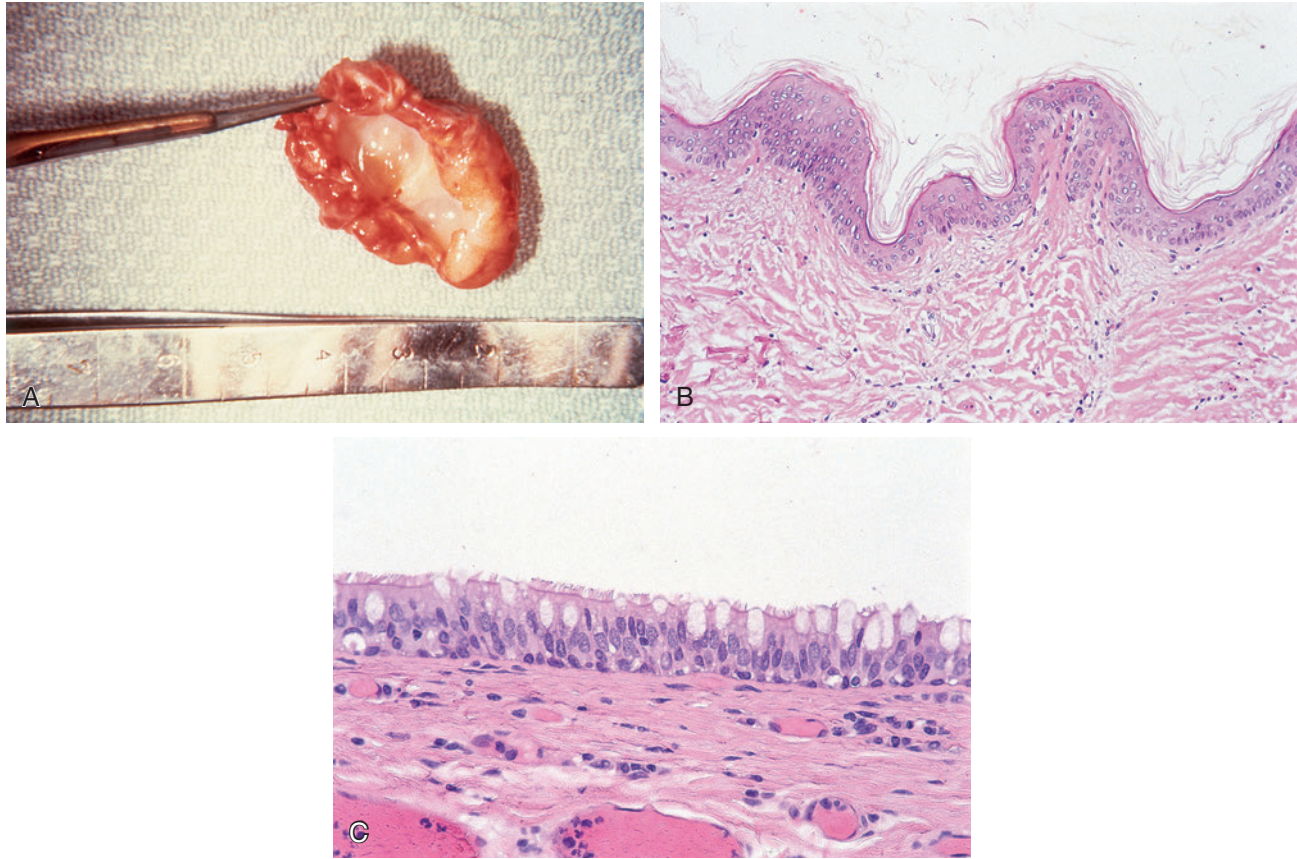


Fig. 12-3. Second branchial cleft cyst.

A, Resected, smooth-walled second branchial cleft cyst. Histologically, branchial cleft cyst wall lining epithelium is typically lined by **(B)** stratified squamous epithelium and **(C)** less frequently a purely ciliated columnar epithelium. Although not depicted here, the cyst wall typically contains a nodular or diffuse lymphoid infiltrate often with germinal centers.

- Radiology:
 - Cysts appear as well-defined, low-density lesions surrounded by a thin, uniform wall.
 - Noninflamed cysts have no or minimal CT mural enhancement.
 - Infected cysts have increased CT density of the central fluid with rim enhancement and poorly defined cyst wall.
 - Fistulas or sinus tracts may extend either toward the skin surface, suprathyroid fossa, as well as between the internal and external carotid arteries.
- Histogenesis of second branchial cleft cysts is controversial:
 - Among the structures proposed as the origins for these anomalies include the branchial apparatus (considered to represent the origin for these abnormalities), salivary gland inclusions, and thymic duct.

Pathology

Gross

- Cysts are thin-walled cystic structures filled with cheesy material or serous, mucoid, or purulent fluid; nodular excrescences may be seen lining the cyst wall.

Histology

- Cyst lining epithelium is predominantly a stratified squamous epithelium seen in approximately 90% of cases; less frequently a purely columnar epithelial lining or a mixed lining may be seen.
- Cyst wall typically contains a nodular or diffuse lymphoid infiltrate often with germinal centers.
- Fibrosis and granulation tissue may be prominent and even replace the surface epithelium in cases associated with repeated infections.

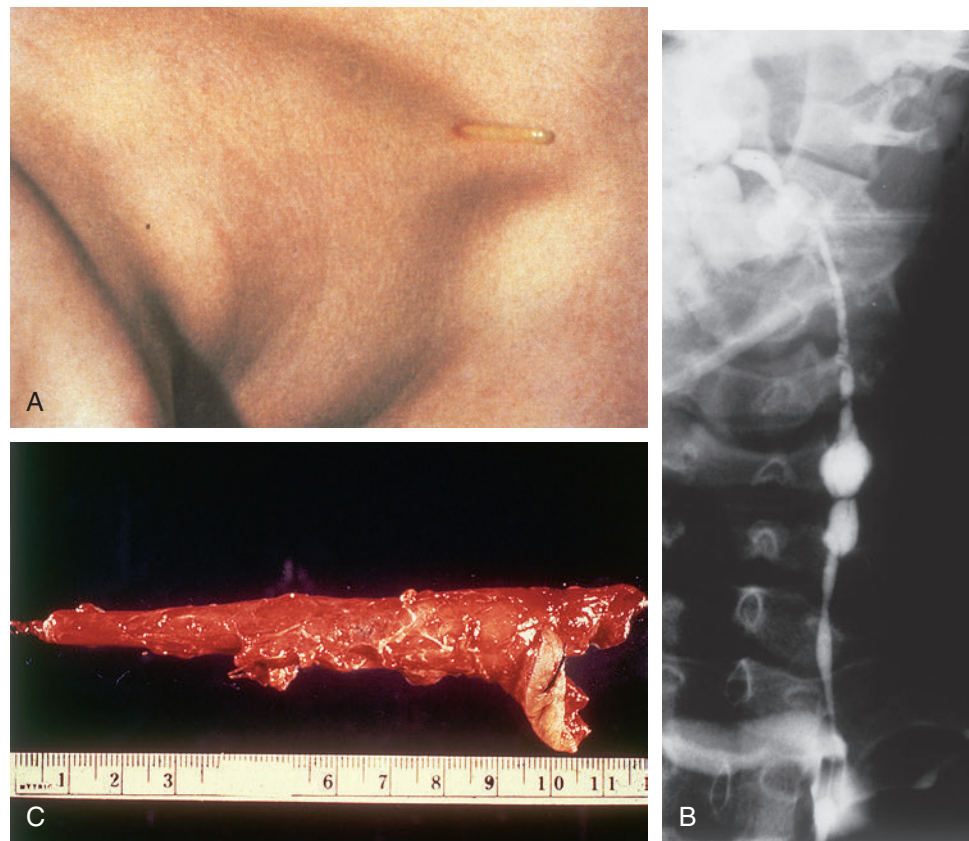


Fig. 12-4. Branchial cleft fistula.

A, Cutaneous drainage in lower neck above the clavicle. **B**, Radiologic imaging showing a "complete" sinus tract extending uninterruptedly from the pharynx to its cutaneous opening. **C**, Surgically excised fistula tract, including its cutaneous end (*lower right*).

- Fistulas often are composed of a stratified squamous epithelium associated with the external segments and a columnar epithelium with the internal segments.
- There is no evidence of thymic (thymic cyst) or thyroid tissue (thyroglossal duct cyst).

Immunohistochemistry

- Cytokeratin(s) positive
- p16 negative:
 - Branchial cleft cysts can exhibit focal patchy weak to strong reactivity limited to the superficial squamous epithelium.
 - Absence of p16 may be helpful in distinguishing branchial cleft cyst from metastatic oropharyngeal nonkeratinizing squamous cell carcinoma but it is not as useful in cases of metastatic keratinizing squamous cell carcinoma as the latter are typically p16 negative.
- Thyroglobulin, TTF1, PAX8 negative
- Low proliferation rate (less than 5%) by Ki67 (MIB1) staining

Differential Diagnosis

- Thymic cyst
- Thyroglossal duct cyst
- Metastatic cystic squamous cell carcinoma, including HPV-associated and non-HPV-associated:
 - Absence of cytologic features of malignancy excludes the diagnosis of a metastatic cystic squamous cell carcinoma
 - Some examples of cystic metastatic squamous cell carcinoma may be composed of relatively bland cytomorphic features but even in such cases there are foci of cytologically atypical/malignant epithelial cells characterized by pleomorphic nuclei and increased mitotic activity:
 - Increased proliferation rate as determined by Ki67 (MIB1) staining would be present in metastatic carcinoma and absent in branchial cyst.
 - Diffuse and strong (nuclear and cytoplasmic) p16 immunoreactivity, representing a surrogate

marker for HPV-16, would confirm the diagnosis of metastatic cystic HPV-associated carcinoma of oropharyngeal origin, differentiating it from a branchial cleft cyst, which should be nonreactive for p16.

- p16 may be overexpressed in almost 50% of benign branchial cleft cysts potentially limiting the diagnostic utility of p16 in this setting; in such an occurrence molecular testing (in situ hybridization, PCR) would be necessary to confirm presence of HPV and the malignant nature of the cyst.
- Confusion and controversy exist between the diagnosis of metastatic cystic squamous cell carcinoma and that of a carcinoma arising in a branchial cleft cyst (so-called branchial cleft carcinoma or branchiogenic carcinoma); criteria for the diagnosis of a branchiogenic carcinoma include:
 - The tumor occurs along the line extending from a point anterior to the tragus along the anterior border of the sternocleidomastoid muscle to the clavicle.
 - Histology supports origin from a branchial cleft-derived structure (i.e., situated in the lateral aspect of the neck).
 - Histology supports carcinoma arising in the wall of an epithelial-lined cyst.
 - A minimum of 5-year follow-up demonstrates no evidence of a primary source for this neoplasm.
 - Despite the fulfillment of these criteria, it is highly unlikely that carcinoma arises in a branchial cleft cyst; rather, these cystic squamous cell carcinomas take origin from a primary tumor in Waldeyer tonsillar ring:
 - Primary (Waldeyer ring) neoplasm may be so small as to defy clinical detection but nevertheless is capable of metastasizing.
 - Histology demonstrates partial or complete replacement of the lymph node by an epithelial-lined structure with central cystic change; the epithelium varies from areas that are bland, composed of uniform cells lacking pleomorphism, crowding, or loss of polarity, to overtly malignant-appearing epithelium composed of pleomorphic cells with increased cellularity, mitoses, and a loss of polarity.
- Metastatic papillary thyroid carcinoma:
 - Absence of architectural and cytomorphologic features associated with papillary thyroid carcinoma would differentiate metastatic papillary thyroid carcinoma from second BA.
 - Cystic metastatic papillary thyroid carcinoma to the neck may occur in the absence of a known history of a primary thyroid carcinoma and/or as an occult metastasis. Further, the primary thyroid-based carcinoma may be very small and clinically

difficult to detect. Most often the metastasis originates from the ipsilateral thyroid lobe. Given the clinical scenario of unsuspected/unknown primary thyroid carcinoma, the histology of the neck mass may include a flattened/attenuated epithelial lining without papillary architecture histologically simulating the appearance of a branchial cleft cyst:

- Attention to the nuclear features may alert the pathologist to the possible presence of metastatic papillary thyroid carcinoma.
- In suspect cases, thyroglobulin, thyroid transcription factor 1 (TTF-1), and PAX8 reactivity would be present in metastatic papillary thyroid carcinoma and absent in BAs:
 - Thyroglobulin reactivity is the single best marker for lesions of thyroid follicular epithelial cell origin and is generally absent in all other (nonfollicular epithelial cell origin) lesions.
 - TTF-1 reactivity is not unique for follicular epithelial-derived lesions of the thyroid but can be present in other lesion types, including (but not limited to) medullary thyroid carcinoma and pulmonary adenocarcinoma; in contrast, thyroglobulin reactivity is a dedicated marker for lesions of thyroid follicular epithelial cell origin and represents the preferred immunomarkers in the evaluation for metastatic carcinomas of thyroid follicular epithelial cell origin.
 - Regardless of the histologic (nuclear) features, thyroid tissue located in lymph nodes situated lateral to the great neck vessels represents metastatic thyroid carcinoma; see Section 8, Thyroid Gland, for more complete discussion.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
 - Depending on the extent of the fistula tract, a tonsillectomy may be needed.

Third Branchial Anomalies

- Third BAs are rare.
- May present as recurrent neck abscesses associated with stridor or as recurrent episodes of acute suppurative unilateral thyroiditis
- A sinus or fistula open externally anterior to the lower third of the sternocleidomastoid muscle:
 - If complete, the internal opening of the sinus or fistula is in the piriform sinus following passage of the tract along the carotid sheath penetrating the thyrohyoid membrane cranial to the superior laryngeal nerve.

- Cysts occur anywhere along the sinus tract but are most commonly found in the region of the laryngeal ventricle or in the anteroinferior cervical triangle.

Pathology

Histology

- Cysts are lined by a stratified squamous epithelium or ciliated epithelium; an associated marked lymphocytic cell infiltrate may be present.
- Thymic tissue, derived from the third branchial cleft pouch, may or may not be present.

Treatment and Prognosis

- Complete surgical resection of a third BA (cyst, sinus, fistula) is the preferred treatment and is necessary to prevent recurrence:
 - Surgical procedure may require a subtotal thyroidectomy.

Fourth Branchial Anomalies

- Fourth BAs are extremely rare.
- The majority of patients presents before the age of 20 years.
- Clinical manifestations of fourth BAs are similar to those of third BAs, including recurrent neck abscesses or recurrent episodes of acute suppurative unilateral thyroiditis.
- Almost all fourth BAs are sinuses that may originate from the piriform sinus:
 - The sinus tract usually has an internal opening at the apex of the piriform sinus caudal to the superior laryngeal nerve, descends translaryngeally beneath the thyroid cartilage, exiting the larynx near the cricothyroid joint below the inferior constrictor muscle, and then continues superficial to the recurrent laryngeal nerve ending in the paratracheal region or in the thyroid gland.
- Like third BAs, fourth BAs may or may not include thymic tissue.
- Complete surgical resection of a fourth BA is the preferred treatment and is necessary to prevent recurrence:
 - Surgical procedure may require a subtotal thyroidectomy.

THYROGLOSSAL DUCT CYST

Definition: Persistence and cystic dilatation of the thyroglossal duct in the midline of the neck.

Embryology

- The thyroid gland is the first endocrine gland to appear during embryonic development.
- Thyroid gland derives from three primordium, the median anlage, and lateral anlages:
 - Median anlage develops around the 24th day of gestation as a small, median endodermal thickening on the primitive pharynx; this thickening forms a diverticulum, which is attached to the tongue by a narrow tube, the thyroglossal duct; its opening in the base of the tongue constitutes the foramen cecum.
 - Proximal opening persists as the foramen cecum of the tongue
- As a result of further cellular proliferations, the hollow thyroid diverticulum obliterates and divides into the right and left lobes, connected by the isthmus around the seventh week of gestation.
- During development the thyroid descends and assumes a definitive position in the anterior neck; by this time the thyroglossal duct degenerates.

Clinical/Pathology

- See Section 8, Thyroid Gland, for a more complete discussion including illustrations.
- Majority of cases occurs in the midline of the neck above the thyroid isthmus but below the level of the hyoid bone:
 - Thyroglossal duct cysts are nearly always connected to the hyoid bone.
 - Uncommonly, thyroglossal duct cysts may occur lateral to midline but do not occur in the lateral portion of the neck (i.e., lateral to the jugular vein).
- Clinical presentation of an uninfected thyroglossal duct cyst is usually that of an asymptomatic midline neck mass:
 - Mass typically moves upward on swallowing.
 - Inflamed or infected thyroglossal duct cysts may be associated with tenderness and pain.
 - Extrinsic airway compression in neonates with apnea, cyanosis, and respiratory compromise may uncommonly occur.
- Thyroglossal duct cysts are smooth-walled, cystic structures that usually measure less than 2 cm.
- In noninflamed cysts, the cyst lining is respiratory (columnar) epithelium but may also include squamous epithelium.
- Presence of thyroid tissue in the cyst wall varies and may be dependent on the extent of specimen sampling; in generally, thyroid tissue can be found in more than 60% of the cases.
- Thyroid tissue may be normal, hyperplastic, and nodular or neoplastic (see below).
- Surgery is the preferred treatment; en bloc surgical resection of the cyst, the middle third of the hyoid bone (Sistrunk procedure), and the suprahyoid tract up to the foramen cecum; this extended surgery prevents recurrence:
 - Adequate surgery results in cure with low, if any, recurrences.

- Benign and malignant neoplasms may occur in the setting of a thyroglossal duct cyst.
- C-cell-related lesions, including medullary carcinoma, do not occur in thyroglossal duct cysts due to the different embryologic derivation of the C-cells.

CERVICAL THYMIC CYST (Fig. 12-5)

Definition: Cervical thymic tissue sequestered from the main thymic gland during its embryologic descent:

- Sequestered thymic tissue may be solid (so-called accessory cervical thymic tissue) or cystic (cervical thymic cyst).

Embryology and Anatomy

- Thymus develops in the sixth week of gestation, arising primarily from the third branchial pouch (mesoderm); the fourth branchial pouch may provide minimal contribution to the development of the thymus.

- Thymic primordia descend in the neck along the course of the carotid sheath.
- Connection of the paired primordia to the pharynx is retained by the thymopharyngeal ducts.
- During the eighth week of gestation the thymic primordia fuse in the midline of the neck and then descend into the mediastinum.
- Failure of descent or failure to involute results in thymic abnormalities, including cervical thymic cyst.
- Cervical thymic cysts are considered to be congenital, although mediastinal thymic cysts are thought to be acquired.

Clinical

- Cervical thymic cysts are uncommon.
- Occur slightly more often in men; the majority of cervical thymic cysts (67%) occurs during the first decade of life with the rest occurring in the second to third decades:
 - Rarely, cervical thymic cysts occur in adults.

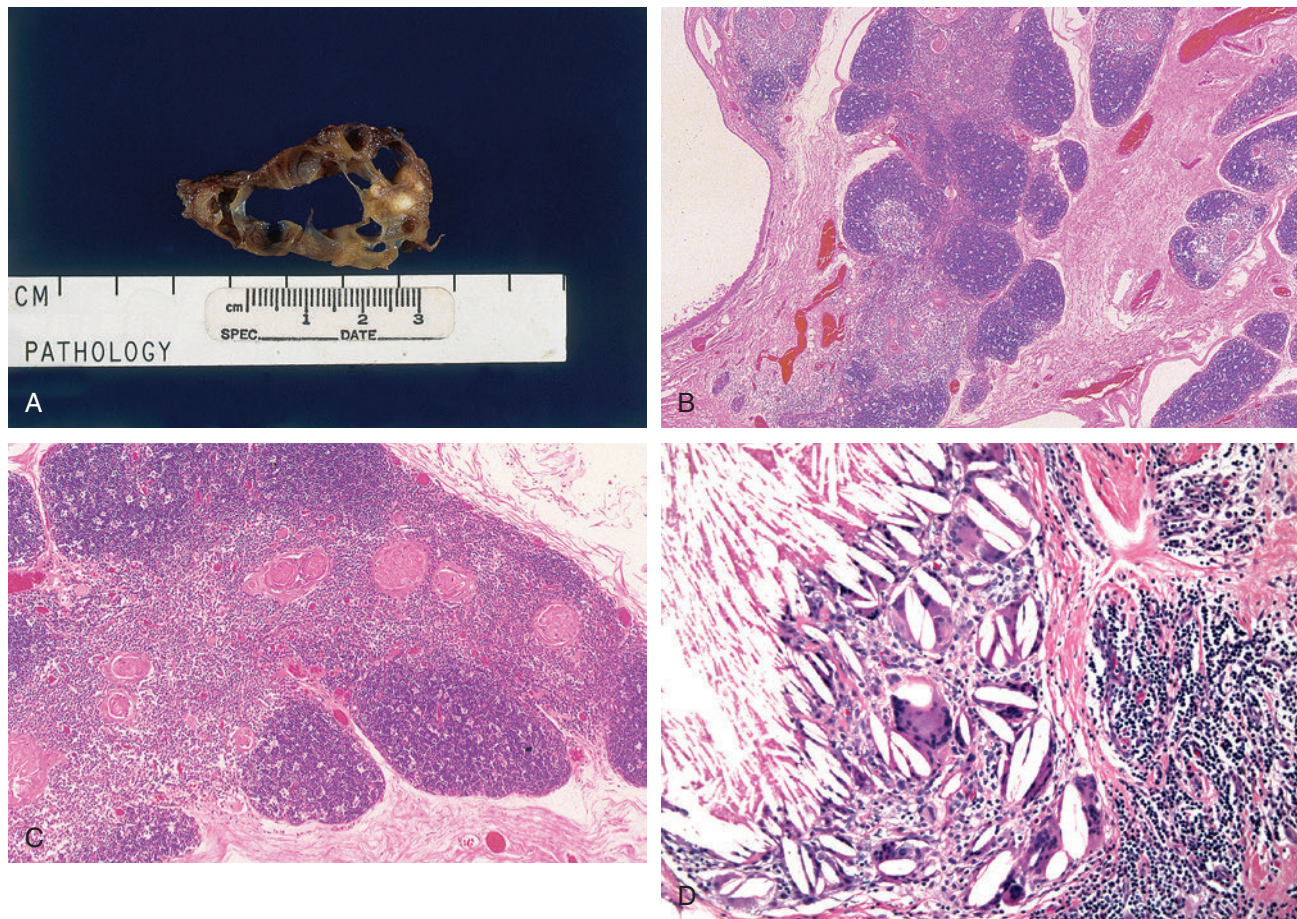


Fig. 12-5. Cervical thymic cyst.

A, Multilocular smooth walled cystic proliferation with focal solid areas. **B** and **C**, Epithelial lined cyst with identification of lymphoid follicles and Hassall corpuscles within the cyst wall. **D**, A rather common finding in thymic cysts is the presence of cholesterol granulomas.

- Found anywhere between the angle of the mandible and the sternum, including the lateral and midline neck
- Majority of patients presents with a slow-growing, painless neck mass that may transiently increase in size during a Valsalva movement; uncommonly, the clinical presentation may include dyspnea, dysphagia, hoarseness, or pain.
- Rarely (if ever) associated with a sinus or fistula
- May represent an isolated cystic lesion in the neck, may extend into the mediastinum, or may be in continuity with an intrathoracic thymus gland:
- Radiology:
 - Connections to intrathoracic structures result in abnormal radiologic findings.
 - Appearance of cervical thymic cyst on CT can be characteristic:
 - The course of the descent of embryologic thymic tissue in the neck to the mediastinum indicates the potential site of deposition of an ectopic cervical thymic cyst.
 - In a child, a cystic lesion that has an intimate relationship to the carotid sheath is likely to be a thymic cyst.

Pathology

Gross

- Cysts are unilocular or multilocular, usually contain clear, serous-appearing fluid, and may measure up to 15 cm in greatest dimension.
- Cyst wall lining is smooth or trabeculated; the cyst wall varies in thickness.

Microscopic

- Cyst wall is lined by cuboidal, columnar, or squamous epithelium, and by definition the wall contains thymic tissue, including characteristic epithelial islands referred to as Hassall corpuscles, as well as lymphoid follicles; the identification of thymic tissue may require extensive sampling.
- When cysts become infected, the surface epithelium may be replaced by fibrous tissue.
- Secondary alterations may often include the presence of foreign body giant cell reaction and/or cholesterol granulomas.
- Due to the fact that the third and fourth branchial pouches give rise to the inferior and superior parathyroid glands, respectively, parathyroid parenchyma may be found in thymic cysts.

Differential Diagnosis

- Branchial cleft cyst:
 - Clinical and histopathologic differences should allow for differentiating a branchial cleft cyst from a thymic cyst.

- Cervical thymic cysts and branchial cleft cysts tend to occur in the anterior cervical triangle.
- In contrast to cervical thymic cysts, which occur typically in the first decade of life, have a slight female predilection, generally are not associated with sinuses or fistulas, and have thymic tissue in their walls
- Branchial cleft cysts tend to occur in the third decade of life, have equal gender predilection, commonly are associated with cysts and fistulas, and have lymphoid tissue in their wall.

Treatment and Prognosis

- Treatment for cervical thymic cyst is simple surgical excision, which is curative.
- Cervical thymic cysts have no potential to undergo malignant transformation, which is not true of mediastinal thymic cysts.

BRONCHOGENIC CYST (Fig. 12-6)

Definition: Bronchogenic cysts originate from buds or diverticula that separate from the foregut during the formation of the tracheobronchial tree:

- The majority of bronchogenic cysts are found in the mediastinum or in the lungs and are referred to as mediastinal bronchogenic cysts.
- Bronchogenic cysts may occur outside the mediastinum, with the skin or subcutaneous tissue representing the most common site of occurrence (referred to as cutaneous bronchogenic cysts), particularly near the suprasternal notch (manubrium sterni), and much less often in the lower neck or shoulder.

Synonym: Bronchial cyst

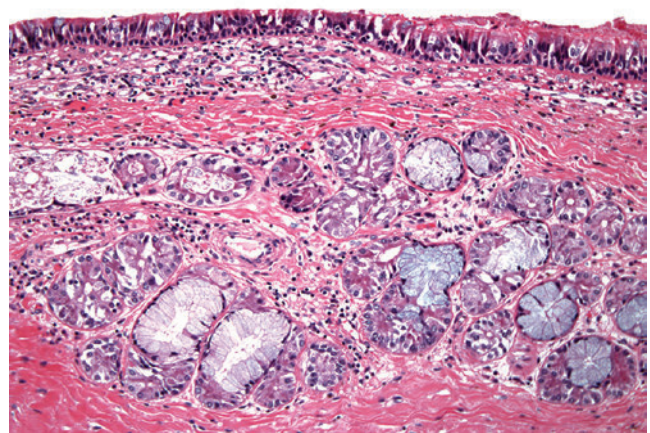


Fig. 12-6. Bronchogenic cyst.

Lower neck cystic lesion lined by ciliated respiratory epithelium; bronchial (sero mucous) glands, as well as cartilage and smooth muscle are present.

Clinical

- No gender predilection; occur over a wide age range from birth to the sixth decade of life:
 - Average age of occurrence is in the third and fourth decades
- In the very young, mediastinal bronchogenic cysts may produce life-threatening respiratory distress with stridor and airway obstruction.
- In adults, mediastinal bronchogenic cysts are usually asymptomatic and identified by routine chest x-rays.
- Radiology:
 - Solitary, smooth, round-to-ovoid cyst in the mediastinum (middle, posterior, or superior) closely associated with the trachea or major bronchi
 - An occasional example may be found within the wall of the bronchus, trachea, or esophagus, attached to the pericardium, or even within the outflow tract of the right ventricle or the interatrial septum.
 - Rare examples have been reported in the pharyngeal region or lateral neck.
- Rare examples of congenital anomalies have been reported in association with mediastinal bronchogenic cyst, but typically these lesions are not associated with developmental anomalies.

Pathology

Gross

- Cysts are typically unilocular and thin-walled and may measure up to 15 cm in greatest dimension.
- Cysts have a smooth-appearing lining that on occasion may be trabeculated; the cyst content varies from serous fluid to serosanguineous to mucoid and, if infected, purulent material.

Microscopic

- Cyst lining usually is a ciliated respiratory epithelium and bronchial (mucous) glands, as well as cartilage and smooth muscle are usually present.
- Squamous metaplasia of the surface epithelium may be identified.

Differential Diagnosis

- Branchial cleft cyst
- Thyroglossal duct cyst
- Dermoid cyst
- Teratoma

NOTE:

- Presence of (sero)mucous glands, cartilage, and smooth muscle in bronchogenic cyst allows differentiation from a branchial cleft cyst and thyroglossal duct cyst, in which these components are not found.

- Presence of thyroid follicles in a thyroglossal duct cyst would assist in differentiating it from a bronchogenic cyst.
- Absence of hair and relative absence of squamous epithelium in bronchogenic cyst would assist in differentiating it from a dermoid cyst.
- Teratomas contain an array of tissue types that are not present in bronchogenic cysts.

Treatment and Prognosis

- Excision of the cyst via an external approach generally is curative.
- Malignant transformation of cervical (and mediastinal) bronchogenic cysts has not been described to date.

DERMOID CYST (Fig. 12-7)

Definition: Benign developmental cystic anomaly originating from ectoderm and mesoderm but not endoderm.

Clinical

- Head and neck are fairly common sites of occurrence for dermoid cysts, accounting for approximately 34% of all dermoid cysts.
- No gender predilection; may occur over a wide age range but are most common in the first decade of life
- In the head and neck, dermoid cysts are predominantly subcutaneous lesions but may occur in other (mucosal) sites:
 - Among the more common sites of occurrence in the head and neck are the orbit, oral cavity, and nasal cavity.

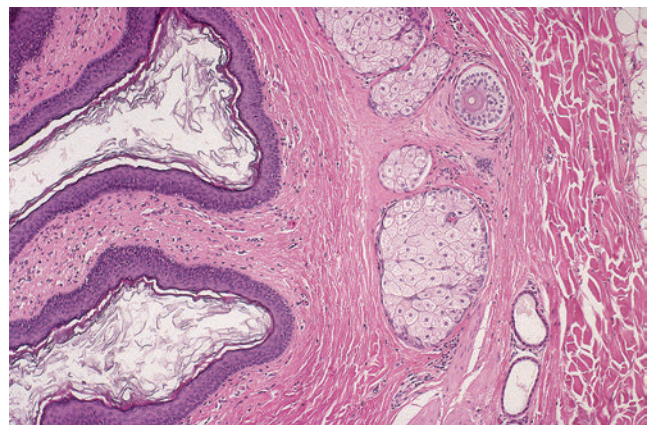


Fig. 12-7. Dermoid cyst.

Cyst is lined by stratified squamous epithelium with cutaneous adnexal structures (e.g., sebaceous glands) in the fibroconnective tissue wall. The adnexal structures may also include eccrine glands or apocrine glands (not shown), which are features not found in epidermoid cysts.

- Less common sites of occurrence include the mandible, maxilla, middle ear, neck (midline or near midline), upper neck, and near the thyroid cartilage or associated with the thyroid gland, suggesting a thyroid nodule.
- Dermoid cysts are slow-growing and not associated with pain.

Pathology

Gross

- Thin-walled cysts containing gray-white friable material and range in size from a few millimeters to 12 cm in greatest dimension; internal aspect of has a smooth lining.

Histology

- Dermoid cysts are lined by stratified squamous epithelium with cutaneous adnexal structures (e.g., hair shafts, sebaceous glands, eccrine glands, or apocrine glands) in the fibroconnective tissue wall.

- Cyst content may include keratin or sebaceous material.
- Dermoid cysts may rupture, resulting in a (florid) foreign body giant cell reaction.

Differential Diagnosis

- Epidermal inclusion cyst:
 - Like dermoid cysts, epidermal inclusion cysts are lined by stratified squamous epithelium and are filled with keratin.
 - In contrast to dermoid cysts, the epidermal inclusion cysts lack adnexal structures in the cyst wall.
- Teratomas:
 - Represent true neoplasms composed of tissues from all three germ layers

Treatment and Prognosis

- Simple surgical excision is the preferred treatment and is curative.

INFECTIOUS DISEASES OF THE NECK

- Infections of the oral cavity, nasopharynx, oropharynx, and cervical neck include fungal, viral, bacterial, mycobacterial, protozoal, and other infectious agents.
- The breadth of infectious diseases of these sites is extensive, and this section focuses on select infectious diseases of these anatomic sites.

MYCOBACTERIAL AND OTHER GRANULOMATOUS DISEASES

Mycobacterial Infections

Definition: Infectious disease caused by *Mycobacterium*, a microorganism classified in the order Actinomycetales and the family Mycobacteriaceae.

- Mycobacteria include:
 - *Mycobacterium tuberculosis*:
 - Strict aerobic bacillus measuring from 1 to 4 μm in length
 - Microorganism identification requires special stains and is based on the capability of forming stable mycolate complexes with certain aryl methane dyes resisting decolorization by acid alcohol referred to as acid-fastness
 - Tubercle bacilli that make up the *M. tuberculosis* complex (MTBC) and are the

etiologic agents in human tuberculosis include:

- *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium bovis* bacille Calmette-Guérin (BCG), *Mycobacterium caprae*, *Mycobacterium pinnipedii*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium canettii*.
- Nontuberculous (“atypical”) mycobacteria are also referred to as mycobacterium other than *tuberculosis* (MOTT):
 - Some of the nontuberculous mycobacteria include *M. avium-intracellulare*, *M. scrofulaceum*, *M. kansasii*, and *M. ulcerans*.

Clinical

- Mycobacterial infection of the head and neck is relatively uncommon.
 - Overall the incidence of *Mycobacterium tuberculosis* has decreased over the past five decades:
 - Of reported cases of extrapulmonary mycobacterial infections, 12% affect head and neck sites.
 - With the advent of the acquired immunodeficiency syndrome (AIDS) associated with immunocompromised conditions, there has been an increased incidence of infection by mycobacteria, especially caused by the nontuberculous (“atypical”) mycobacteria.

- Nontuberculous (“atypical”) mycobacteria (MOTT):
 - Only some are human pathogens.
 - In the immune-competent patient, the nontuberculous mycobacteria do not cause pulmonary disease but often cause localized disease such as lymphadenitis (e.g., scrofula, see below) or a subcutaneous infection.
 - In the immune-compromised patient these microorganisms cause pneumonia and potentially disseminated (systemic) disease.
 - In the head and neck, all sites may be involved but infection usually involves the lymph nodes; less often involvement may include the tonsils, pharynx, oral cavity, sinonasal region, larynx, salivary glands, middle ear, and temporal bone.
 - Head and neck involvement may result as a complication of pulmonary involvement (direct infection via expectoration of infected sputum), via hematogenous or lymphatic spread, or as an isolated occurrence as a primary upper aerodigestive tract infection.
 - May occur in patients with coexisting carcinoma (e.g., squamous cell carcinoma)
 - Symptoms vary according to the site(s) infected and include a neck mass (cervical adenopathy), sore throat, nasal obstruction, hoarseness, dysphagia.
 - Clinical work-up in suspected cases includes chest x-ray, tuberculin skin test, microbiologic cultures, and molecular diagnostics:
 - Reference (“gold”) standard is microbiologic cultures and identification on specific media:
 - Allows for testing of drug susceptibility
 - Depending on the media used, incubation (i.e., growth) takes from 2 to as long as 6 to 10 weeks (or longer), potentially resulting in delay in diagnosis and treatment.
 - Media used in testing for tuberculosis includes:
 - Solid media includes Löwenstein-Jensen
 - Liquid media include the nonradiometric BACTEC Mycobacteria Growth Indicator Tube 960 (MGIT) system, which has replaced radiometric BACTEC 460 system susceptibility testing.
 - Liquid media-based culture is more sensitive and growth is more rapid as compared with solid media:
 - In liquid media growth may occur from 1 to 3 weeks as compared with 3 to 8 weeks for solid media.
 - Most rapid method for diagnosis of tuberculosis is the nucleic acid amplification test for direct detection of MTBC in clinical specimens (e.g., sputum, fluids, and tissue [formalin-fixed paraffin embedded]):
 - Sensitive as cultures but requires significantly less time to perform and result (4 to 5 hours)
 - Allows for more rapid diagnosis but these tests do not differentiate species in MTBC
 - Can detect as few as 10 organisms in clinical specimens as compared with more than 10,000 organisms required for positive identification on smears
 - Available tests include Amplified Mycobacterium Tuberculosis Direct Test (Gen-Probe Inc.) and AMPLICOR Mycobacterium Tuberculosis Test (Roche Diagnostics).
 - Sensitivity of nucleic acid amplification tests generally slightly lower for nonrespiratory specimens but useful in the diagnosis of extra-pulmonary tuberculosis
 - Susceptibility testing:
 - Once an isolate is available, drug susceptibility testing is performed.
 - New diagnostics using liquid media-based cultures are more sensitive and growth is more rapid as compared with solid media.
 - For MTBC, the initial isolate from every patient should be tested to all primary drugs:
 - Agar proportion is the standard method of testing susceptibility of MTBC to antituberculosis agents:
 - Isolates showing greater than 1% resistance to a single concentration of drug considered resistant to that drug
 - Liquid-based system allowing for quicker turnaround time for results as compared to agar is recommended:
 - Results available 5 to 7 days after bottles inoculated with MTBC
 - Molecular methods, including polymerase chain reaction, developed for rapid detection of mutations known to be associated with drug resistance including multidrug-resistant organisms (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).
- Lupus vulgaris:
 - Represents mucocutaneous lesions of secondary tuberculosis
 - Results from hematogenous or lymphatic spread of disease
 - Nose and cheeks are the most common sites of occurrence.
 - May be ulcerative and destructive:
 - Destructive nature thought to be due to hypersensitivity to the microorganisms in patients with strong immune responses
 - Association in approximately 40% of cases with upper aerodigestive tract lesions and cervical lymphadenitis
 - Healing may result in scarring and deformity of involved region.

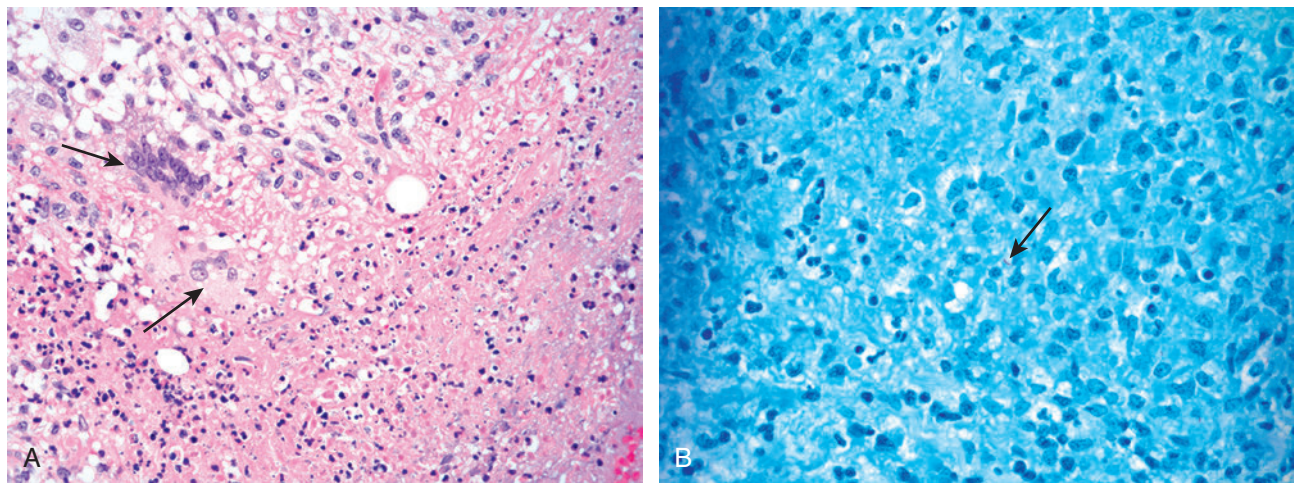


Fig. 12-8. *Mycobacterium tuberculosis*.

A, The histologic hallmark of mycobacterial disease in the presence of normal immune status includes the presence of caseating (necrotizing) granulomatous inflammation characterized by well-formed granulomas including central areas of necrosis surrounded by histiocytes and multinucleated giant cells. **B**, By acid-fast bacilli (AFB) stain the microorganisms appear beaded with a red color. The microorganisms may be difficult to identify and may be located in necrotic foci and/or within multinucleated giant cells.

Pathology (Fig. 12-8)

Histology

- In the presence of normal immune status, changes include caseating (necrotizing) granulomatous inflammation in which the granulomas are:
 - Well formed
 - Surrounded by histiocytes and multinucleated giant cells
 - Composed of central areas of necrosis
- May also include noncaseating type of granuloma formation
- Histochemistry:

NOTE: Microorganisms are often extremely difficult to identify and may defy detection despite an extensive and diligent effort:

 - Identification of microorganisms requires special stains and is based on the capability of forming stable mycolate complexes with certain aryl methane dyes referred to as acid-fastness
 - Depending on the stain (acid-fast bacilli [AFB], Ziehl-Neelsen), the microorganisms when identified appear beaded with a red or purple color
 - May be located in necrotic foci and/or within giant cells

Differential Diagnosis

- Sarcoidosis
- Other infectious necrotizing granulomatous diseases

Treatment and Prognosis

- The cornerstone for treatment is multidrug (antituberculous) therapy:
 - First line:
 - Isoniazid, rifampicin, ethambutol, and pyrazinamide
 - Duration of 6 months:
 - 2-month intensive therapy with the four drugs
 - 4-month continued therapy with isoniazid, rifampicin
 - Second line:
 - Streptomycin, ethionamide, kanamycin, capreomycin, ofloxacin, rifabutin
- Among new cases of tuberculosis, approximately 5% worldwide are due to multidrug-resistant organisms (MDR-TB) defined as tubercle bacilli resistant to isoniazid and rifampin.
- Mismanagement of drugs used to treat MDR-TB can result in extensively drug-resistant tuberculosis (XDR-TB) defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable anti-tuberculosis agent.
- In association with AIDS, therapy is lifelong.

Scrofula (Fig. 12-9)

Definition: Cervical lymph node involvement by mycobacteria is referred to as scrofula.

Synonym: Scrofulous gumma



Fig. 12-9. Mycobacterial involvement of cervical lymph nodes (scrofula).

A, Unilateral, firm, red neck mass with focal ulceration of the skin. **B**, Extensive cutaneous ulceration. **C**, Histologic appearance includes replacement of the nodal architecture by caseating granulomas characterized by central necrosis surrounded by histiocytes and giant cells. **D**, Mycobacteria are extremely difficult to identify and require the aid of special histochemical stains (acid-fast bacilli [AFB] stain) with the microorganism appearing as a slender, beaded, red/purple rod seen here in a multinucleated giant cell.

Clinical

- More common in women than men; may occur over a wide age range but primarily affects children
- Most commonly involves high cervical lymph nodes in the region of the submandibular gland
 - Periparotid, periauricular, and submental lymph nodes may be involved but are much less often affected.
- Usually presents as a unilateral neck mass when caused by nontuberculous mycobacteria; bilateral involvement generally is related to systemic involvement caused by dissemination of *M. tuberculosis*
- Patients are afebrile.
- Causative microorganism may include *M. tuberculosis* but most commonly caused by nontuberculous mycobacteria (*M. scrofulaceum*, *M. avium-intracellulare*, *M. kansasii*)
- Although scrofula may be an isolated infection, it may also be the initial presentation in patients with pulmonary disease.
- May occur in patients with immune reconstitution inflammatory syndrome (IRIS):
 - IRIS represents a cohort of HIV-infected patients receiving combined antiretroviral therapy (cART).

Pathology

Gross

- Involved lymph nodes are enlarged and firm.
- Mucosal involvement appears as a granular exudate with or without associated ulceration; cutaneous ulceration may occur.

Histology

- Irrespective of the causative microorganism, the histologic picture of mycobacterial infection is the same.
- In the immune-competent host, the histologic hallmark of mycobacterial infection regardless of the causative microorganism is caseating (necrotizing) granulomatous inflammation characterized by:
 - Central necrosis surrounded by histiocytes and giant cells
- In up to 25% of cases of nontuberculous mycobacterial infections, a caseating granulomatous inflammatory response is not present.
- In the immune-compromised patient the typical caseating granulomatous inflammatory response may not be present; rather, diffuse sheets of foamy histiocytes are present within which are AFB-positive microorganisms.
- Histochemistry:

NOTE: Microorganisms are often extremely difficult to identify and may defy detection despite an extensive and diligent effort:

- Identification of microorganisms requires special stains and is based on the capability of forming stable mycolate complexes with certain aryl methane dyes referred to as acid-fastness.
- Depending on the stain (acid-fast bacilli [AFB], Ziehl-Neelsen), the microorganisms, when identified, appear beaded, showing a red or purple color.
- Cytogenetic and molecular genetics:
 - In situ hybridization and polymerase chain reaction have improved the diagnostic identification of mycobacterial organisms and, along with cultures, allow for differentiating *M. tuberculosis* from nontuberculous mycobacteria.

Differential Diagnosis

- Sarcoidosis
- Cat scratch disease

Treatment and Prognosis

- Treatment for scrofula caused by nontuberculous mycobacteria is surgical excision, which is considered curative:
 - Nontuberculous mycobacteria are nonresponsive to anti-mycobacterial tuberculosis medications.
- For infection caused by *M. tuberculosis*, treatment consists of antituberculous chemotherapy, including:
 - Isoniazid, streptomycin, or rifampin

Mycobacterial Spindle Cell Pseudotumor (Fig. 12-10)

Definition: Pseudoneoplastic spindle cell proliferation almost exclusively occurring in HIV-infected patients.

Synonyms: Mycobacterial pseudotumor; *M. avium-intracellulare* pseudotumor; spindled nontuberculous mycobacteriosis; histoid mycobacteriosis

Clinical

- Uncommon lesion
- No gender predilection; occurs over wide age range
- Almost always found in immune-compromised individual due to:
 - AIDS/HIV-positive patients
 - Patients receiving immunosuppressive therapy, including steroids
- Causative microorganism is *M. avium-intracellulare*
- Sites of involvement includes lymph nodes, as well as extranodal sites such as skin, spleen, brain, and bone marrow:
 - Rarely may occur in mucosal sites of the upper aerodigestive tract
- Presentation includes subcutaneous firm nodule or lymphadenopathy.

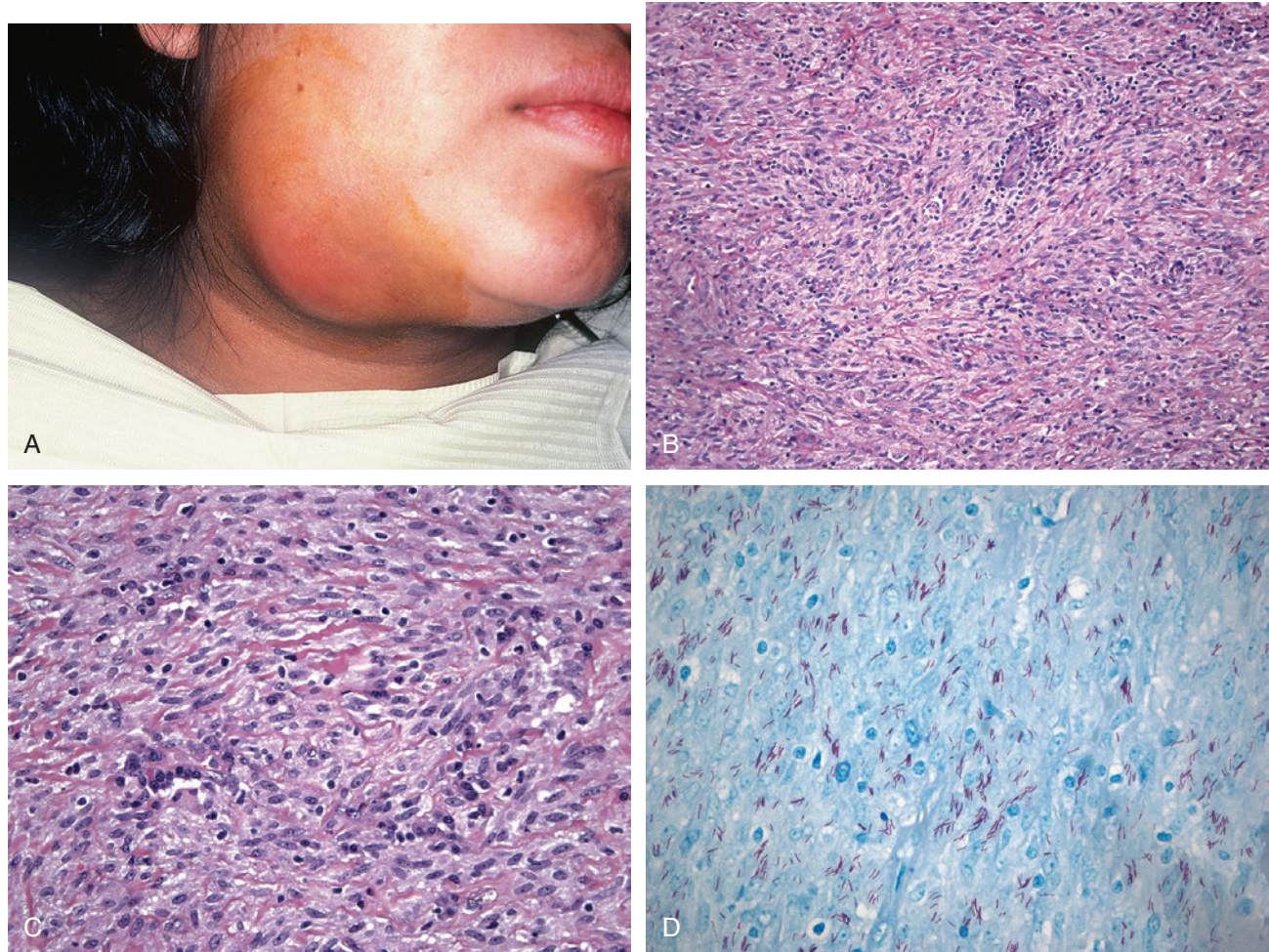


Fig. 12-10. Mycobacterial spindle cell pseudotumor.

A, Immunocompromised patient presenting with subcutaneous firm nodule. **B** and **C**, Cellular proliferation composed of bland-appearing, spindle-shaped cells in a storiform pattern with multinucleated giant cells and foamy histiocytes are not present. **D**, Special stains for mycobacteria (AFB) show the presence of numerous AFB-positive microorganisms within the cytoplasm of the spindle cells.

Pathology

Histology

- Cellular proliferation composed of bland-appearing, spindle-shaped cells in a storiform pattern.
- Multinucleated giant cells and foamy histiocytes are not present.
- Partial or complete effacement of nodal architecture
- Histochemistry:
 - Special stains for mycobacteria, including AFB and Ziehl-Neelsen, show the presence of numerous AFB-positive organisms within the cytoplasm of the spindle cells.
- Immunohistochemistry:
 - Spindle cells are CD68, lysozyme, α -antichymotrypsin, and vimentin positive.

- Based on the CD68 reactivity the spindle cells represent macrophages.
- S100 protein, desmin, and muscle-specific actin may be positive.
- CD31 and CD34 negative
- Cytogenetics and molecular genetics:
 - Polymerase chain reaction assists in identifying mycobacteria.

Differential Diagnosis

- Kaposi sarcoma:
 - May occur concomitantly (in same lymph node) as mycobacterial spindle cell tumor
 - Morphologic features that favor Kaposi sarcoma over mycobacterial spindle cell tumor include:
 - Prominent fascicular arrangement of spindle cells and slit-like spaces

- Absence of granular, acidophilic cytoplasm
- Presence of increased mitotic activity
- Presence of hyaline globules and extravasated red cells
- Immunohistochemical features seen in the spindle cells of Kaposi sarcoma that assist in differentiating it from mycobacterial spindle cell tumor include:
 - Reactivity for human herpesvirus-8 (HHV-8), also referred to as Kaposi sarcoma–associated herpesvirus (KSHV)
 - Reactivity for CD31 and CD34
 - Absence of CD68 and S100 protein, as well as muscle-specific actin and desmin
- Fibrohistiocytic tumor(s)
- Hodgkin disease, nodular sclerosing

Treatment and Prognosis

- Treatment guidelines are based on the species of mycobacteria and susceptibility testing of the isolate that, in some cases, would be modified because of the immune status of the patient or other concurrent therapy.
- If no isolate is obtained, recommendation would be to treat for tuberculosis:
 - Specific drugs chosen would depend on the likelihood of drug resistance based on demographic/epidemiologic factors.

Cervicofacial Actinomycosis

(Fig. 12-11)

Definition: Chronic granulomatous and suppurative disease caused by gram-positive, microaerophilic, and anaerobic bacteria, the most common isolate in humans causing disease being *Actinomyces israelii*:

- Actinomyces are endogenous saprophytic organisms in the oral cavity and tonsil.
- Actinomyces are often seen within tonsillar crypts, which represent a saprophyte and are unaccompanied by an inflammatory response.
- Disease is classified according to the anatomic site involved and includes cervicofacial, abdominal, and pulmonary.

Cervicofacial Actinomycosis

Clinical

- Cervicofacial actinomycosis is the most common form of disease and is thought to arise secondary to dental manipulation and/or trauma.
- No gender predilection; occurs in all age groups
- Neck and area around the angle of the mandible are the most common sites of occurrence; however,

clinical infection can occur anywhere in the head and neck.

- Most common symptom is that of a painless, slowly enlarging, indurated mass with or without suppuration; skin overlying the lesion has a characteristic purple color from which a draining sinus may be seen; fistulization is not uncommon.
- A definitive diagnosis is made bacteriologically; however, the organisms are difficult to culture.

Pathology

Histology

- Granulomatous reaction with central accumulation of polymorphonuclear leukocytes (abscess formation) and necrosis is identified.
- Within the abscess and enveloped by the neutrophils, microorganism colonies are seen:
 - Microorganisms form a characteristic appearance referred to as sulfur granules.
 - Granules are lobular, deep purple, and composed of a central meshwork of filaments that typically have eosinophilic club-shaped ends.
 - Sulfur granules can be identified in pus.
- Diagnosis can be made by fine-needle aspiration biopsy:
 - Smears and cell blocks of the aspirate may show characteristic colonies (sulfur granules) of actinomyces.
- Histochemistry:
 - Microorganisms stain best with gram and Gomori methenamine silver (GMS) stains.

Differential Diagnosis

- *Nocardia* infection

Treatment and Prognosis

- Intravenous penicillin G followed by oral penicillin is the preferred treatment.
- Patients allergic to penicillin can be given tetracycline.
- Prognosis is good if treated early.
- Osteomyelitis of the jaw is the most common complication; once infection reaches bone, tissue destruction may be extensive and involvement of the cranium, meninges, and brain may occur with lethal implications.

Sarcoidosis (Fig. 12-12)

Definition: Multisystem chronic granulomatous disease of unknown cause.

Clinical

- No gender predilection; occurs in all age groups but seen most commonly in young adults

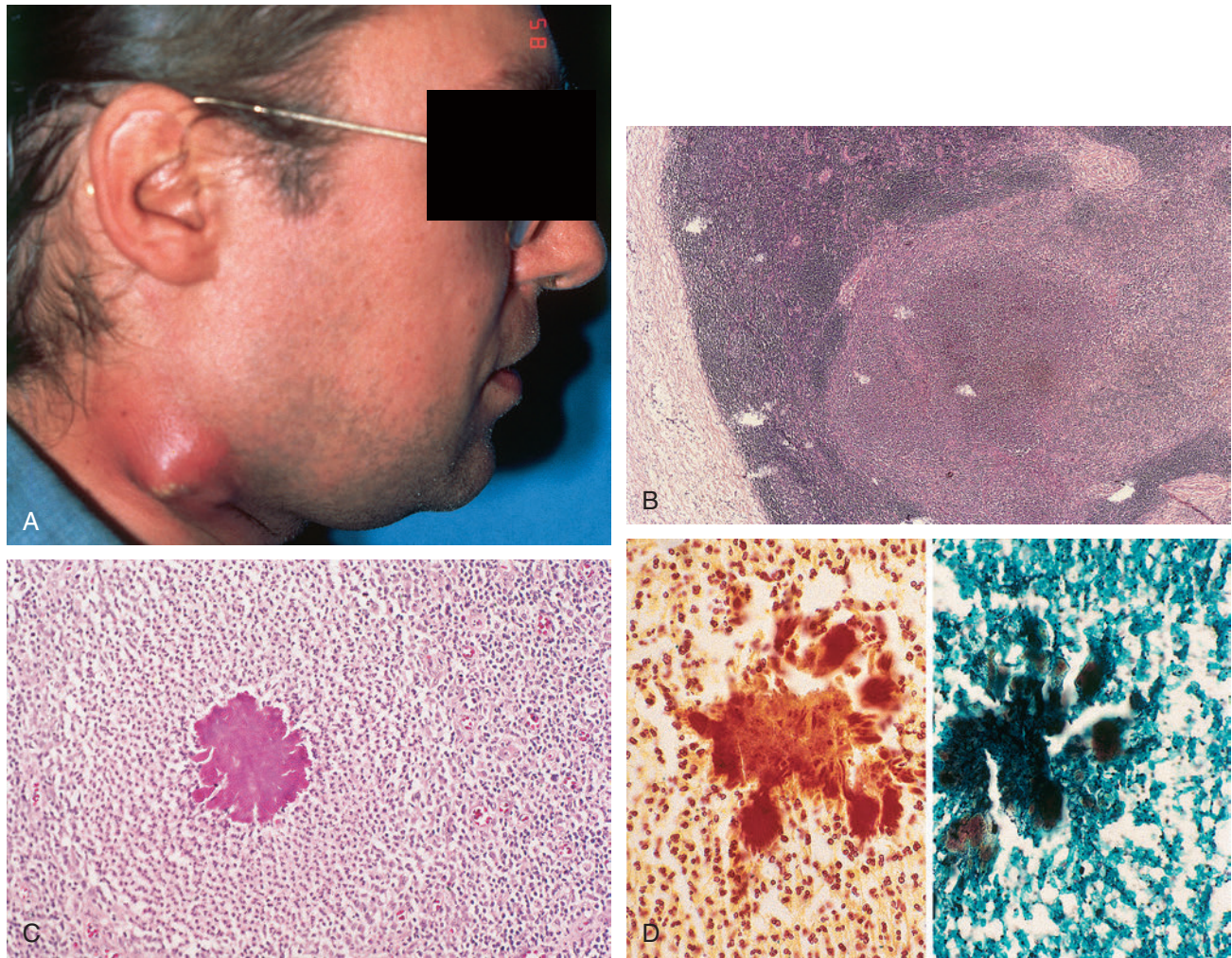


Fig. 12-11. Cervicofacial actinomycosis.

A, Indurated, suppurative neck mass around the angle of the mandible; the skin overlying the lesion has a characteristic purple color. **B**, Cervical lymph node with central accumulation of polymorphonuclear leukocytes (abscess formation) and necrosis. **C**, Within the abscess and enveloped by the neutrophils, actinomycotic colonies are seen with a characteristic appearance referred to as “sulfur granules”; the granules are lobular, deep purple, and composed of a central meshwork of filaments, which typically have eosinophilic club-shaped ends. **D**, Microorganisms stain best with Gram (*left*) and Gomori methenamine silver (GMS) stains (*right*).

- Any organ system may be involved; the most common include the lungs, skin, and lymph nodes.
- Most common clinical presentation is with fever, weight loss, and hilar adenopathy
- Isolated extranodal head and neck involvement occurs only in a small percentage of cases and includes:
 - Pharynx and tonsils
 - Ear and temporal bones
 - Sinonasal region, salivary glands, and larynx
- Site-specific involvement may occur as an isolated phenomenon or may coexist with systemic disease.
- Otolaryngologic symptoms vary according to site and include:
 - Cervical adenopathy, pharyngotonsillitis with tonsillar enlargement, airway obstruction, nasal discharge, epistaxis
 - Salivary gland involvement may clinically simulate Sjögren syndrome with salivary gland enlargement, xerostomia, and xerophthalmia
 - Involvement of the parotid gland and uveal tract referred to as uveoparotid fever or Heerfordt syndrome may present with facial nerve paralysis.

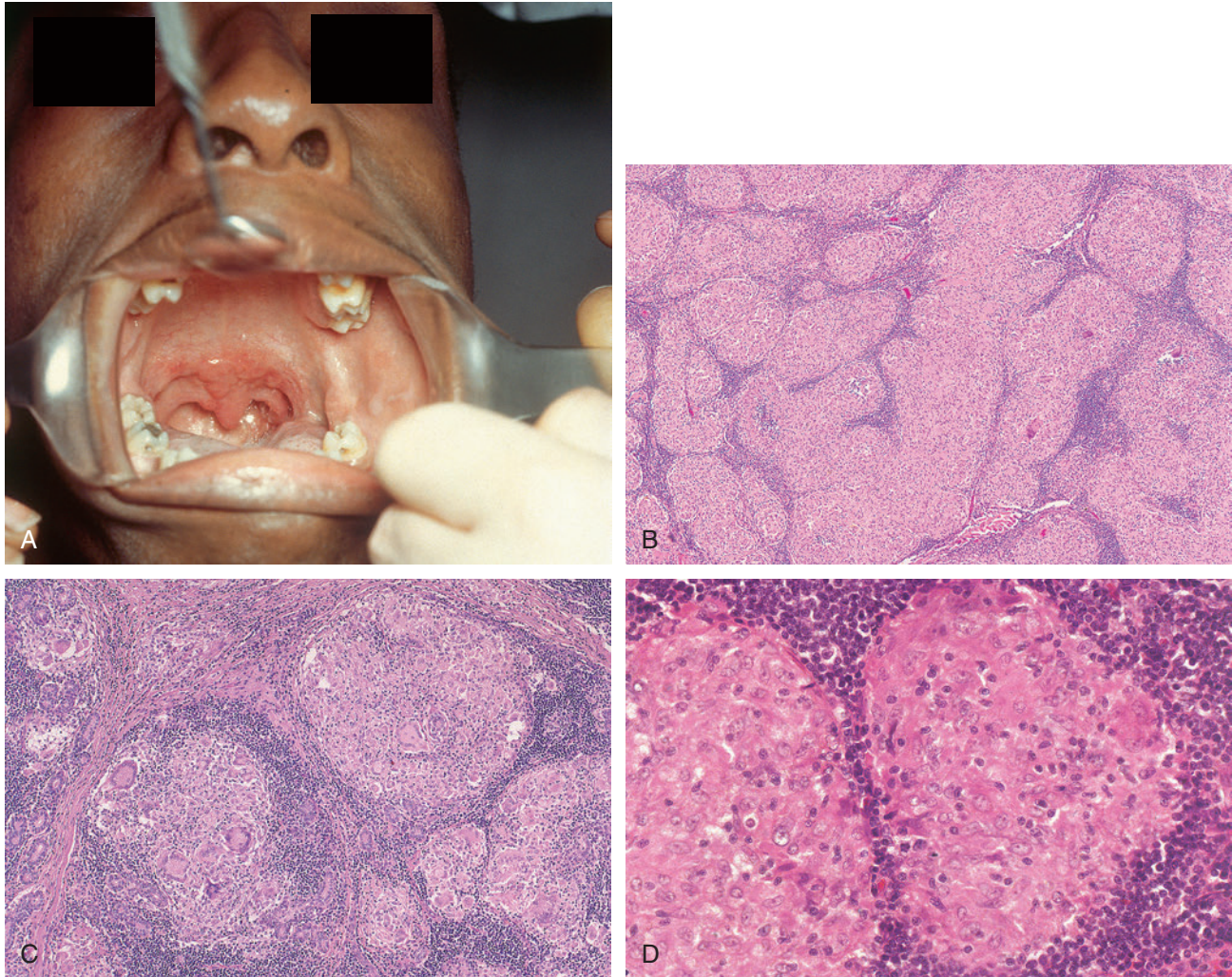


Fig. 12-12. Sarcoidosis.

A, Oral cavity (soft palate) sarcoidosis appearing as multiple, irregular nodules with a cobblestone appearance. **B** through **D**, Histologic picture of sarcoidosis irrespective of location includes multiple well-formed, noncaseating granulomas consisting of nodules of epithelioid histiocytes surrounded by a mixed inflammatory infiltrate; Langhans-type giant cells are seen in some of the nodules. A diagnosis of sarcoidosis is suggested/established following exclusion of a possible infectious cause; to this end, special stains for microorganisms are negative.

- No laboratory findings specific for or diagnostic of sarcoidosis:
 - Cutaneous anergy to skin test antigens (Kveim test) is positive in 60% to 85% of patients.
 - Elevated angiotensin converting enzyme (ACE):
 - Used as a marker for sarcoid disease activity
 - Not unique to sarcoidosis but can be elevated in other diseases including diabetes, hyperthyroidism, multiple sclerosis, asthma, nephrotic syndrome, others
 - ACE inhibitors used with varying success in the treatment of patients with sarcoidosis
- Cause remains unknown, but there is increasing evidence of finding mycobacterial DNA by polymerase chain reaction in sarcoid granulomas.

Pathology

Histology

- Presence of multiple noncaseating granulomas consisting of well-formed nodular foci composed of epithelioid histiocytes surrounded by a mixed inflammatory infiltrate:
 - Typically there is no associated caseation
 - Occasionally caseating granulomas may occur in sarcoidosis:

- Necrosis is absent but some examples, especially extranodal lesions, may have small foci of centrally located necrosis.
- Langerhans-type giant cells may be present.
- Intracytoplasmic inclusions including star-shaped and/or calcific laminated bodies called asteroid and Schaumann bodies, respectively, can be seen.
- Calcium oxalate crystals may be present in the cytoplasm of giant cells.
- Histochemistry:
 - All special stains for microorganisms are negative.
- Diagnosis of sarcoidosis is generally one of exclusion and is made by correlation of clinical, radiologic, and pathologic findings; although the pathologic features are characteristic, they are not specific for sarcoidosis and the diagnosis of sarcoidosis can be rendered only in the absence of identifying an infectious agent.
- In the majority of cases, a history of exposure to a cat can be obtained and the primary inoculation site identified typically seen from 7 to 12 days following contact.
- Primarily occurs in immunocompetent individuals:
 - May occur as localized disease in solid organ transplant recipients
- Symptoms include enlarged and often tender lymph nodes with potential involvement of the submental, submandibular, cervical, occipital, and supraclavicular lymph nodes as well as cervical lymph nodes in the anterior and posterior triangles of the neck:
 - Obstruction and inflammation may be seen in salivary glands with involved lymph nodes.
- Constitutional symptoms include low-grade fever, malaise, myalgias, headaches, and anorexia; less common manifestations/complications include granulomatous conjunctivitis (Parinaud oculoglandular syndrome), thrombocytopenic purpura, encephalitis, osteomyelitis, and hepatosplenomegaly. A positive skin test can confirm the diagnosis.
- Cutaneous lesions appear as a red papule, which may become crusted or pustular.

Differential Diagnosis

- Noncaseating granulomatous inflammation can be seen in:
 - Tuberculosis (typical and atypical), fungal diseases, leprosy, cat scratch disease, and many other infectious diseases
- Noninfectious diseases of the upper aerodigestive tract (e.g., Crohn disease) may also be associated with noncaseating granulomatous inflammation.

Treatment and Prognosis

- Treatment for symptomatic sarcoidosis is with corticosteroid therapy.
- Prognosis is generally good, with up to 70% of patients improving or remaining stable following therapy.
- Advanced multisystem disease leading to extensive pulmonary involvement and respiratory failure may occur but is seen in only a small percentage of cases.

BACTERIAL DISEASES

Cat Scratch Disease (Fig. 12-13)

Definition: Infectious disease is caused by a pleomorphic, gram-negative bacterium, *Bartonella henselae*, resulting in lymphadenopathy.

Clinical

- No gender predilection; occurs in all ages
- Mode of transmission is by direct contact from a cat scratch, bite, or lick through a skin break:
 - There is no evidence to support transmission from human to human.
 - The infected cat is not ill and appears to be infectious for only a limited time.

Pathology

- Changes in the affected lymph node vary with time:
 - Early lesions show:
 - Follicular hyperplasia and histiocytic proliferation
 - Intermediate stage lesions show:
 - Granulomatous inflammation
 - Late lesions show:
 - Abscess formation
 - Appearance of the abscess includes a central area of necrosis with a stellate pattern and an admixture of polymorphonuclear leukocytes surrounded by palisading of histiocytes; this pattern is suggestive of the diagnosis
 - Nodal sinuses are packed with monocytoid B-cells.
- Skin lesions show necrotic areas within the dermis surrounded by histiocytes.
- Histochemistry:
 - Cat scratch bacilli can be identified by Warthin-Starry stain and appear as extracellular pleomorphic coccobacilli.
 - Staining and culturing for acid-fast microorganisms are negative.

Differential Diagnosis

- Toxoplasmosis
- Lymphogranuloma venereum

Treatment and Prognosis

- Treatment is supportive and includes analgesics and warm compresses.

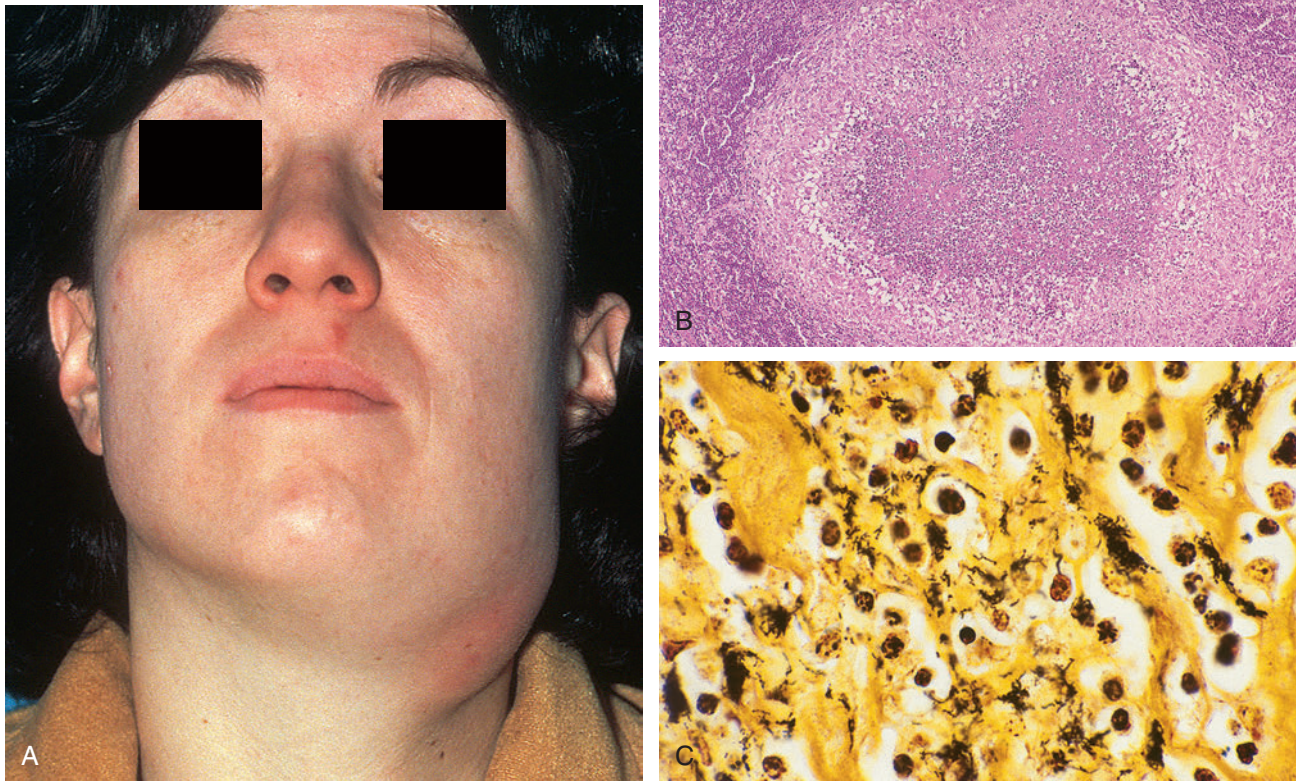


Fig. 12-13. Cat scratch disease.

A, Woman presenting with enlarged (and tender) lymph nodes. **B**, Characteristic but not pathognomonic appearance of the abscess composed of a central area of necrosis with a stellate pattern admixed with polymorphonuclear leukocytes surrounded by palisading of histiocytes. **C**, Causative bacterium (*Bartonella henselae*) identified by Warthin-Starry stain appear as extracellular pleomorphic coccobacilli.

- Self-limiting disease that typically runs its course within a few months
- In cases with suppuration, needle aspiration may relieve pain; incision and drainage may produce sinus tract inflammation.
- Antibiotic therapy appears to be of little benefit.

Bacillary Angiomatosis (BA) (Fig. 12-14)

Definition: Pseudoneoplastic capillary proliferative lesion that occurs as a complication of HIV infection and usually presents as a cutaneous vascular lesion and is caused by an opportunistic bacterial infection belonging to *Rochalimaea* species (*R. henselae*) as well as by *Bartonella quintana*.

Synonyms: Epithelioid angiomatosis; epithelioid hemangioma-like vascular proliferation

Clinical

- No gender predilection; occurs in over a wide age range
- Most commonly presents as a cutaneous lesion commonly associated with systemic symptoms, including fever, chills, weight loss, and night sweats
- Clinically, lesions are similar in appearance to lobular capillary hemangioma (pyogenic granuloma) and Kaposi sarcoma and characterized by the presence of multiple erythematous papules with or without crusting.
- May involve other organs sites including lymph nodes, spleen, and liver, as well as mucosal sites of the upper respiratory tract and conjunctiva
- Occurs most often in immunocompromised patients but may occur in patients with intact immune system
 - May occur in association with Kaposi sarcoma
 - May occur in solid organ transplant recipients (adults and pediatric patients)

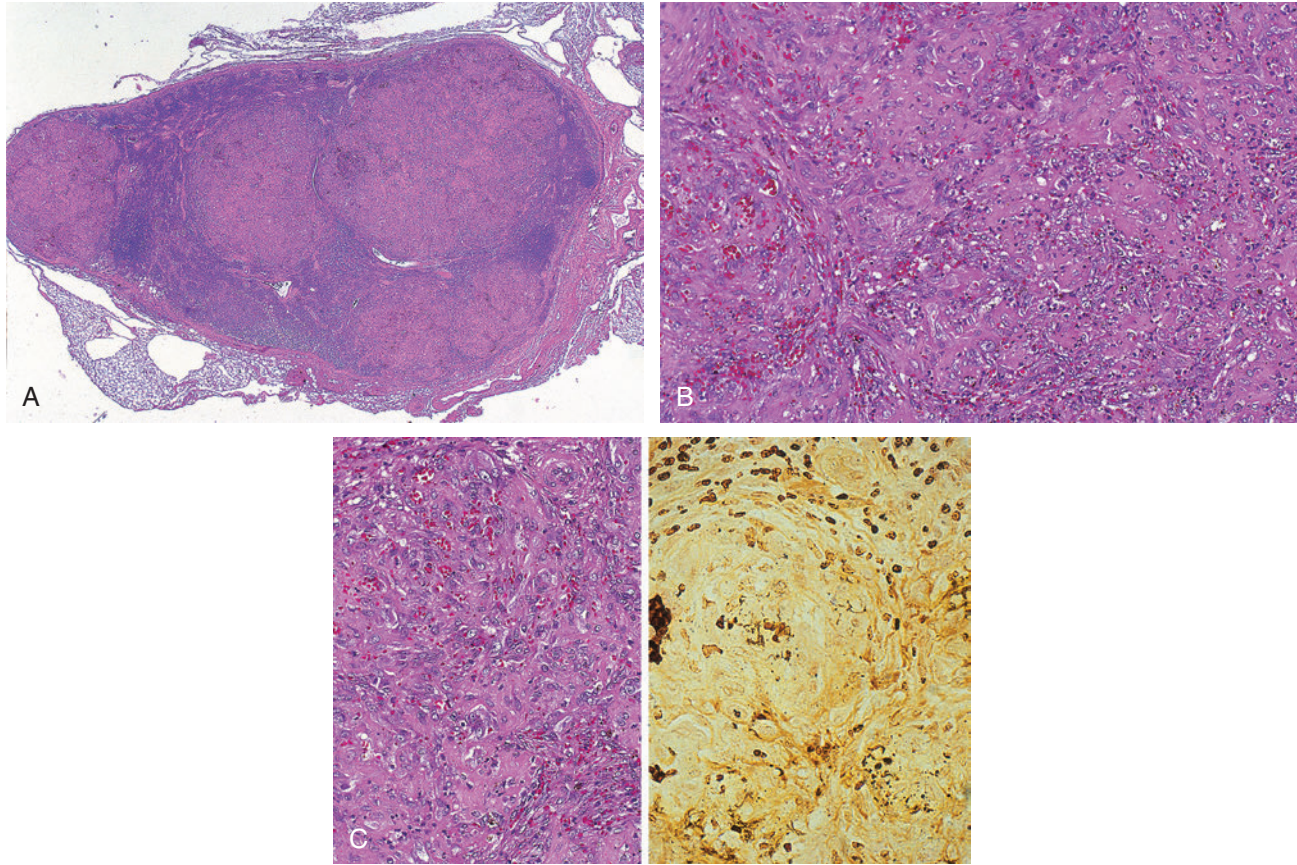


Fig. 12-14. Bacillary angiomatosis.

A, Lymph node replacement by well-circumscribed lobular proliferations. **B**, Small capillaries are arranged around ectatic vessels, which are lined by prominent appearing endothelial cells; fibrotic stroma is seen separating the lobular proliferation. Scattered neutrophils and neutrophilic debris can be seen adjacent to the capillary proliferation. **C, Left**, Vascular proliferation with prominent endothelial cells and scattered neutrophils associated with granular-appearing areas; **right**, Warthin-Starry staining shows the granular material to contain bacteria; bacteria are interstitially located.

- Laboratory diagnosis:
 - Serologic demonstration of antibodies by direct immunofluorescence and enzyme immunoassay
 - Proteomic analysis with identification of immunoreactive antigens found to be useful for an improved *Bartonella*-specific serodiagnosis.

Pathology

Gross

- Varies widely from cutaneous erythematous papules to mushroom-shaped papules and nodules to deep-seated rounded lesions without change in skin color.
- Exceptionally, may appear as a mucosal-based, erythematous nodular proliferation

Histology

- Regardless of its clinical presentation, the histologic features are the same and include a well-circumscribed

lobular capillary proliferation with overall features similar to those seen in lobular capillary hemangioma.

- Small capillaries are arranged around ectatic vessels, which are lined by prominent-appearing endothelial cells.
- Cytologic atypia, mitotic figures, and necrosis are not usually present but occasionally may be seen.
- Solid areas may be present and may obscure the vascular proliferation.
- A variable edematous, mucinous, or fibrotic stroma is seen separating the lobular proliferation.
- An important histologic feature in BA is the presence of neutrophils and neutrophilic debris adjacent to the capillary proliferation; associated with the neutrophils are granular clumps.
- BA typically lacks spindled cells, interconnecting vascular channels, or hyaline globules.

- Overlying epithelium may be ulcerated, thinned, or show pseudoepitheliomatous hyperplasia.
- Histochemical stains:
 - Warthin-Starry staining shows the granular material to contain bacteria; bacteria are interstitially located.
- Immunohistochemistry:
 - HHV-8 negative

Differential Diagnosis

- Lobular capillary hemangioma (pyogenic granuloma)
- Epithelioid hemangioma
- Angiosarcoma
- Kaposi sarcoma:
 - Presence of granular material, neutrophils, and neutrophilic debris and the absence of cytologic atypia, ramifying and interconnecting vascular channels, necrosis, mitotic activity, and hyaline globules assist in differentiating BA from these other vascular lesions
 - Presence of HHV-8 immunoreactivity
- Verruga peruana, another vascular proliferation process caused by an infectious agent (*Bartonella bacilliformis*), is endemic to Peru. The presence of characteristic inclusions, referred to as Rocha-Lima inclusions, allows for differentiation.

Treatment and Prognosis

- Treatment for BA is directed at the causative microorganism:
 - Full-dose erythromycin is effective, often resulting in the resolution of the lesions.
- If left untreated, BA is progressive and potentially life threatening.

FUNGAL, VIRAL, AND PROTOZOAL DISEASES

- Fungal, viral, and protozoal diseases of the cervical neck are rare.
- HPV-associated and EBV-associated carcinomas originating from the oropharynx (tonsil, base of tongue) and nasopharynx, respectively, may metastasize to cervical neck lymph nodes (see Section 3, The Pharynx, and Chapter 13 for more complete discussion of these cancer types).

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Neoplasms of the Neck

CLASSIFICATION OF NEOPLASMS OF THE NECK

BOX 13-1 Classification of Neoplastic Lesions of the Neck

Benign

Mesenchymal/Neuroectodermal

- Fibromatosis
- Nodular fasciitis
- Paraganglioma
- Lipomas
- Nerve sheath tumors
- Rhabdomyoma
- Vascular neoplasms (e.g., angiofibroma, hemangioma, lymphangioma)
- Lymphatic malformation (lymphangiomas)
- Others

Malignant

Hematolymphoid Malignant Neoplasms

- Non-Hodgkin lymphomas
- Hodgkin lymphoma
- Others

Sarcomas

- Malignant peripheral nerve sheath tumors
- Rhabdomyosarcoma
- Leiomyosarcoma
- Liposarcoma
- Angiosarcoma
- Synovial sarcoma
- Others

Metastatic Cervical Carcinoma with an Unknown Primary Tumor (MCCUP)

Secondary Neoplasms

tract, pharynx, salivary glands, and thyroid gland.

- The most common neoplastic lesions of the neck are metastatic tumors to cervical neck lymph nodes, including those originating from head and neck sites (most common) and those originating from non-head and neck sites (less common).
- Metastatic carcinomas originating from head and neck sites include:
 - Squamous cell carcinoma and variants thereof (most common)
 - Adenocarcinomas (less common)
- Metastatic carcinomas occurring in the absence of a known primary carcinoma are referred to as metastatic carcinoma with unknown primary (MCCUP); see later in this chapter.
 - Primary carcinoma in MCCUP may be extremely small and clinically/radiographically difficult to detect.
 - There is no correlation between the size of the primary carcinoma, which may be a few millimeters in greatest dimension, to the size of the metastasis, which may be several centimeters in greatest dimension:
 - Size differential/discrepancy between a small primary carcinoma and a large metastasis often (but not exclusively) applies to viral-associated carcinomas, including human papillomavirus (HPV) and Epstein-Barr virus (EBV) originating in the oro- and nasopharynx, respectively.
- Metastatic squamous cell carcinoma:
 - May be keratinizing or nonkeratinizing:
 - Those metastatic carcinomas that are predominantly keratinizing are usually not viral associated and are more likely to be associated with tobacco and alcohol use.
 - Those metastatic carcinomas that are predominantly nonkeratinizing are more often viral associated, including HPV-associated and EBV-associated.
 - HPV-associated metastatic carcinoma is diffusely and strongly (nuclear and cytoplasmic) immunoreactive for p16:
 - p16 staining is a surrogate marker for HPV16.
 - p16 immunoreactivity correlates to a primary oropharyngeal (tonsil, base of tongue) carcinoma.

GENERAL CONSIDERATIONS

- Primary neoplasms of the cervical neck are uncommon and include:
 - Soft tissue neoplasms (benign and malignant):
 - Fibromatosis and nodular fasciitis previously classified as nonneoplastic lesions are now recognized based on molecular analyses to be true neoplasms.
 - Hematolymphoid (non-Hodgkin and Hodgkin lymphomas):
 - The spectrum of lymphomas is extensive and beyond the scope of this book.
 - Selective lymphoma types are discussed under site-specific locations, including the sinonasal

- EBV-associated metastatic carcinoma is strongly positive (nuclear) by in situ hybridization for Epstein-Barr-encoded RNA (EBER):
 - EBER-positive metastatic carcinomas often originate from the nasopharynx.
 - Histologically, EBER-positive metastatic carcinomas may be nonkeratinizing differentiated type or nonkeratinizing undifferentiated type.
- MCCUP may be cystic and/or solid.
- Metastatic adenocarcinoma to cervical neck lymph nodes occur and may originate from a primary head and neck site or from a site other than head and neck:
 - May originate from a wide variety of head and neck sites, including but not limited to the sino-nasal tract, oral cavity, salivary glands
 - In contrast to metastatic squamous cell carcinomas of head and neck sites that may originate from an occult primary tumor, metastatic adenocarcinomas from a head and neck site typically originate from a known primary tumor and rarely from an occult primary tumor.
- Metastatic papillary thyroid carcinoma commonly metastasizes to cervical lymph nodes and may do so in the absence of a known primary thyroid carcinoma:
 - Usually, nodal metastasis of papillary thyroid carcinoma originates from the ipsilateral thyroid lobe.
 - Given its affinity for lymph-vascular spaces, nodal metastasis from a thyroid carcinoma represents papillary carcinoma even in the absence of diagnostic nuclear features.
 - Isolated (“naked”) psammoma bodies in lymph nodes are highly suggestive for nodal metastatic papillary thyroid carcinoma.
- Neuroendocrine carcinomas (NECs) may metastasize to cervical lymph nodes and may (infrequently) do so in the absence of a known primary head and neck carcinoma; such NECs may originate from the:
 - Thyroid gland, representing metastatic medullary thyroid carcinoma:
 - Associated with elevated serum calcitonin levels
 - Immunoreactive for calcitonin, neuroendocrine markers (synaptophysin, chromogranin, CD56, others), TTF1, and cytokeratins but negative for thyroglobulin
 - May originate from a nonthyroid origin, in particular the larynx:
 - Laryngeal NEC not associated with elevated serum calcitonin levels
 - Most common histologic type of laryngeal NEC is moderately differentiated NEC or atypical carcinoid.
 - Immunoreactive for calcitonin in majority of cases (>80%), neuroendocrine markers (synaptophysin, chromogranin, CD56, others), and cytokeratins but negative for thyroglobulin
- Metastatic malignant neoplasms from sites other than head and neck occur to the cervical neck lymph nodes:
 - Often metastasize to supraclavicular lymph nodes
- In the pathology report of nodal metastasis it is imperative to document presence or absence of extranodal extension (ENE):
 - Presence of ENE portends worse prognosis, including increased incidence of recurrence and distant spread.

SURGICAL SPECIMENS

Neck Dissection (Fig. 13-1)

- The neck is divided into anterior and posterior triangles by the sternocleidomastoid muscle.
- Currently, the neck is divided into six levels encompassing the complete topographic anatomy of the neck (Table 13-1), although a seventh level (level VII) may be included:
 - Level I:
 - Submental, submandibular nodes
 - Levels II through IV:
 - Upper, middle, and lower deep cervical nodes
 - Level V:
 - Posterior triangle nodes
 - Level VI:
 - Lymph nodes around thyroid gland (referred to as the central compartment)
 - Level VII:
 - Lymph nodes in the tracheoesophageal groove and superior mediastinum
- The classification of neck dissections depends on the divisions of the lymph node groups in the neck (Box 13-2).
- Types of neck dissections include:
 - Radical neck dissection:
 - Removal of all lymph node regions as well as the sternocleidomastoid muscle, internal jugular vein, and spinal accessory nerve
 - Considered to represent the standard basic procedure for cervical lymphadenopathy in patients with squamous cell carcinoma of the head and neck region
 - Modified radical neck dissection:
 - Preservation of one or more nonlymphatic structures routinely removed in the radical neck dissection

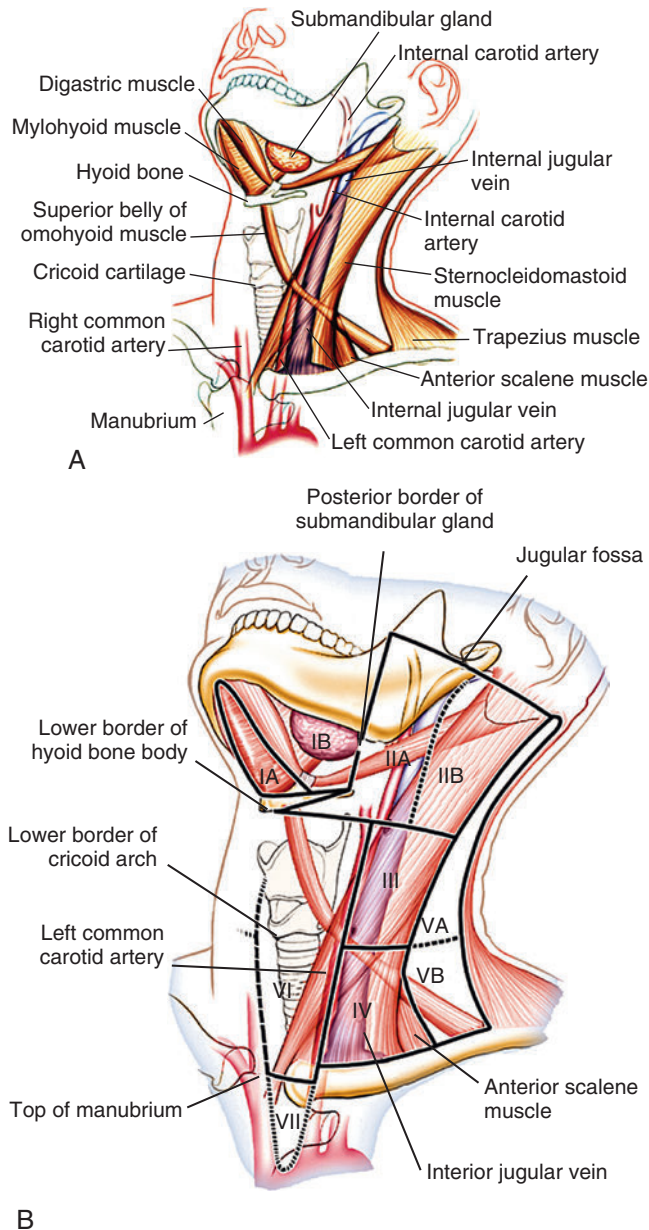


Fig. 13-1. Cervical neck anatomy and lymph node stations.

A, Cervical neck anatomic landmarks used in imaging-based nodal classification. **B**, Nodal stations delineated in a node-negative neck. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 2298, Fig. 38-9.)

- Includes removal of lymph nodes in levels I through V with preservation of one or more nonlymphatic structures, including:
 - Sternocleidomastoid muscle
 - Internal jugular vein
 - Spinal accessory nerve
- Classified into three types (Box 13-3):
 - Differences in types relate to the number of neural, vascular, and muscular structures preserved

BOX 13-2 Classification of Neck Dissections

Radical Neck Dissection

- All nodes levels I through V
- Internal jugular vein (IJV)
- Spinal accessory nerve (CN XI)
- Sternocleidomastoid (SCM)

Modified Radical Neck Dissection

- All node levels I through V
 - Type I: preserve CN XI
 - Type II: preserve CN XI and IJV
 - Type III: preserve CN XI, IJV, and SCM

Selective Neck Dissections (SND)

- Remove only selective lymph node levels, sparing all vital structures; variations include:
 - SND I-III/IV
 - SND II-IV
 - SND (II-V, postauricular, suboccipital)
 - SND VI

Extended Neck Dissection

- Removal of additional lymph node levels or groups and/or nonlymphatic structures (e.g., muscle, nerves, blood vessels) not normally removed with a radical neck dissection

Super-Selective Neck Dissection

- Complete removal of all fibrofatty contents, including lymph node along defined boundaries of one or two contiguous neck levels

CN XI, Spinal accessory nerve; IJV, internal jugular vein; SCM, sternocleidomastoid muscle.

BOX 13-3 Classification of Modified Radical Neck Dissections

Type I

- Removal of SCM and IJV
- Preservation of XI n

Type II

- Removal of SCM
- Preservation of IJV and XI n

Type III

- Preservation of all three nonlymphoid structures, including SCM, IJV, XI n

IJV, Internal jugular vein; SCM, sternocleidomastoid muscle; XI n, spinal accessory nerve.

- Selective neck dissections subdivided into:
 - Preservation of one or more lymph node groups/levels routinely removed in the radical neck dissection
 - Subdivided into:
 - Supraomohyoid:
 - Includes removal of lymph nodes in levels I through III
 - Posterolateral:
 - Includes removal of lymph nodes in levels II through V, as well as suboccipital and retroauricular lymph nodes

TABLE 13-1 Lymph Node Levels and Sublevels

Lymph Node Level	Description
I	<p>Sublevel IA: submental—lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone</p> <p>Sublevel IB: submandibular—lymph nodes within the boundaries of the anterior belly of the digastric muscle, stylohyoid muscle, and the body of the mandible</p>
II (upper jugular)	<p>Lymph nodes located around the upper third of the internal jugular vein and the adjacent spinal accessory nerve extending from:</p> <p>Above: level of the skull base</p> <p>Below: level of the inferior border of the hyoid bone</p> <p>Medial (anterior): stylohyoid muscle (radiologic correlate is the vertical plane defined by the posterior surface of the submandibular gland)</p> <p>Lateral (posterior): posterior border of the SCM</p> <p>Sublevel IIA: nodes located anterior (medial) to the vertical plane defined by the spinal accessory nerve</p> <p>Sublevel IIB: nodes located posterior (lateral) to the vertical plane defined by the spinal accessory nerve</p>
III (midjugular)	<p>Lymph nodes located around the middle third of the internal jugular vein extending from:</p> <p>Above: inferior border of the hyoid bone</p> <p>Below: inferior border of the cricoid cartilage</p> <p>Medial (anterior): lateral border of sternohyoid muscle</p> <p>Lateral (posterior): posterior border of the SCM</p>
IV (lower jugular)	<p>Lymph nodes located around the lower third of the internal jugular vein extending from:</p> <p>Above: inferior border of cricoid cartilage</p> <p>Below: clavicle</p>
V (posterior triangle)	<p>Lymph nodes in this group are predominantly located around the lower half of the spinal accessory nerve and the transverse cervical artery and extend from:</p> <p>Superior: apex formed by convergence of the SCM and trapezius muscle</p> <p>Inferior: clavicle</p> <p>Medial (anterior): posterior border of SCM</p> <p>Lateral (posterior): anterior border of trapezius muscle</p> <p>Sublevels include V-A and V-B separated by a horizontal plane marking the inferior border of the anterior cricoid arch:</p> <p>V-A: above this plane includes the spinal accessory lymph nodes</p> <p>V-B: below this plane includes the lymph nodes that follow the transverse cervical vessels and the supraclavicular nodes with the exception of the Virchow node, which is located in level IV</p>
VI (anterior compartment)	<p>Boundaries of this compartment include:</p> <p>Superior: hyoid bone</p> <p>Inferior: suprasternal notch</p> <p>Lateral: common carotid arteries</p> <p>Lymph nodes in this level include:</p> <ul style="list-style-type: none"> • Pretracheal and paratracheal nodes • Precricoid (delphian) nodes • Perithyroidal nodes, including those along the recurrent laryngeal nerves

SCM, Sternocleidomastoid muscle.

Modified from Houck JR, Medina JE: Management of cervical lymph nodes in squamous carcinomas of the head and neck, *Semin Surg Oncol* 11(3):228-239, 1995.

- Lateral:
 - Includes removal of lymph nodes in levels II through IV
- Anterior:
 - Includes removal of lymph nodes in level VI (pretracheal and paratracheal)
- Extended radical neck dissection:
 - Removal of additional lymph node groups or nonlymphatic structures not encompassed by radical neck dissection
 - Examples of nodal groups may include:
 - Parapharyngeal and retropharyngeal lymph nodes
 - Lymph nodes in levels VI and VII
 - Carotid artery
- Super-selective neck dissection:
 - Complete removal of all fibrofatty contents, including lymph node along defined boundaries of one or two contiguous neck levels
- Current neck staging based on a consensus between the European UICC and the American Joint Cancer Committee (AJCC) ([Table 13-2](#))
 - System uses clinical features of nodal size, number, and laterality.
 - Does not integrate imaging features, suggestive of extranodal extension

TABLE 13-2 UICC-AJCC Cervical Lymph Node Staging System

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1*	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2*	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a*	Metastasis in a single ipsilateral lymph node more than 3 cm, but not more than 6 cm in greatest dimension
N2b*	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c*	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3*	Metastasis in lymph node more than 6 cm in greatest dimension
M0	No distant metastasis
M1	Distant metastasis

*A designation of "U" or "L" may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical/radiologic ECS should be recorded as E- or E+, and histopathologic ECS should be designated as En, Em, or Eg.

Used with permission from Edge et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer-Verlag, p 25.

BENIGN NEOPLASMS OF THE NECK

FIBROBLASTIC/ MYOFIBROBLASTIC

Aggressive Fibromatosis

(Figs. 13-2 and 13-3)

Definition: Locally aggressive, nonmetastasizing (myo) fibroblastic neoplasm characterized by locally infiltrative growth.

Synonyms: Desmoid-type fibromatosis; desmoid tumor; aggressive fibromatosis; extraabdominal desmoid, extra-abdominal fibromatosis; tumefactive fibroinflammatory tumor; inflammatory pseudotumor

General Findings

- Fibromatoses can be divided into three groups, including:
 - Sporadic:
 - Most (but not all) are extra-abdominal
 - Associated with familial adenomatous polyposis (FAP) or Gardner syndrome:
 - Most (but not all) arise intra-abdominally, especially mesentery:
 - Often occur following previous surgery (i.e., colectomy)
 - May be multifocal:
 - Multicentric or familial
- Fibromatoses can also be divided anatomically, including:
 - Extra-abdominal (60%)
 - Abdominal wall (25%)
 - Intra-abdominal (15%)

Clinical

- Identified in the head and neck in from 10% to 15% of cases; in children, this area of the body may be affected in up to 30% of cases.
- Head and neck fibromatosis occurs over a wide age range but tends to be most common in the second to fourth decades of life; there is no gender predilection:
 - Sinonasal lesions seen in children and adults but most commonly occur in the third to fourth decades of life
- Involvement of the head and neck region occurs primarily in the soft tissues of the neck:
 - Excluding the neck, the common sites of occurrence in the head and neck include the sinonasal tract, nasopharynx, and oral cavity (tongue).
 - In the sinonasal tract, the maxillary sinus is the most common site.
- Symptoms vary according to site:
 - In the neck, the clinical presentation includes enlarging painless mass:
 - In this setting lesions may involve the parotid gland.
 - In the sinonasal tract and nasopharynx, the clinical presentation includes a painless enlarging mass or nasal obstruction.
 - With progression of disease, other symptoms, including epistaxis, facial deformity, proptosis, and dysphagia, may occur.
- Radiology:
 - Often show isodense or high attenuation on post-contrast CT
 - High signal intensity on T2-weighted image

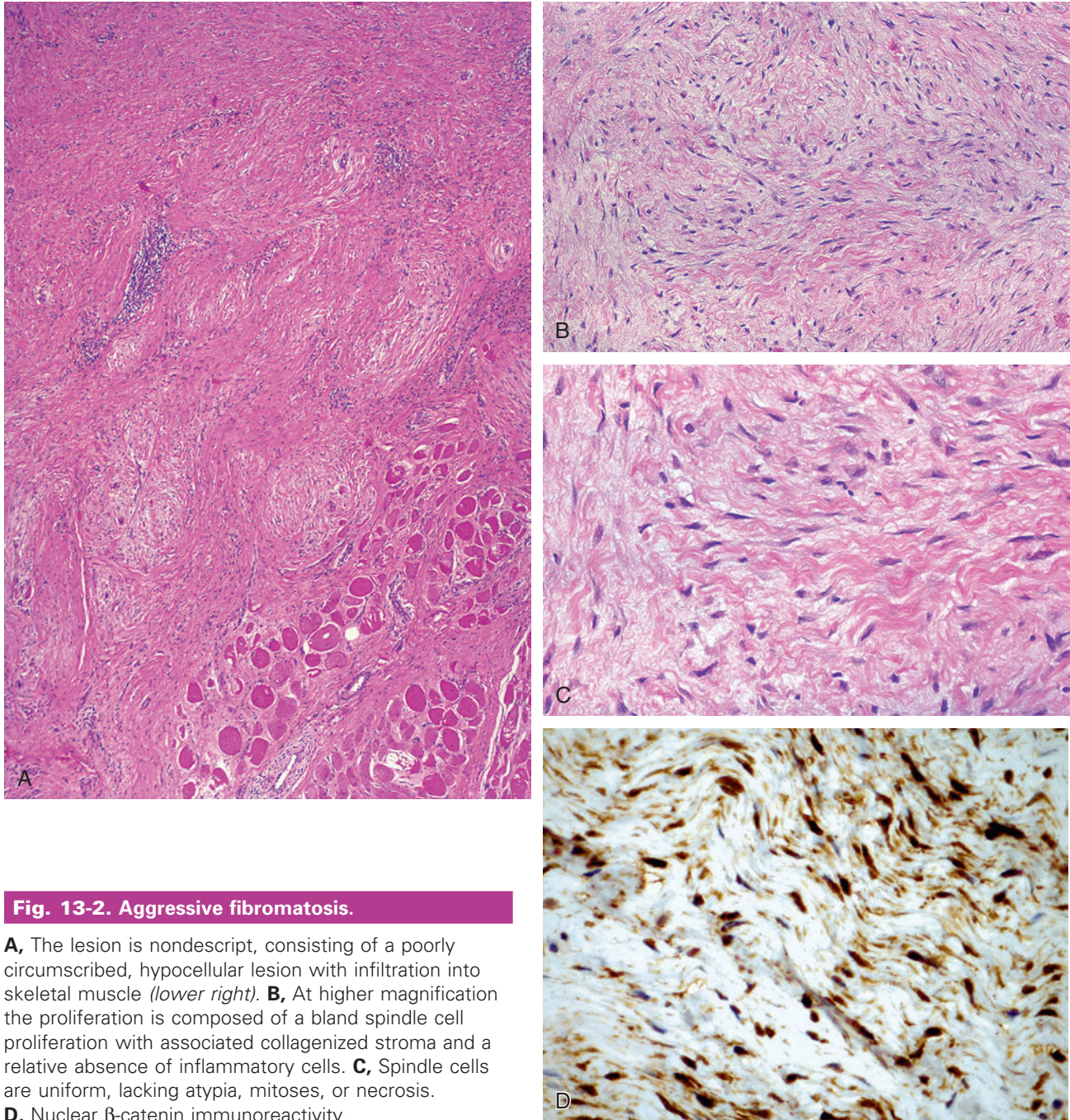


Fig. 13-2. Aggressive fibromatosis.

A, The lesion is nondescript, consisting of a poorly circumscribed, hypocellular lesion with infiltration into skeletal muscle (*lower right*). **B,** At higher magnification the proliferation is composed of a bland spindle cell proliferation with associated collagenized stroma and a relative absence of inflammatory cells. **C,** Spindle cells are uniform, lacking atypia, mitoses, or necrosis. **D,** Nuclear β -catenin immunoreactivity.

- Isodense signal intensity on T1-weighted image
- Strong MR enhancement
- Characteristic nonenhancing low signal intensity bands on all MR sequences correlate with dense collagenous stroma.
- Cause:
 - Multifactorial including genetic, endocrine, and physical factors:
 - Genetic:
 - Existence of familial cases
 - Presence of lesions in association with Gardner syndrome or Gardner-type familial adenomatous polyposis (FAP):
 - Autosomal-dominant inherited disorder characterized by the presence of intestinal polyposis, desmoid tumor, osteomas of the skull, epidermoid cysts, lipomas, and fibroma (Gardner fibroma); tumors arising in setting of FAP/Gardner syndrome harbor inactivating mutations of APC gene

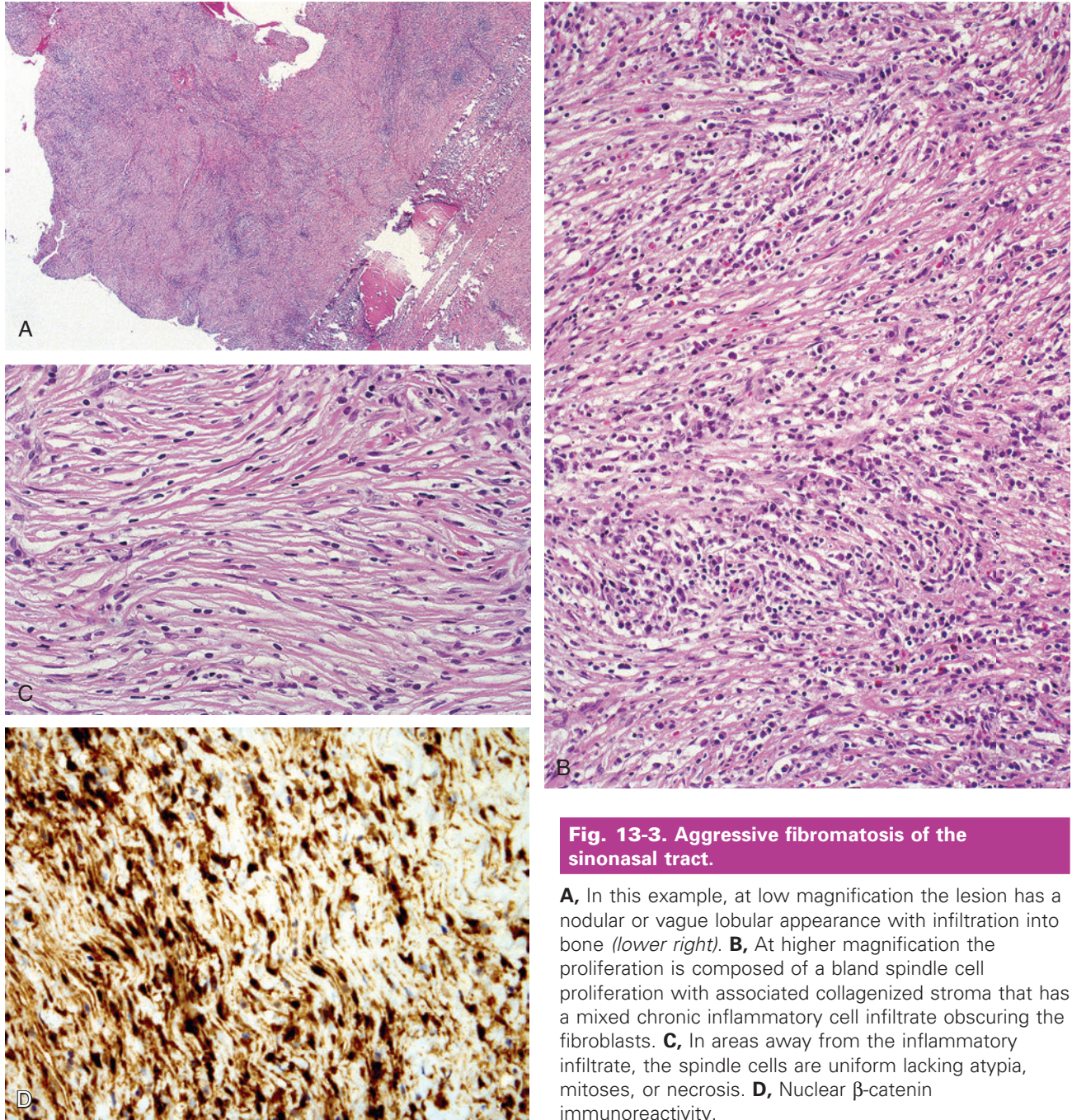


Fig. 13-3. Aggressive fibromatosis of the sinonasal tract.

A, In this example, at low magnification the lesion has a nodular or vague lobular appearance with infiltration into bone (*lower right*). **B,** At higher magnification the proliferation is composed of a bland spindle cell proliferation with associated collagenized stroma that has a mixed chronic inflammatory cell infiltrate obscuring the fibroblasts. **C,** In areas away from the inflammatory infiltrate, the spindle cells are uniform lacking atypia, mitoses, or necrosis. **D,** Nuclear β -catenin immunoreactivity.

- Gardner fibroma:
 - Uncommon lesion most often presenting in childhood or adolescence
 - Predilection for the trunk, particularly paraspinal region
 - Majority (more than 80%) associated with FAP often preceding the development of polyps; considered a sentinel event for FAP
 - Mesenteric Gardner fibroma in FAP referred to as desmoid precursor lesion
- Histologically, poorly demarcated, hypocellular hyaline collagen bundles with artifactual cleft-like spaces, lesional cells have appearance of bland fibroblasts, entrapment of normal tissues (e.g., small nerves, fat, muscle); nuclear positivity for β -catenin; CD34 immunoreactive
- Physical factors:
 - Trauma most often related to surgery may be a contributory factor.

Pathology

Gross

- Firm, tan-white, poorly delineated, or infiltrating lesion of varying size
- On cut section, the lesion has a trabecular or whorled appearance.

Histology

- Poorly circumscribed, composed of uniform-appearing spindle-shaped cells with sharply defined, pale-staining nuclei associated and separated by abundant collagen production
- Cellularity varies but in general only moderately cellular:
 - Cellular variability including hypocellular (collagenized) lesions to markedly cellular lesions.
 - Cells are uniform with tapering or plump-appearing vesicular-appearing nuclei, small nucleoli, indistinct cytoplasm.
 - Lack hyperchromasia, pleomorphism, or mitotic activity
 - Variations of the nuclear appearance may include the presence of stellate-appearing nuclei.
 - Fascicular growth pattern including broad, elongated fascicles; tends to be less well defined as compared with that seen in fibrosarcoma
- Stromal component includes:
 - Variably collagenized
 - May focally be myxoid or mucoid-appearing
 - Some examples may be characterized by the presence of keloid-like collagen or extensive hyalinization.
- Vascularity varies but is generally not a prominent feature:
 - A varying number of blood vessels are present and tend to be more thick-walled than in fasciitis.
 - Characteristic vascularity associated with some sarcomas, including delicate plexiform pattern, is absent in fibromatosis.
- Mild pleomorphism and rare mitotic figures may be identified; atypical mitoses and necrosis not identified.
- Chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils may accompany the lesion and varies from being scant to dense in appearance.
- Typically, these lesions are poorly circumscribed and infiltrative along the periphery into striated muscle: at advancing edge of the tumor, lymphoid aggregates and degenerate skeletal muscle cells with bizarre sarcolemmal nuclei are commonly seen.
 - Sinonasal tract lesions may extend into bone.

- Metaplastic components such as bone or cartilage may be present but tend to be focal and not a prominent part of the lesions.
- Histochemical stains of little contribution to the diagnosis
- Immunohistochemistry:
 - Vimentin positive
 - Nuclear β -catenin reactivity:
 - Seen in 70% to 75% of cases, in particular those associated with FAP, but also can be seen in sporadically occurring cases:
 - Not specific as can be seen in lesions other than fibromatosis
 - Variable staining for actins (muscle specific and smooth muscle)
 - Typically negative for S100 protein and desmin, but one or both may be focally present
 - Negative for MUC4, CD34, ALK1, epithelial markers, melanocytic markers
 - Calretinin-positive and keratin-positive cells may be present.
 - Generally limited in extent
- Molecular and cytogenetic:
 - Cytogenetic abnormalities (e.g., trisomies) on chromosomes 8 and 20 identified:
 - Support neoplastic rather than reactive nature of fibromatosis
 - Germline mutations of APC gene on long arm of chromosome 5:
 - Primarily identified in setting of Gardner-type FAP
 - Mutations in gene encoding β -catenin (*CTNNB1*):
 - Identified in up to 85% of sporadic lesions
 - APC and *CTNNB1* mutations result in intranuclear accumulation of β -catenin.

Differential Diagnosis

- Reactive fibrosis
- Fibrosarcoma:
 - In contrast to fibrosarcoma, fibromatoses lack a herringbone growth pattern, hypercellularity, and increased mitotic rate.
- Peripheral nerve sheath tumor (neurofibroma, benign schwannoma)
- Solitary fibrous tumor
- Myofibromatosis
- Nodular fasciitis:
 - Presence of stellate cytomorphology, loose myxoid stroma, and hemorrhage not features typically seen in fibromatosis
 - Absence of nuclear β -catenin reactivity
- Myofibroblastic tumors (inflammatory myofibroblastic tumor, low-grade myofibroblastic sarcoma)
- Myxoma and fibromyxoma
- Fibro-osseous lesion (fibrous dysplasia, ossifying fibroma)

Treatment and Prognosis

- Preferred treatment is wide surgical excision, including several centimeters beyond the apparent macroscopic extent of the lesion.
- In general, the prognosis is good; however, these lesions present difficulties in management due to insinuation of the lesion into adjacent structures without clear demarcation, making complete excision difficult.
- As a result of the difficulties in completely excising the lesion, recurrent disease is common:
 - Recurrence usually occurs within the first few years following surgery.
 - Local recurrences usually appear within 2 years of surgery, likely correlating to the presence of positive margins.
- Radiotherapy has been used with some success in patients with residual tumor and/or recurrent disease:
 - Because head and neck fibromatosis often occurs in young patients, caution should be exercised in using radiotherapy because of the potential of these patients to develop complications secondary to radiation treatment.
- Imatinib and sorafenib have been used with varying efficacy in the treatment of primary and recurrent disease.
- Other therapies including hormonal therapy, estrogen antagonists, nonsteroidal anti-inflammatory drugs, and low-dose chemotherapy are used with varying results.
- Death due to uncontrolled local disease may occur but is an extraordinary occurrence.
- Spontaneous regression of the lesion may occur but is rare.
- Regression following radiotherapy may take up to 2 to 3 years.
- In extremely rare cases, transformation to an overt malignancy (fibrosarcoma) has been reported to occur and possibly relates to prior radiation therapy.

Nodular Fasciitis (NF) (Fig. 13-4)

Definition: Benign (myo)fibroblastic neoplastic proliferation presenting as a rapidly enlarging lesion that typically occurs in subcutaneous tissue.

Synonyms: Pseudosarcomatous fasciitis; infiltrative fasciitis, pseudosarcomatous fibromatosis

NOTE: The classification of NF as a non-neoplastic lesion or as a neoplasm is the subject of debate, although the identification of *MYH9-USP6* gene fusion as a recurrent event in NF supports its clonal neoplastic nature rather than a reactive, non-neoplastic lesion.

Clinical

- Represents one of the more common soft tissue lesions
- No gender predilection; predominantly occurs in the third to fifth decades of life:
 - Although considered to occur primarily in adults and infrequently affects infants and children, head and neck involvement is common in the latter group and rare in the former group.
- Most commonly occurs in the upper extremities but is seen involving head and neck sites in up to 20% of cases:
 - In the head and neck, the most common site of involvement is the neck, but NF may occur in and around the external ear.
 - Rarely, involves mucosal sites of the oral cavity and sinonasal tract
 - Can also arise within muscle (intramuscular fasciitis), deep fascia (fascial fasciitis), blood vessels (intravascular fasciitis), soft tissues of the scalp or skull (cranial fasciitis), and in areas lacking fascia including mucosal sites of the upper and lower respiratory tract mucosa and esophagus
 - Characteristically arises from the superficial fascia, accounting for its predominant occurrence in subcutaneous areas
- Most common symptom is that of a painless mass noted for its rapid growth occurring over a 1- to 2-week period:
 - Soreness, tenderness, and even pain may be present.
 - On the basis of a rapidly growing soft tissue mass a primary clinical consideration is that of a sarcoma.
- Cause is unknown; however, trauma is considered a possible initiating factor.

Pathology

Gross

- Tends to be solitary and rarely, if ever, is multiple
- Lesions are typically firm, nodular, tan-white, and unencapsulated but well delineated, measuring less than 3 to 4 cm; larger lesions measuring up to 10 cm infrequently occur.
- On cut section the lesion may be smooth or whorled, varying from firm and tan-white to soft and gelatinous or myxoid; cystic areas may be seen.

Histology

- Circumscribed but unencapsulated lesion composed of a proliferation of plump-appearing spindle-shaped cells arranged in short, irregular fascicles and bundles or in a whorled to nodular appearance

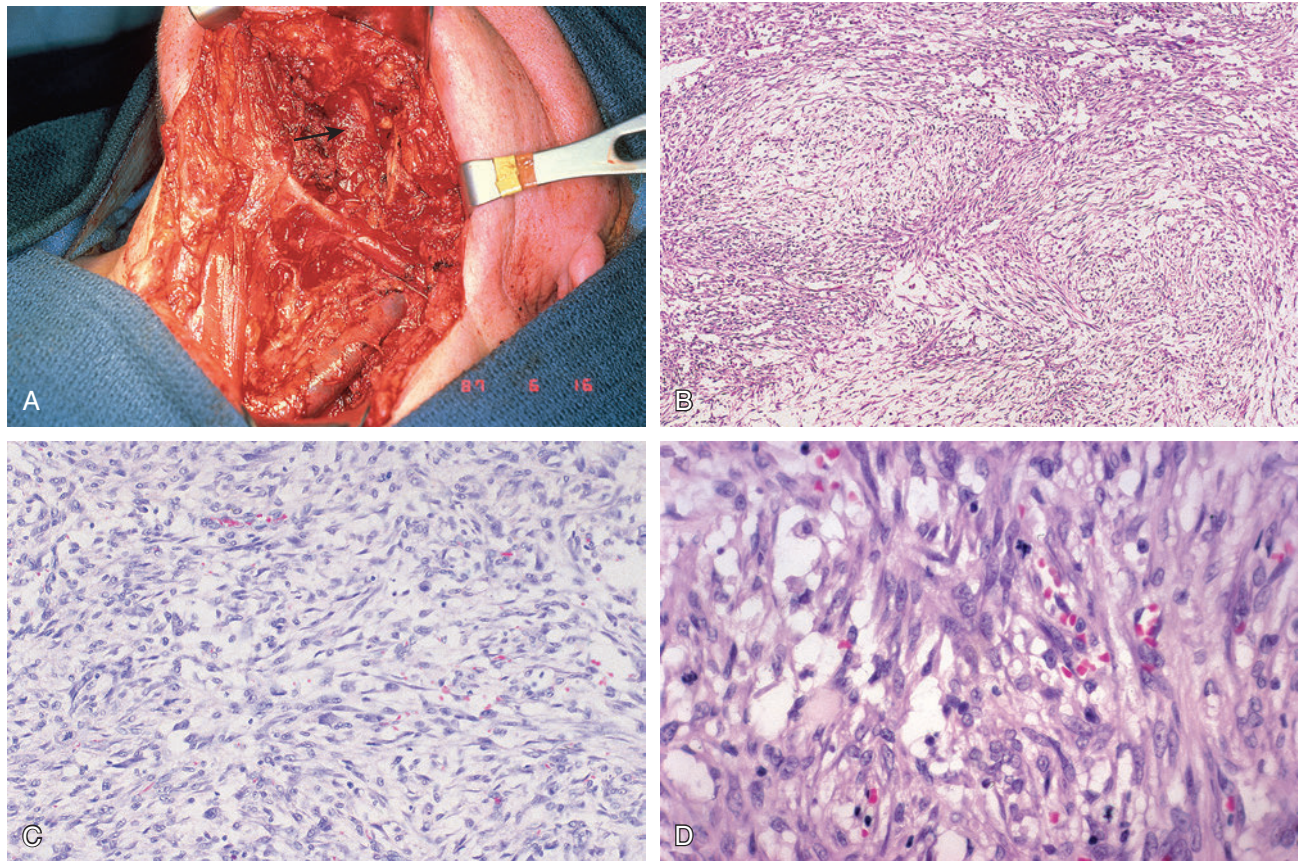


Fig. 13-4. Nodular fasciitis.

A, Surgical excision of a roughly rectangular soft tissue mass immediately above and to the right of the tendon identified in the center of the illustration. **B**, Proliferation of fibroblasts arranged in short, irregular fascicles to whorled appearance in a stroma with abundance ground substance creating a loose or “feathery” growth pattern. **C**, Cellular (myofibroblastic) component includes oval to plump to spindle-shaped cells with oval vesicular nuclei, prominent nucleoli, and basophilic appearing fibrillar cytoplasm; mature lymphocytes and extravasated red cells are present. **D**, Increased mitotic activity is a readily identifiable feature, but atypical mitoses are not seen.

- Stroma is rich in mucopolysaccharides, and this abundance of ground substance imparts a loose or “feathery” growth pattern characteristic of nodular fasciitides.
- Cells are oval, plump, or spindle shaped, vary slightly in size and shape, and have pale-staining nuclei with prominent nucleoli:
 - Cellularity varies and may demonstrate hypercellular and hypocellular areas even within the same lesion.
 - Increased mitotic activity is a prominent feature; however, atypical mitoses are not seen.
- Mature lymphocytes and extravasated erythrocytes are commonly seen scattered throughout the lesion.
- Less commonly identified features include the presence of multinucleated (osteoclast-like) giant cells and lipid-laden macrophages in the central portions of the lesion with plasma cells and histiocytes at the periphery of the lesion.
- Non-endothelial-lined slits or clefts are seen throughout the lesion.
- Collagen fibers may be seen but are thin and delicate rather than arranged in thick bundles; with time, fibrosis and microcysts are seen; the latter may coalesce to form large cystic spaces.
- Immunohistochemistry:
 - Immunoreactivity is present for actins (smooth muscle and muscle-specific) and vimentin:
 - CD68 (KP1) reactivity primarily seen in multinucleated giant cells and occasionally in spindle cells
 - Absence of nuclear β -catenin staining
 - Typically, nonreactive for S100 protein, epithelial markers, and ALK1

- Desmin is usually negative but may rarely be positive.
- Calretinin-positive and keratin-positive cells may be present:
 - Generally limited in extent
- Cytogenetic and molecular biology:
 - Consistent *MYH9-USP6* gene fusion

Differential Diagnosis

- Fibrous histiocytoma
 - Fibrous histiocytoma is less well circumscribed than NF but may share many histologic features with NF.
 - Fibrous histiocytoma and NF are closely related, and transitional forms between these entities occasionally occur.
- Myxoma
 - In contrast to NF, myxoma is a paucicellular to hypocellular lesion typically with poor vascularization.
- Fibromatosis
 - Fibromatosis often is an infiltrative lesion involving muscle, tends to be larger than NF, and is composed of spindle-shaped fibroblastic cells in long, sweeping fascicles separated by a collagenized stroma; nuclear β -catenin positive.
 - Mitotic activity may be seen but are less numerous as compared with NF (see later).
- Inflammatory myofibroblastic tumor (IMT):
 - IMTs are usually immunoreactive for ALK1 whereas NF is not.
- Benign peripheral nerve sheath tumors (schwannoma, neurofibroma):
 - In contrast to NF the cellular component includes wavy to buckled-appearing spindle-shaped cells that lack mitotic activity and that are S100 protein positive.
- Most important aspect of the pathologic diagnosis of nodular fasciitis is not to mistake it for a sarcoma:
 - Malignant neoplasms included in the differential diagnosis are malignant fibrous histiocytoma, fibrosarcoma, malignant peripheral nerve sheath tumors.
 - Differentiation from a sarcoma may be based on invasive growth pattern, increased cellularity characterized by the presence of hyperchromatic nuclei with cellular pleomorphism, atypical mitotic figures, and necrosis.
- Rarely, NF may occur in mucosal sites and in these locations the differential diagnosis can be expanded to include epithelial malignancies such as spindle cell squamous carcinoma (SCSC):
 - Similar to sarcomas the presence of cellular pleomorphism, atypical mitotic figures assist in differentiating NF from SCSC.

- Further, although cytokeratin and p63 reactivity in SCSC is variable, NF are nonreactive with cytokeratin and the presence of cytokeratin and/or p63 staining even if limited in extent would differentiate SCSC from NF.

Treatment and Prognosis

- Conservative but complete surgical excision is the preferred treatment.
- Local recurrence may occur in approximately 2% of all cases; usually occurs shortly following surgery; however, this is not necessarily an indication for additional surgery.
- Spontaneous regression may occur.
- Response (resolution) following intralesional corticosteroid injection has been reported.

Nuchal-Type Fibroma (NTF) (Fig. 13-5)

Definition: Benign fibroblastic proliferation involving dermis and subcutis.

Synonym: Extranuchal or nuchal-like fibroma

Clinical

- Rare lesion
- More common in men than women; occurs over a wide age range including first to eighth decades of life with a peak incidence in the third to fifth decades of life
- Predilects to the subcutaneous tissue of the posterior neck (i.e., nucha); extranuchal sites of involvement may include the upper back (interscapular and paraspinal regions), shoulder, face, extremities, and buttocks:
 - Owing to identical histologic findings shared by nuchal and extranuchal fibromas, the designation nuchal-type fibroma was proposed to encompass all histologically similar lesions.
- Presents as a painful subcutaneous mass; usually solitary but may be multifocal:
 - Notably associated with diabetes mellitus (30% to 40% of patients)
- Early reports documented apparent association of NTF with Gardner syndrome:
 - Such fibromas represent Gardner-associated fibromas rather than NTF.
 - Sufficient differences exist in the clinical and pathologic features between Gardner-associated fibroma and NTF to allow for their distinction.

Pathology

Gross

- Poorly circumscribed, firm to hard, gray to white mass attaining sizes larger than 3 cm

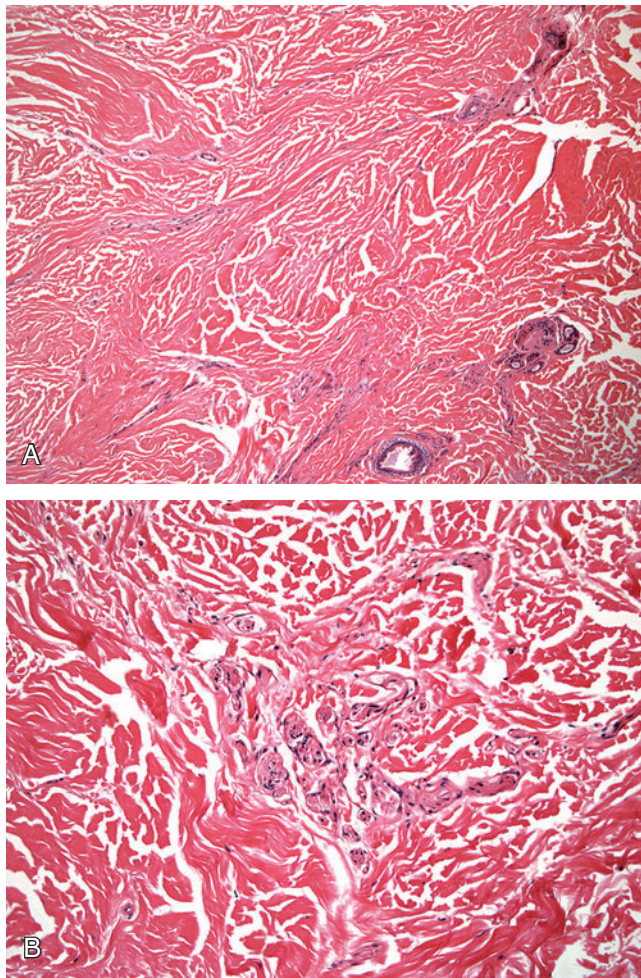


Fig. 13-5. Nuchal fibroma.

A, Acellular lesion composed of dense collagen with vaguely lobular appearance, entrapped cutaneous adnexa, and absent inflammatory cells. **B**, Entrapment of small nerves can be identified.

Histology

- Unencapsulated, acellular, or paucicellular lesion composed of dense collagen, haphazardly arranged collagen fibers forming a vaguely lobular appearance
- Entrapment and/or encasement of cutaneous adnexa, adipocytes, and small nerves may be identified.
- Expansion into subjacent skeletal muscle may be identified.
- Inflammatory cells are absent to sparse.

Differential Diagnosis

- Scar
- Lipoma and fibrolipoma

- Elastofibroma:
 - Deep-seated lesions of connective tissues typically located between the lower portion of the scapula and the chest wall:
 - Rare examples occur in lower extremity.
 - Peak incidence in the seventh and eighth decades of life; marked predilection for females
 - Slowly growing, poorly defined mass attached to periosteum of the ribs
 - Believed to develop from long-standing repeated trauma to tissues between scapulae and chest wall:
 - Clustering of cases (in particular in Japan) suggests genetic predisposition.
 - Cytogenetic and molecular analyses have shown clonality, further supporting genetic predisposition.
 - Irregular bands of dense hypocellular to paucicellular collagenous fibrous tissue and abundant eosinophilic elastic fibers; entrapped mature fat is present.
 - Elastic stain highlights beaded and lobular elastic fibers.
 - Scattered spindle cells are negative for smooth muscle actin, desmin, and S100 protein.
 - Surgical excision is preferred treatment.
 - No tendency for local recurrence
- Gardner-associated fibroma (GAF):
 - Usually occurs in younger patients than NTF:
 - Majority present in first decade of life
 - Mean age of 5 years reported
 - Most common locations include the back and paraspinal region.
 - Histologically composed of densely collagenized tissue with sparse population of bland spindle-shaped cells interspersed with lobules of mature adipose tissue
 - Entrapment of nerves, blood vessels, and fat at the periphery of the lesion can be identified but increased numbers of small nerve bundles as seen in NTF are not present in GAF.
 - Immunoreactivity for CD34, CD99, and β -catenin
 - May recur following incomplete excision
 - May be associated with desmoids (synchronous, metachronous)
 - Association with FAP; development of fibroma may precede years prior to manifestations/diagnosis of the syndrome
- Fibromatosis

Treatment and Prognosis

- Simple excision is the preferred treatment but NTF often recurs.
- No metastatic potential

LYMPHATIC MALFORMATIONS (TUMORS OF LYMPHATIC VESSELS)

General Considerations

- Believed to represent developmental malformation rather than true neoplasm; hence the current designation as lymphatic malformations
- Subclassified according to size, including:
 - Microcystic
 - Macrocystic (cysts greater than 0.5 cm)
 - Combined
- Diffuse lymphatic malformations involving multiple organs referred to as lymphangiomatosis
- Much less common than hemangiomas
- Majority are benign
- Differences between vascular and lymphatic endothelium can be achieved by immunohistochemical staining:
 - Lymphatic endothelium:
 - PROX1, LYVE1, VEGFR3 D2-40 (podoplanin) and CD31 positive
 - CD34 negative to weakly positive
 - Absence of type IV collagen and laminin around lymphatic endothelium correlates ultrastructurally to absence of basement membrane or pericytes investing lymphatic endothelial cell
 - Vascular endothelium:
 - CD34, CD31, and D2-40 positive
 - PROX1, LYVE1, VEGFR3 negative
 - Presence of type IV collagen and laminin around vascular endothelium correlates ultrastructurally to presence of basement membrane or pericytes investing vascular endothelial cell
- Classification of lymphangiomas includes:
 - Cavernous lymphangioma
 - Cystic hygroma
 - Lymphangioma circumscriptum
 - Acquired progressive lymphangioma (benign lymphangioendothelioma)
 - Lymphangiomatosis (diffuse lymphatic malformation involving multiple organs)
 - Multifocal lymphangiomatosis and thrombocytopenia
- May be further subclassified by size, including:
 - Microcystic
 - Macrocystic (cysts greater than 0.5 cm)
 - Combined
- In the head and neck, the most common type of lymphatic malformation (lymphangioma) is cystic hygroma.

Lymphatic Malformation (Cystic Hygroma) (Figs. 13-6 through 13-8)

Definition: Benign lesion of lymphatic spaces.

- Name derived from Greek: fluid (*hygros*) tumor (*oma*)
- Appears to be a variant of cavernous lymphangioma

Clinical

- No gender predilection; usually present at birth:
 - Up to two thirds of cases diagnosed at birth
 - From 80% to 90% identified by 2 years of age
 - Rarely occurs in adults
- May occur anywhere in the body but most commonly are seen in the head and neck region
- In the head and neck, majority are identified in the lateral neck (posterior and anterior triangles)
 - Rarely seen in the midline
 - May extend into the thorax
- Presentation is usually as a painless, soft neck mass, which can achieve large sizes, filling the entire side of the neck:
 - Large lesions compress adjacent structures, potentially causing dysphagia, dyspnea, and stridor.
 - Pain is not commonly seen unless infection is present.
- Presumed to arise as congenital anomalies of the jugular lymphatic sac.
- Due to the potential for extension of the lesion away from the neck (e.g., intrathoracic), appropriate clinical evaluation should include complete radiographic evaluation including chest radiographs.
- Radiology:
 - Well-circumscribed, fluid-filled, solitary, or multicystic mass varying in density based on the presence or absence of intracystic hemorrhage or infection
- Congenital or acquired:
 - Commonly seen in patients with Turner syndrome
 - Can be associated with other congenital anomalies, including:
 - Thyroglossal duct cysts, harelip, congenital heart anomalies, hand and feet deformities, Down syndrome
 - Associated with raised amniotic fluid levels of alpha-fetoprotein, which may be seen in cases of in utero cystic hygromas

Pathology

Gross

- Soft, single or multiloculated, compressible mass varying in size from a few centimeters to greater than 30 cm

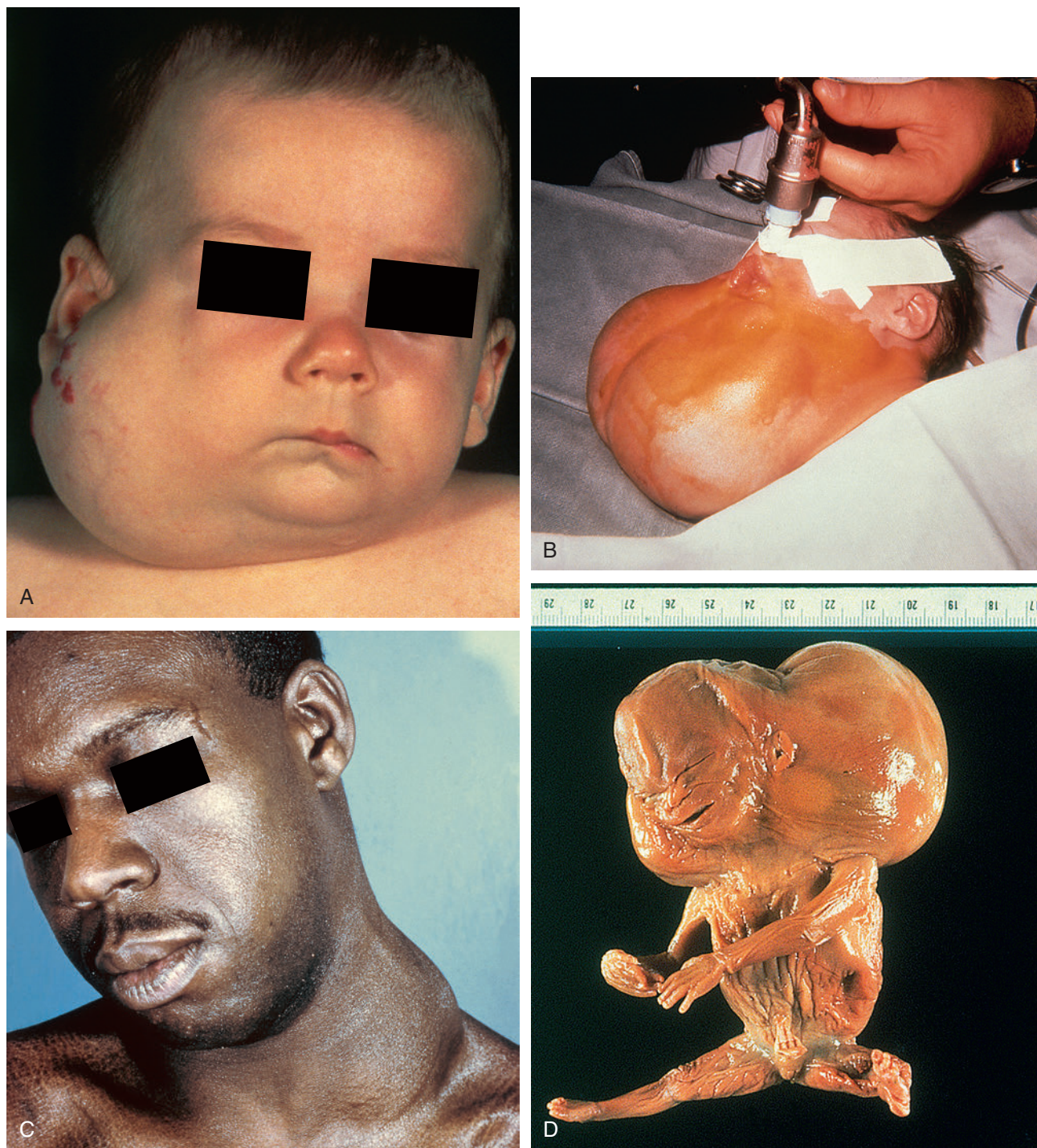


Fig. 13-6. Cystic hygroma.

A through **D**, Lateral neck masses in different aged patients, including one (**D**) that occurred in utero.

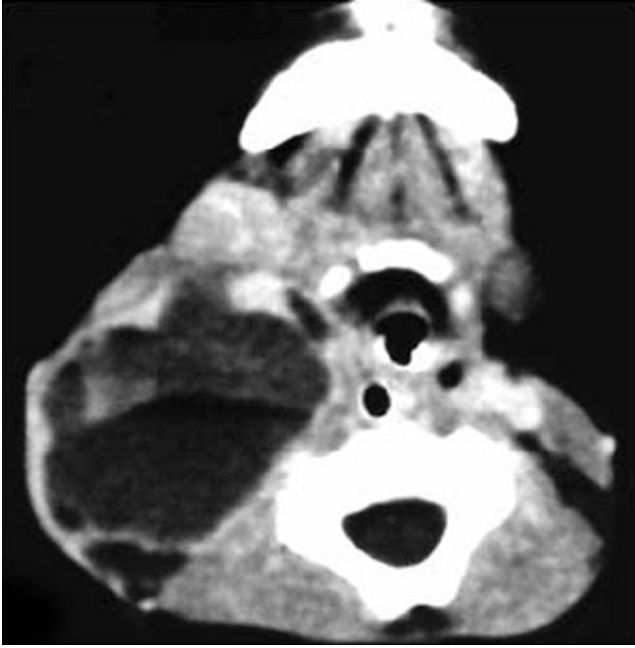


Fig. 13-7. Cystic hygroma.

Axial CT scan of this 3-year-old child shows multiple cystic masses in the right supraclavicular fossa and the lower posterior triangle of the neck. This is a typical appearance of cystic hygromas (cystic lymphangiomas). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 2267, Fig. 37-48, A.)

- Overlying skin may appear unremarkable or atrophic and may have a blue hue.
- In cases uncomplicated by hemorrhage or infection, the cysts contain clear to lightly pink watery fluid.

Histology

- Large, irregularly shaped spaces lined by a single layer of endothelial cells and containing proteinaceous fluid and lymphocytes
- Intervening stroma contains small amounts of fibrous connective tissue and muscle with lymphoid aggregates; however, the stroma may become inflamed and fibrotic following repeated infections.
- Immunohistochemistry:
 - Podoplanin (D2-40) reactivity
 - PROX1 and VEGFR3 positive:
 - Greater sensitivity than podoplanin
 - CD31 positive and CD34 absent but may be variably reactive
 - Glucose transporter protein 1 (GLUT1) negative

Differential Diagnosis

- Branchial cleft cyst
- Thyroglossal duct cyst
- Teratoma
- Ranula

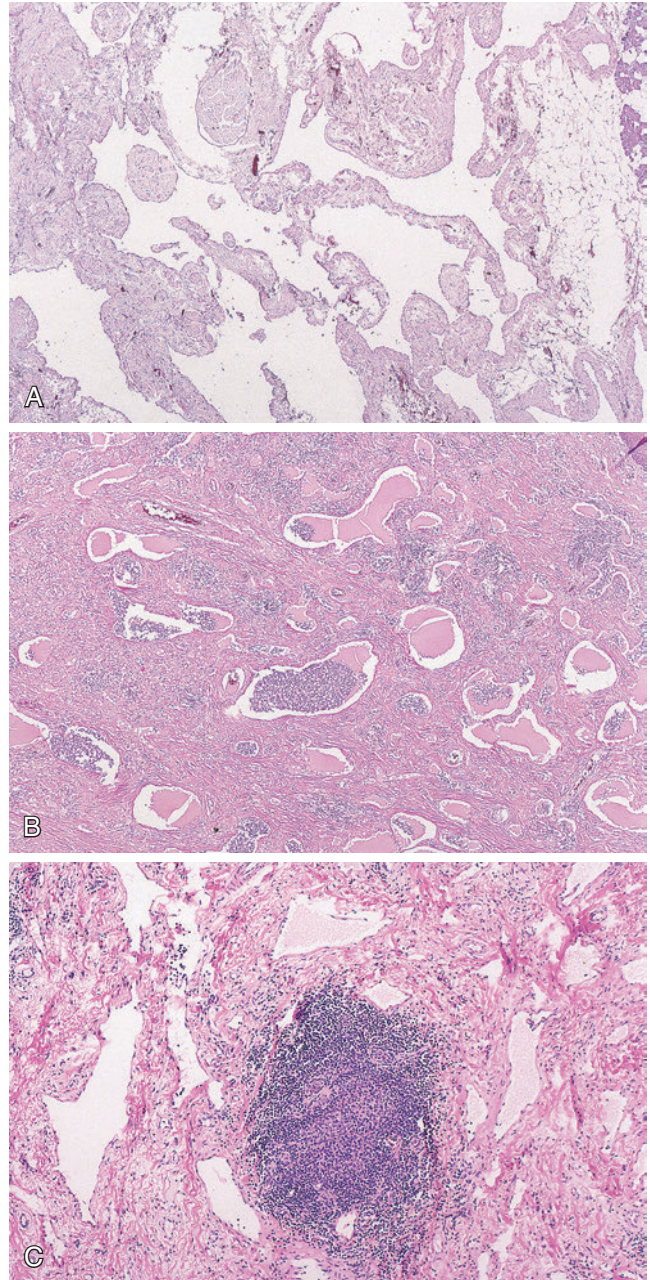


Fig. 13-8. Cystic hygroma.

A and B, The histology of lymphatic malformation (cystic hygroma) is characterized by large, irregularly shaped spaces lined by a single layer of endothelial cells and containing proteinaceous fluid and lymphocytes. **C,** The intervening stroma may contain lymphoid aggregates as seen in the center of this image. Other mesenchymal structures that may be present include small amounts of fibrous connective tissue, smooth muscle, and adipose tissue. The latter is present in part **A** at the extreme right of that illustration.

Treatment and Prognosis

- Some lymphangiomas may undergo spontaneous regression and in infants with uncomplicated lesions, surgery should be postponed until 3 to 5 years of age to allow for regression of the lesion:
 - If no sign of involution by age 5, then surgery is indicated.
 - Complete excision is recommended.
 - Recurrent infections and symptoms of compression or life-threatening symptoms necessitate surgical intervention at younger ages.
 - Other therapeutic modalities that have been used with varying success include radiation, intralesional injection of corticosteroids, sclerosing agents, and cryosurgery.
 - Advances in sclerotherapy with OK-432 (picibanil), a lyophilized mixture with group A *Streptococcus pyogenes*, have shown significant promise:
 - Approximately one third of cases respond to sclerotherapy with OK-432.
 - Initial and long-term response rates are equally good and reported to be 84% and 76%, respectively.
 - Safe, effective, and associated with few side effects
 - Factors predicting good response include:
 - Location in head and neck
 - Size less than 5 cm
 - Macrocystic architecture
- Recurrence rates following surgery range from 5% to 10% and may represent persistence rather than true recurrence of the lesion.
- No malignant potential
- Lesions may extend extensively through soft tissue structures and can extend to the base of skull, floor of mouth, and into the mediastinum and/or thoracic cavity.
- Death due to pneumonia, airway obstruction, or atelectasis may rarely occur.

NEUROENDOCRINE NEOPLASMS

Paragangliomas

Definition: Benign neuroendocrine tumor arising from the neural crest–derived paraganglia of the autonomic nervous system.

General Considerations

- Paragangliomas can be divided into adrenal and extra-adrenal.
- Adrenal-derived paraganglioma arising from the adrenal medullary chromaffin cells is traditionally referred to as a pheochromocytoma.
- Extra-adrenal paraganglia are divided into sympathetic and parasympathetic types:
 - Differences include anatomic distribution and secretory product:
 - Sympathetic paraganglia:
 - Axial region of the trunk along prevertebral and paravertebral sympathetic chains and in connective tissue in and around pelvic organs
 - Produce catecholamines
 - Tumors associated with sympathetic system produce epinephrine (adrenaline)
 - Tumors associated with clinical symptomatology related to excess catecholamine production are usually of the sympathetic paraganglia.
 - Less likely to be familial
 - More likely to be malignant
 - Parasympathetic paraganglia:
 - Localized to head and neck along branches of the glossopharyngeal nerve (jugulotympanic paraganglioma) and vagus nerve (carotid body paraganglioma)
 - Produce catecholamines:
 - Secretory product tends to be dopamine
 - Not usually associated with clinical symptoms due to secretory product
 - Greater tendency to occur in patients with hypoxemia
 - More often familial
 - Less likely to be malignant
- Terminology/classification of extra-adrenal paraganglia includes paraganglioma prefaced by the anatomic site of occurrence:
 - Paragangliomas of the head and neck include:
 - Carotid body paraganglioma
 - Jugulotympanic paraganglioma (middle ear and temporal bone)
 - Vagal paraganglioma
 - Rare head and neck sites of occurrence include:
 - Laryngeal paraganglioma
 - Primary thyroid paraganglioma
 - Paraganglioma of the nasal cavity and nasopharynx
 - Most common site of occurrence in the head and neck is the carotid body; jugulotympanic paragangliomas represent the second most common site of occurrence (see Section 7, Ear).

Carotid Body Paraganglioma (Figs. 13-9 through 13-11)

Definition: Benign neuroendocrine tumor arising from the carotid body paraganglia with characteristic histologic findings:

- Carotid body paraganglia are paired, bilateral aggregates of neuroendocrine tissues identified in the

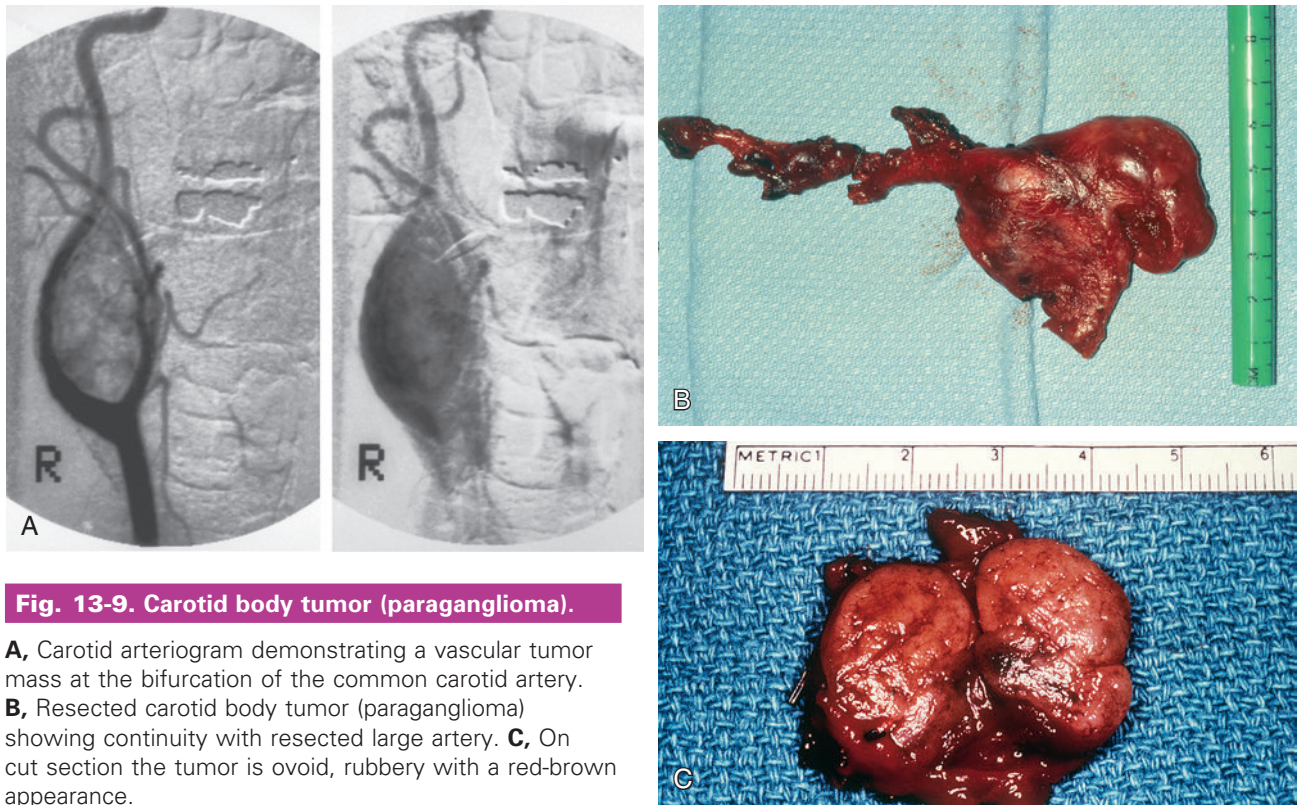


Fig. 13-9. Carotid body tumor (paraganglioma).

A, Carotid arteriogram demonstrating a vascular tumor mass at the bifurcation of the common carotid artery.

B, Resected carotid body tumor (paraganglioma) showing continuity with resected large artery. **C,** On cut section the tumor is ovoid, rubbery with a red-brown appearance.

medial aspect of the common carotid artery and its bifurcation:

- Along with the aortic body paraganglia function as chemoreceptors
- Sensitive to changes in oxygen tension, carbon dioxide content, and hydrogen ion concentration

Synonyms: Chemodectoma; carotid body tumor; glomus tumor; nonchromaffin paraganglioma

Clinical

- Uncommon tumor but considered to be the most common paraganglioma in the head and neck
- No gender predilection in tumors occurring at sea level; significant female predilection in tumors occurring at higher altitudes:
 - Female predilection at higher altitudes hypothesized to be related to monthly menstrual loss of blood and larger pulmonary capacity with resulting (chronic) hypoxia.
- Occurs over a wide age range but is most common in the fifth to sixth decades of life; uncommon in children
- Most common symptom is a painless, slowly enlarging neck mass typically localized deep to the anterior border of the sternocleidomastoid muscle just below the angle of the mandible:
 - Often, the mass has been present for years prior to the patient seeking medical attention
 - Frequently a palpable (anterolateral) neck mass
- Typically vertically fixed and laterally mobile due to its fixation to the carotid artery
- May be pulsatile; bruits reported in 10% to 16% of cases
- May become adherent or invasive as they enlarge:
 - May encase carotid arteries (external and/or internal)
 - May extend to parapharyngeal space, causing submucosal bulging in the lateral oropharynx
- Typically unilateral but may infrequently be bilateral and/or multifocal:
 - Other paragangliomas seen may include vagal paraganglioma and jugulotympanic paraganglioma
 - May be combined in association with a pheochromocytoma
 - May occur in association with thyroid carcinoma
 - May be a component of multiple endocrine neoplasia (MEN) syndrome or Carney's triad
- In general, this is a slow-growing tumor but it can attain a large size, leading to additional symptoms including:
 - Parapharyngeal or hypopharyngeal mass
 - Hoarseness
 - Cranial nerve deficits (10% to 30%), pain (25%), vocal cord paralysis, dysphagia, and Horner syndrome
 - Horner syndrome results from an interruption of the sympathetic nerve supply to the eye and

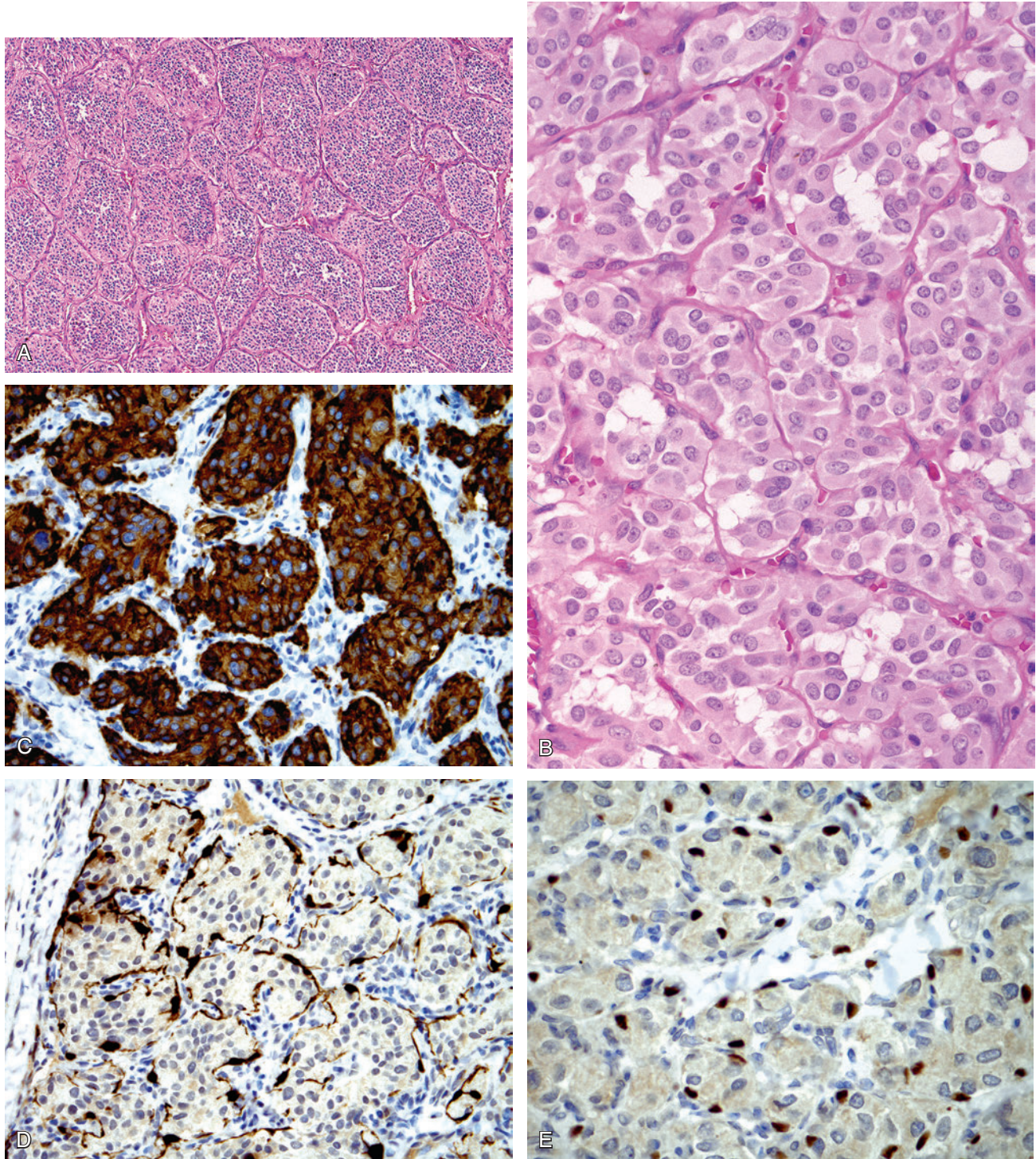


Fig. 13-10. Carotid body tumor (paraganglioma).

A, Characteristic histologic picture includes a cell nest or “Zellballen” growth pattern with a prominent fibrovascular connective tissue stroma surrounding and separating the nests. **B**, The neoplasm is composed predominantly of chief cells, which are round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm peripherally surrounded by sustentacular cells, which are often difficult to identify by light microscopy and appear as spindle-shaped, basophilic cells. **C**, Chief cells are diffusely immunoreactive with synaptophysin. **D**, Characteristic S100 protein staining is identified in peripherally situated sustentacular cells. **E**, Sox10 is another marker showing reactivity in the sustentacular cells in paragangliomas.

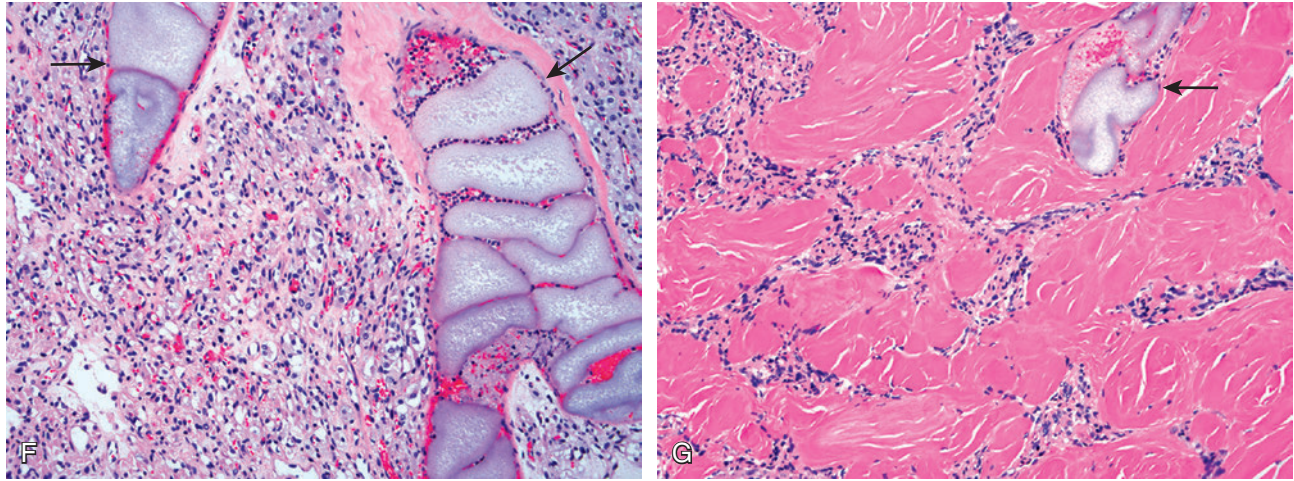


Fig. 13-10, cont'd

F, Intravascular foreign material (*arrows*) is evidence of preoperative embolization. Note the absence in the tumor of characteristic organoid or cell nest pattern of growth typically seen in paragangliomas. **G**, In addition to absence of organoid pattern of growth there is associated dense fibrous stroma, suggesting infiltrative growth that may result in erroneous interpretation, including a malignant neoplasm; note the intravascular embolization material (*arrow*).

- is characterized by the classic triad of miosis (i.e., constricted pupil), partial ptosis, and loss of hemifacial sweating (i.e., anhidrosis)
- Headache and syncope
- Rarely, may be functional but, in general, is nonfunctional, which is true relative to other paragangliomas of the head and neck
- Increased incidence of carotid body hypertrophy and carotid body paragangliomas in populations living in high altitudes likely related to chronic hypoxemia:
 - Ninefold increase in carotid body paragangliomas in people living between 2000 and 3000 m above sea level and 12-fold increase in incidence in people living between 3000 and 4500 m above sea level
 - In addition, carotid body tumors occurring in patients at higher altitudes as compared with those occurring in patients at sea level:
 - Predilect to women
 - Lower rate of bilaterality
 - Less frequent familial history
 - A higher incidence of carotid body hypertrophy and carotid body paragangliomas in patients with chronic obstructive pulmonary disease likely related to chronically low pO_2 levels.
- Radiology
 - Carotid arteriogram:
 - Hypervascular tumor mass at the bifurcation of the common carotid artery that may (eventually) result in splaying of the internal and external carotid arteries
 - Tumor may extend superiorly and involve the parapharyngeal space.
 - Contrast-enhanced CT:
 - Homogeneous, hypervascular, well-delineated soft tissue mass
 - MRI with gadolinium:
 - T1-weighted:
 - Well-defined hypointense mass with areas of signal void
 - T2-weighted:
 - Due to areas of high vascularity associated with hemorrhage or slow blood transfusion, a “salt and pepper” pattern is identified.
 - May allow for detection of smaller lesion
 - Octreotide scintigraphy:
 - As a neuroendocrine tumor, paragangliomas have a high density of somatostatin 2 receptors on their cell surface.
 - Octreotide is a somatostatin analog; when coupled with radioisotope indium III, octreotide creates a scintigraphic image of tumors expressing somatostatin type 2 receptors.
 - Noninvasive imaging modality used to confirm diagnosis:
 - Diagnostic accuracy of 90%, sensitivity of 94%, and specificity of 75% in tumor detection
 - Used to detect additional small and/or occult tumors
 - Used to screen patients at risk for familial (inherited) paraganglioma(s)

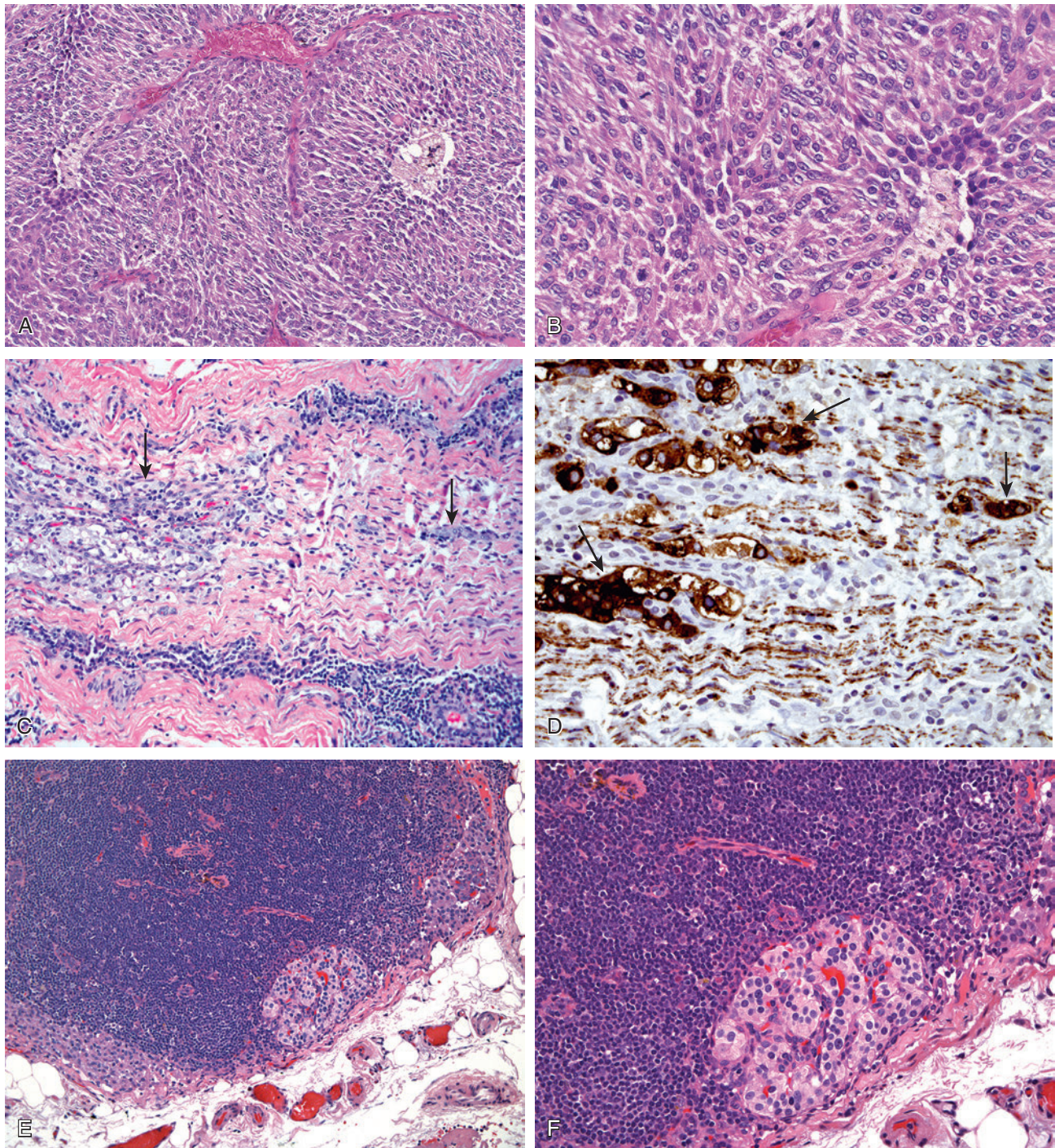


Fig. 13-11. Malignant paraganglioma.

Features that may be associated with malignancy but that are not definitive for malignancy include **(A and B)** increased mitotic activity and necrosis, the latter usually seen within the center of the cell nests. **(C)** Perineural and intraneural invasion (*arrows*) may be seen in paragangliomas but is not considered evidence of malignancy. **(D)** Synaptophysin strongly details the paraganglioma (*arrows*) lying adjacent to and within a peripheral nerve, the latter with less intense but positive synaptophysin staining. **E and F**, Definitive evidence for malignancy in a paraganglioma is predicated on the presence of metastatic disease as seen in these illustrations showing the tumor within the subcapsular sinus of a cervical neck lymph node diagnostic for metastatic paraganglioma.

- Cause includes chronic hypoxia and familial inheritance (hereditary paraganglioma)
- May develop in association with various hereditary disorders, including:
 - MEN type 2A
 - MEN type 2B
 - von Hippel-Lindau syndrome
 - Neurofibromatosis type 1 (NF1)
- Familial or hereditary paraganglioma:
 - Overall 10% to 50% of paragangliomas are familial
 - Autosomal-dominant inheritance with genomic imprinting:
 - Paternal transmission of the gene
 - No tumor when gene inherited from the mother
 - One third of familial carotid body paragangliomas are bilateral, which may be synchronous or asynchronous.
 - Hereditary deficiency of clotting factors VII and X identified in few patients with familial carotid body paraganglioma
 - Genetic analysis in hereditary paragangliomas have shown three loci associated with these tumors:
 - Paraganglioma 1 (PGL1) on chromosome 11q23
 - Paraganglioma 2 (PGL2) on chromosome 11q13.1
 - Paraganglioma 3 (PGL3) on chromosome 1q21-q23
 - Genetic testing may assist in early diagnosis and/or identification of patients at risk for familial (hereditary) paraganglioma.
 - Germline mutations in succinate dehydrogenase (SDH) genes implicated in the pathogenesis of hereditary paraganglioma:
 - SDH is a mitochondrial enzyme complex with important role in oxidative phosphorylation and intracellular oxygen sensing and signaling
 - Mutations in three genes (*SDHB*, *SDHC*, and *SDHD*) implicated in the pathogenesis of hereditary paraganglioma
 - These genes appear to function as tumor suppressor genes.
 - Genes participate in encoding distinct subunits of a hetero-oligomeric electron transport chain in the Krebs cycle.
 - Identification of the causative genes allows for detection of individuals at risk for these tumors.
 - Paraganglioma (PGL) syndrome includes inherited head and neck paragangliomas and adrenal or extra-adrenal pheochromocytomas and are classified according to the susceptibility genes *SDHB*, *SDHC*, and *SDHD*.
- Germline mutations of genes encoding *SDHB* and *SDHC* predispose to paraganglioma syndromes:
 - *SDHD* gene identified as the susceptibility gene for PGL type 1 (PGL1)
 - *SDHB* gene identified as the susceptibility gene for PGL type 4 (PGL4)
 - Very few PGL type 3 (PGL3) families have been identified with a germline mutation of *SDHC* gene.
 - Susceptibility gene for PGL type 2 (PGL2) remains unidentified.
 - Head and neck paragangliomas associated with *SDHC* mutations are virtually exclusively benign and seldom multifocal.
 - *SDHD* mutation carriers (PGL1) have more frequent multifocal paragangliomas and are rare in patients with sporadic single tumors.
 - *SDHB* mutation carriers (PGL4) are more likely to develop malignant disease and possibly extraparaganglial neoplasias, including renal cell carcinoma and thyroid carcinomas
- If a diagnosis of carotid body paraganglioma is clinically suspected, then open biopsy is contraindicated due to risk of hemorrhage.
- Grouping of carotid body tumors according to size and vessel involvement is inconsistent in the literature; classification of carotid body paragangliomas (Shamblin's surgical classification) is based on surgical findings related to carotid artery involvement (Table 13-3).

Pathology

Gross

- Encapsulated or well-circumscribed, ovoid, rubbery to firm, red-pink to tan-gray tumor of varying size from 2 to 6 cm in greatest dimension
- A centrally or peripheral placed identifiable large artery may be identified associated with the tumor mass.

TABLE 13-3 Shamblin's Surgical Classification of Carotid Body Tumors

Group I	Tumors are relatively small with minimal attachment to carotid vessels
Group II	Tumors are larger with moderate arterial attachment and can be resected with precise surgical dissection
Group III	Larger tumors encasing the carotid arteries and can be resected only with arterial sacrifice

Histology

NOTE: Regardless of the site of origin, the histologic appearance of all extra-adrenal paragangliomas is the same.

- Characteristic cell nest, organoid, or “Zellballen” pattern of growth with tumor nests surrounded and separated by fibrovascular stroma
- Neoplasm is composed predominantly of chief cells and peripherally situated sustentacular cells:
 - Chief cells (so-called type I cells):
 - Round or oval with uniform nuclei, dispersed chromatin pattern and abundant eosinophilic, granular, or vacuolated cytoplasm
 - Sustentacular cells (so-called type II or supporting cells):
 - Represent modified Schwann cells
 - Identified at the periphery of the cell nests as spindle-shaped, basophilic-appearing cells
 - May be difficult to identify by light microscopy
- No glandular or alveolar differentiation seen
- Cellular pleomorphism may be present; mitoses and necrosis are infrequently identified:
 - Necrosis may be identified in those tumors successfully embolized prior to surgery.
- Spindling of the chief cells may be seen and infrequently may predominate.
- Preoperative embolization:
 - Very useful adjunct to surgery of large paragangliomas
 - Used in the attempt to shrink the size of the tumor as well as reducing intraoperative bleeding is generally associated with easier dissection (e.g., more obvious tissue planes, less risk to normal anatomic structures)
 - Risks include escape of embolizing particles into cerebral circulation with risk of stroke
 - May result in the identification of intravascular and extravascular foreign material (with or without associated multinucleated giant cells) in resection specimens
- Similar to jugulotympanic paragangliomas (see Section 7), carotid body paragangliomas, and other paragangliomas may not display characteristic cell nest or organoid growth but appear compressed due to artifactual distortion secondary to surgical manipulation (“squeezing”) of the tissue during removal:
 - In addition to the loss of an organoid pattern of growth, carotid body paragangliomas may be associated with a dense fibrous stroma and an appearance of infiltrative growth.
 - These findings may result in overlooking a diagnosis and thus in an erroneous interpretation including a malignant neoplasm.
- Awareness of this occurrence and use of appropriate special stains should allow for a correct diagnosis.
- Infiltrative growth including perineural invasion and/or lymph-vascular invasion may be identified but is not indicative of malignancy and/or considered to have prognostic import (see later for criteria of malignancy).
- Histochemistry:
 - Tumor cells are argyrophilic positive.
 - Reticulin staining delineates the cell nests.
 - Argentaffin, mucin, and periodic acid Schiff stains are negative.
- Immunohistochemistry:
 - Chief cells:
 - Chromogranin, synaptophysin, CD56, neuron-specific enolase and GATA3 (nuclear) positive
 - Calcitonin negative
 - Cytokeratins, carcinoembryonic antigen, and other epithelial markers negative (rarely, cyto-keratin staining reported)
 - CD10 negative
 - Myogenic markers and melanocytic markers (HMB45, melan-A, tyrosinase, MITF1) negative
 - Sustentacular cells:
 - S100 protein and glial fibrillary acidic protein positive
 - Sox10, a transcription factor in neural crest developed and differentiation of neural crest cells into melanocytic and schwannian lineage, may also be reactive (nuclear staining) in the sustentacular cells of paragangliomas (and pheochromocytoma)
- Electron microscopic:
 - Hallmark of the EM findings is the presence of neurosecretory granules.

Differential Diagnosis

- Rhabdomyoma
- Hemangiopericytoma
- Neuroendocrine carcinoma
- Alveolar soft part sarcoma
- Metastatic medullary carcinoma of the thyroid gland
- Metastatic renal cell carcinoma

Treatment and Prognosis

- Surgical excision is the preferred treatment, which may necessitate excision of one or more branches of the carotid arterial system:
 - Relative contraindications to surgery include:
 - Extensive skull base or cranial involvement
 - Advanced patient age
 - Medical comorbidities

- Bilateral or multifocal tumors that may result in unacceptable postoperative morbidity with resultant bilateral lower cranial nerve palsies
- If surgery is the chosen treatment course, then preoperative embolization is performed:
 - Embolization is a useful adjunct in treatment, especially of large paragangliomas
 - Main objective of embolization is directing the embolism material to selectively permeate only the vascularity of the paraganglioma without proximal occlusion of the feeding artery
 - Postembolization arteriography is performed to document the absence of tumor “blush” with continued patency of the external carotid system
 - Successful embolization results in improved surgical resection directly related to decreased tumor vascularity with reduction in tumor size as much as 25% due to diminished tumoral blood flow
 - Reduction of tumor size results in less manipulation of surrounding structures required for exposure during surgery.
 - In addition, embolization results in less blood loss during surgical dissection of the tumor.
 - Essential that surgery be performed within 48 hours of embolization to avoid recruitment of collateral circulation
- Radiotherapy initially used to treat unresectable tumors (i.e., extensive skull base involvement or intracranial extension) or for surgical treatment failures has become an established treatment modality in untreated lesions and has been incorporated into the treatment algorithms for head and neck paragangliomas:
 - External beam radiation, intensity modulated radiation therapy, and stereotactic radiation therapy have been used with excellent results.
 - Most commonly treated site has been jugulotympanic paraganglioma > carotid body or vagal paraganglioma.
 - Conventional fractionated radiotherapy and stereotactic radiosurgery have been used:
 - Stereotactic radiosurgery (SRS) offers the possibility of a single, highly focused small-field treatment with a steep dose gradient to maximally spare surrounding normal tissue.
 - SRS delivered by either radioactive cobalt sources (gamma knife) or generation of radiation from a linear accelerator (LINAC)
 - Successful treatment with radiotherapy defined as local control with stability or regression of tumor size and nonprogression or improvement in neurologic symptoms
 - Rarely, total resolution of the tumor occurs following radiotherapy.
- Prognosis is excellent following complete resection:
 - Recurrence may occur in up to 10% of patients and generally is correlated to inadequate surgical excision.
- Benign tumors with indolent biology; however, some tumors may be locally invasive (and not malignant)
- Approximately 10% may be malignant as manifested by local invasion or metastases to regional lymph nodes or to the lung.
- Malignant paragangliomas:
 - Sporadic (nonfamilial) tumors are more likely to be malignant than familial or inherited paragangliomas.
 - SDHB mutation carriers (PGL4) are more likely to develop malignant disease and possibly extraparaganglial neoplasias including renal cell carcinoma and thyroid carcinomas.
 - Incidence of malignancy in carotid body paragangliomas is from 2% to 13% of cases.
 - Morphologic features correlating with malignant behavior not well defined and histology is not predictive of behavior:
 - Local invasion considered poor predictor of metastasis; absence of invasion does not preclude development of metastatic disease.
 - Histologic criteria for malignancy:
 - Unequivocal evidence:
 - Metastatic tumor to lymph nodes or viscera (e.g., lung, liver, bone)
 - Features that may be associated with malignancy but that are not definitive for malignancy include:
 - Increased mitotic activity
 - Necrosis usually seen within the center of the cell nests
 - Lymph-vascular invasion
 - Perineural invasion
 - DNA ploidy
 - Absence of sustentacular cells
 - Histologic criteria for malignancy can also be identified in benign paragangliomas; therefore metastasis is considered to represent the only true criterion for malignant paraganglioma.
 - Estimated 10% malignancy rate associated with carotid body paragangliomas may be high and may represent multicentric occurring paragangliomas.
 - Treatment for malignant paragangliomas includes resection of the primary and metastatic lesions with postoperative radiotherapy.
 - Limited literature relative to follow-up/prognosis of malignant carotid body paragangliomas but include disease-free survival from 15 months to 6 years

BENIGN NEOPLASMS OF ADIPOSE TISSUE

General Considerations

- Adipose tissue is divided into two types:
 - White fat:
 - Contains a high percentage of lipids (80% to 90%) with a greater concentration of triglycerides
 - Ultrastructurally, contains few mitochondria lying with little direct contact with fat vacuoles
 - With age, amount of white fat increases
 - Most lesions/tumors of adipose tissue are of white fat
 - Tumors of white fat collectively referred to as lipomas
 - Brown fat:
 - Contains lower percentage of lipids (40% to 50%) with a greater percentage of phospholipids
 - Ultrastructurally, contains numerous pleomorphic mitochondria lying in intimate contact with fat vacuoles
 - With age, amount of brown fat decreases
 - Tumors of brown fat referred to as hibernoma
- Adipocytic tumors represent one of the largest single groups of soft tissue tumors:
 - Primarily due to high incidence of benign subcutaneous lipomas
- Other than lipomas and hibernoma, other lesions/tumors of fat include:
 - Fat necrosis
 - Lipoblastoma and lipoblastomatosis
 - Benign symmetric lipomatosis

Lipomas

Definition: Benign tumor of mature (white) adipose tissue.

Clinical

- Overall, lipomas represent the most common mesenchymal tumor in adults:
 - Primarily due to high incidence of benign subcutaneous lipomas
- Lipomas of childhood are uncommon.
- Approximately 15% of all lipomas occur in the head and neck region.
- Lipomas can be seen in all areas of the head and neck, but the most common site of occurrence is the neck area, especially the posterior neck:
 - Other sites in which lipomas are seen include parotid gland, oral cavity (buccal mucosa), pha-

ryngeal region (hypopharynx and retropharynx), and larynx (see Section 5 for discussion on laryngeal lipomas)

- Intraoral lipomas:
 - Most common site is the buccal mucosa followed by the tongue, lips, and floor of mouth.
- More common in men than women; occur in all age groups but most commonly seen in the fifth and sixth decades of life
- Symptoms are generally related to a painless soft tissue mass; exceptions include:
 - Pain and/or sensory and motor nerve disturbances are rarely seen but may occur by compression of nerves by large tumors
 - Upper respiratory tract lipomas present with symptoms related to airway obstruction, problems with deglutition, or voice disturbances (hoarseness, voice changes); often, symptoms manifest only after the tumor has reached a considerably large size.
- Usually solitary but may be multiple
- Radiology:
 - Homogeneous soft tissue mass isodense to the subcutaneous tissue

Pathology

Gross

- Well-circumscribed to encapsulated, soft and round, and varying in size from a few millimeters to greater than 20 cm
- Cut section shows an irregular lobular pattern with a yellow color and a soft, greasy consistency.

Histology

- Classification of lipomas based on histologic findings, as well as other parameters (e.g., clinical) and include:
 - Conventional or ordinary lipoma
 - Angiolipoma
 - Relatively unique clinical and histopathologic findings to merit specific categorization except not common in the head and neck region
 - Angiomyolipoma:
 - Belong to family of perivascular epithelioid cell tumor (PEComa), see later
 - Myxoid lipoma
 - Fibrolipoma
 - Angiomyolipoma
 - Myolipoma
 - Myelolipoma
 - Chondroid lipoma
 - Intramuscular (infiltrating) lipoma
 - Pleomorphic lipoma and spindle cell lipoma:
 - Relatively unique clinical and histopathologic features, including common occurrence in the neck region and cytogenetic findings,

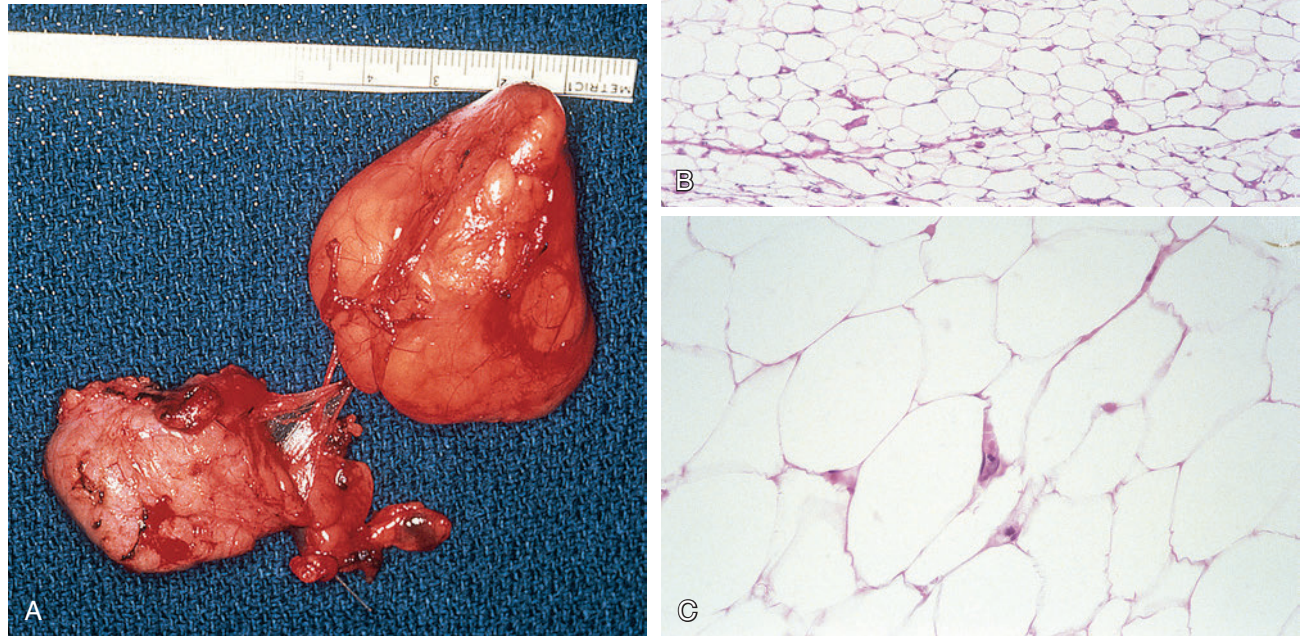


Fig. 13-12. Cervical neck lipoma.

A, The tumor is encapsulated, irregularly shaped, yellow, and focally attached to the submandibular gland (*lower left*). **B**, Characteristic histologic appearance of a lipoma composed of uniform-appearing mature fat cells (adipocytes) with little variation in size and shape. **C**, At higher magnification the adipocytes consist of vacuolated cells with compression and peripheral placement of the nuclei.

respectively, to merit more specific categorization rather than simply representing a histologic type/variant of lipoma (see later)

Conventional Lipoma (Fig. 13-12)

- Thin capsule surrounding a tumor arranged in a lobular growth pattern
- Tumor is composed of mature fat cells (adipocytes) consisting of a vacuolated cell with compression and peripheral placement of the nucleus; little variation in size and shape of the adipocytes.
- Lipoblasts are not seen.
- Richly vascularized but typically the vascular network is difficult to identify due to compression by distended lipocytes
- Secondary changes due to trauma or vascular compromise include necrosis, hemorrhage, infarction, calcification, and cyst formation.
- Cytogenetics and molecular genetics:
 - Chromosome aberrations found in 55% to 75% of cases with three cytogenetically defined subgroups:
 - Translocations involving 12q13-15 (65%)
 - Rearrangements of 13q (10%):
 - Deletions and structural rearrangements of the long arm of chromosome 13 are frequently observed in benign (and low-malignant) lipomatous tumors.
 - Rearrangements of 6p21-23 (5%)
 - Rearrangements of *HMGIC* gene (also referred to as *HMG2* gene) found
 - Some have gains of *MDM2*.
- Histologic types of lipomas include:
 - Myxoid lipoma:
 - Presence of mucoid or myxoid stroma replacing portions of the tumor
 - Fibrolipoma and sclerotic lipoma:
 - Fibrolipoma: admixture of fibrous connective tissue (not associated with the capsule or fibrous septa), which may be hyalinized
 - Sclerotic lipoma: predominance of sclerotic fibrous tissue with only focal lipocytic areas:
 - Predilection for sclerotic lipoma to occur on the scalp or hands of young men

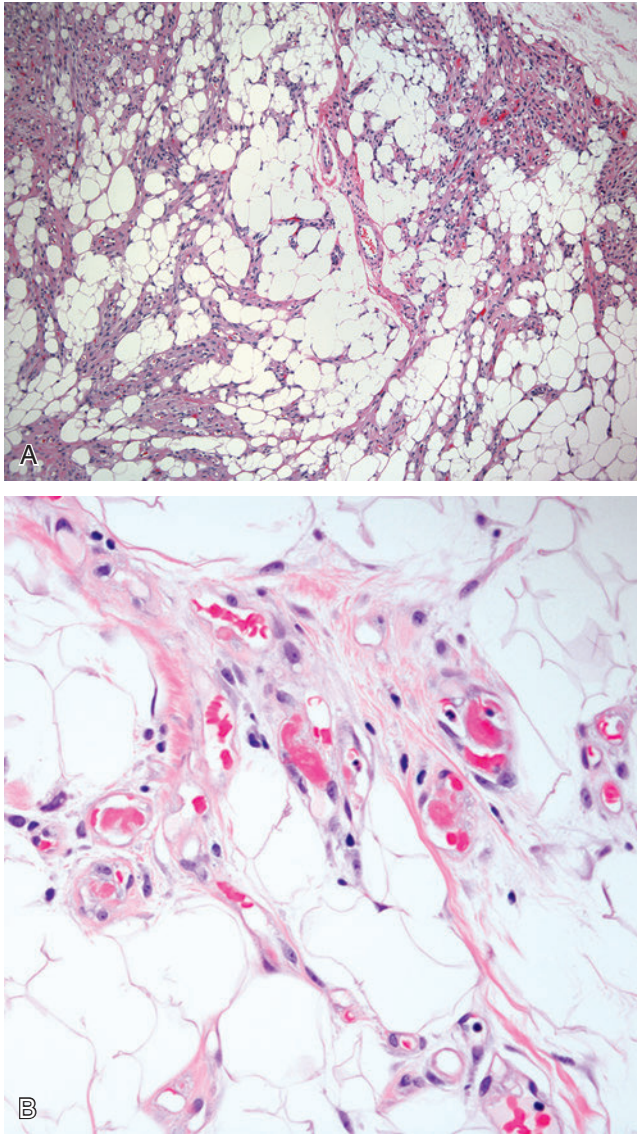


Fig. 13-13. Angiolipoma.

A, Angiolipoma is characterized by the presence of mature adipose tissue separated by branching network of small blood vessels. **B**, Intravascular fibrin thrombi are seen at higher magnification.

○ Angiolipoma (Fig. 13-13):

- Primarily is a subcutaneous nodule localized to the forearm in young adults
 - Other sites of occurrence include the trunk and upper arm.
- Striking male predominance; most common in early adulthood
- Characteristically are painful.
- Multiple angiolipomas are more common than solitary angiolipomas.

- Histologically, characterized by:
 - Presence of mature adipose tissue proliferation separated by branching network of small blood vessels
 - Fibrin thrombi identified within vascular component, a feature not seen in conventional lipoma
 - Prominent mast cell component
- Cellular angiolipoma represents a histologic subtype, in which the tumor is hypercellular and predominantly composed of vascular channels.
- May be familial
- Trauma implicated as potential contributing or initiating factor
- Angiomyolipoma (AML) (Fig. 13-14):
 - Specific lesion usually localized to one or both kidneys
 - Belongs to family of perivascular epithelioid cell tumor (PEComa):
 - PEComas are mesenchymal tumors composed of distinctive cells that show focal association with blood vessel walls and usually express melanocytic and smooth muscle markers
 - PEComa family includes:
 - Angiomyolipoma (AML)
 - Clear cell “sugar” tumor of the lung
 - Lymphangioleiomyomatosis (LAM)
 - Lesions known as malignant epithelioid angiomyolipoma of the kidney that may also occur in the retroperitoneum and are better termed malignant PEComa.
 - Less common extrarenal sites of occurrence include liver, heart, lung, colon, skin, nasal cavity, and oral cavity.
 - More common in women than men
 - Associated with abdominal or flank pain, hematuria, or chills and fever
 - Associated lesions may include:
 - Tuberous sclerosis complex occurring in approximately 50% of cases
 - Renal cell carcinoma
 - Neurofibromatosis
 - Pulmonary lymphangiomyoma and lymphangiomyomatosis
 - Angiomyolipomas are histologically characterized by the presence of three tissue components:
 - Mature adipose tissue
 - Thick-walled blood vessels often with hyalinization of the media and minimal to abnormal elastica
 - Bundles of smooth muscle often with prominent perivascular localization:

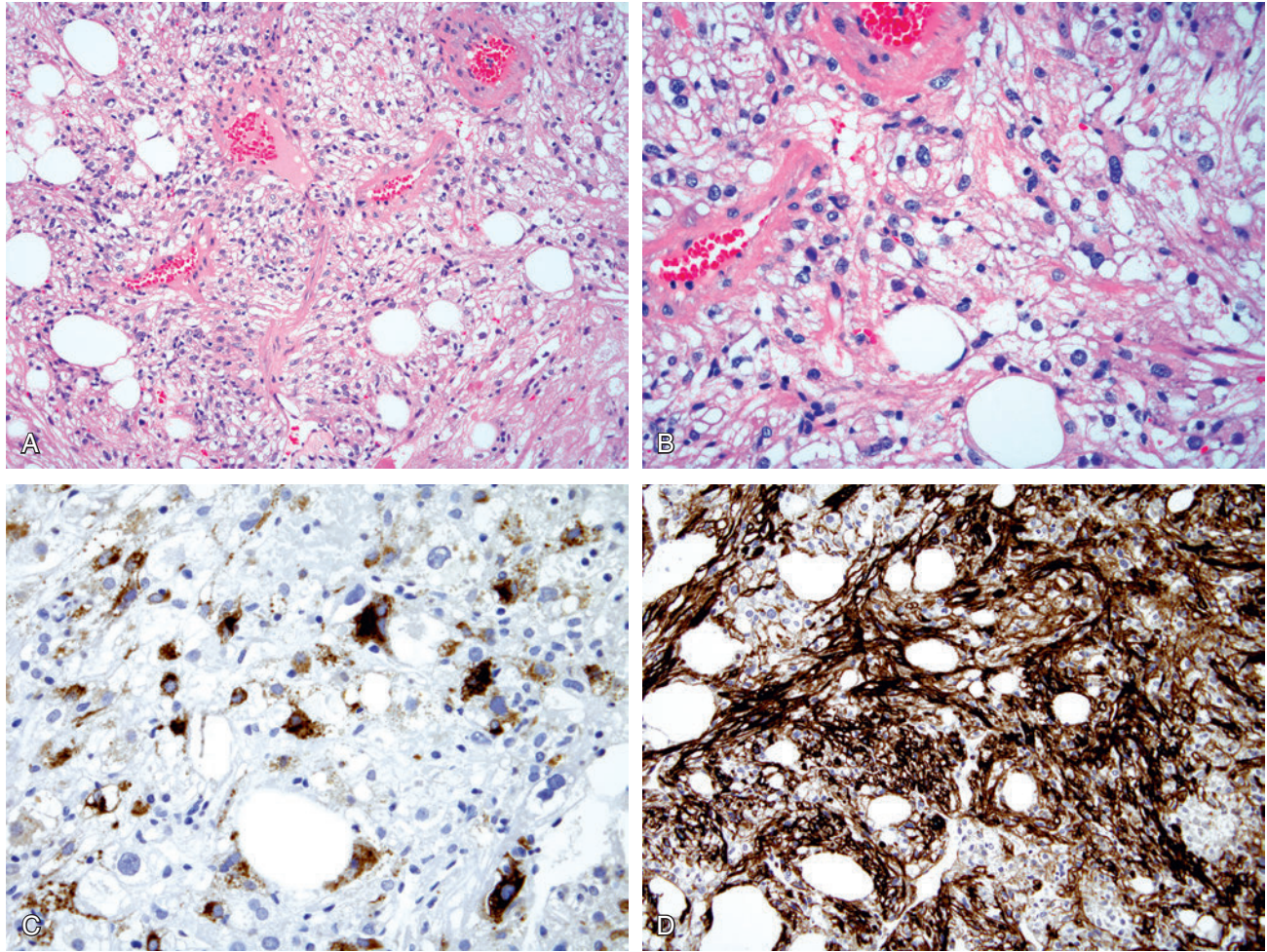


Fig. 13-14. Angiomyolipoma.

A, Angiomyolipoma is characterized by the presence of mature adipose, thick-walled blood vessels surrounded by smooth muscle. **B**, At higher magnification the smooth muscle cells predominantly appear epithelioid with round nuclei and abundant granular eosinophilic to clear cytoplasm, although scattered spindle-shaped smooth muscle cells can be seen (*bottom right*). The cells are immunoreactive for **(C)** HMB45 and **(D)** smooth muscle actin.

- Smooth muscle cells typically spindle-shaped but may be polygonal or rounded with epithelioid appearance and abundant eosinophilic cytoplasm
- May show marked nuclear pleomorphism with hyperchromatic nuclei, multinucleated giant cells and necrosis; mitotic figures may be present
- Such findings have no adverse prognostic significance in most cases.
- Immunohistochemical findings include myo-melanocytic reactivity:
 - Melanocytic markers include expression of:
 - HMB-45, melan-A, MART1, tyrosinase, MITF1
 - Myoid markers include expression of:
 - Smooth muscle actin, and less commonly desmin and caldesmon
 - May also be immunoreactive for:
 - CD117 (cytoplasmic) in majority of cases
 - Progesterone receptor and less commonly estrogen receptor
 - CD1a and podoplanin (D2-40)
- Cutaneous angiomyolipoma:
 - Rare benign tumor unrelated to its renal counterpart
 - Not associated with tuberous sclerosis
 - Skin of ear is a common location
 - Usually negative for HMB-45
 - May be considered angioleiomyoma with fat

- Myelolipoma:
 - Tumor-like growth of mature fat and bone marrow elements
 - Often seen in the adrenal gland; rarely seen in extra-adrenal locations, including pelvic (presacral) soft tissues and retroperitoneum
- Myolipoma:
 - Rare variant characterized by proliferation of mature fat and a distinct smooth muscle component
 - Smooth muscle component is immunoreactive for smooth muscle actin and desmin; HMB45 negative.
- Chondroid lipoma:
 - Rare variant composed of mature fat, lipoblasts with bland nuclei, and hibernoma-like cells in myxohyaline pseudochondroid matrix
 - Found in subcutaneous tissue or deep soft tissues of the proximal extremities and limb girdles, especially in adult women
 - Encapsulated with (multi)lobular growth composed of strands and nests of round cells with associated myxochondroid or hyalinized fibrous background
 - Some cells have multiple intracytoplasmic lipid vacuoles resembling lipoblasts
 - Some cells have granular, eosinophilic cytoplasm
 - Highly vascular, often with associated hemorrhage
 - Immunoreactivity includes S100 protein (strongly positive in mature fatty component, weaker in lipoblastic cells, negative in cells without lipoblastic differentiation); rarely cytokeratin positive but EMA negative.
 - Ultrastructural evaluation shows characteristic knob-like cytoplasmic protrusions
 - Reproducible t(11;16)(q13;p13) chromosomal translocation
 - Surgery is curative.
- Intramuscular lipoma:
 - Also referred to as infiltrating lipoma
 - Characterized by the poor circumscription and presence of mature adipocytes infiltrating skeletal muscle
 - Recurs in up to 20% if incompletely excised:
 - Approximately 10% are well-circumscribed, noninfiltrative, and do not appear to recur.
 - Often presents as a slow-growing, deep-seated mass; thigh and trunk most common locations
 - The presence of a deep-seated fatty tumor, a diagnosis of atypical lipomatous tumor, should be excluded.

Differential Diagnosis

- For conventional lipoma:
 - Well-differentiated (lipoma-like) liposarcoma
 - Presence of *MDM2* and *CDK4* immunoreactivity absent in lipomas
 - FISH analysis for *MDM2* gene amplification much more specific than immunohistochemistry in the diagnosis of well-differentiated liposarcoma
- For myxoid lipoma:
 - Myxoid liposarcoma
- For angiomyolipoma:
 - Leiomyosarcoma
 - Carcinoma
 - Sarcoma
- For myolipoma:
 - Other lipomas
 - Leiomyoma with fatty degeneration
- For chondroid lipoma:
 - Myxoid liposarcoma
 - Extraskeletal myxoid chondrosarcoma
 - Cellular pleomorphic adenoma, including epithelial-predominant and/or myoepithelial-predominant

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
- Prognosis is excellent following surgical removal.
- Local recurrence may be seen and occurs in approximately 5% of cases.

Specific Types of Lipomas

- Pleomorphic and spindle cell lipomas have overlapping clinical and morphologic features and may be regarded as variations of a single entity. Nevertheless, they will be discussed separately.

Pleomorphic Lipoma (Fig. 13-15)

Clinical

- More common in men than in women; occurs over a wide age range from fourth to ninth decades of life with an average age in the sixth decade
- Majority of cases (>80%) occur in the subcutaneous tissue of the posterior neck, shoulder, and back region; 10% develop more anteriorly in the head and neck including face; rarely may occur in the oral cavity
- Typically presents as an asymptomatic, slowly enlarging solitary mass:
 - Freely mobile dermal or subcutaneous mass
 - Often, history is that of a long-standing lesion

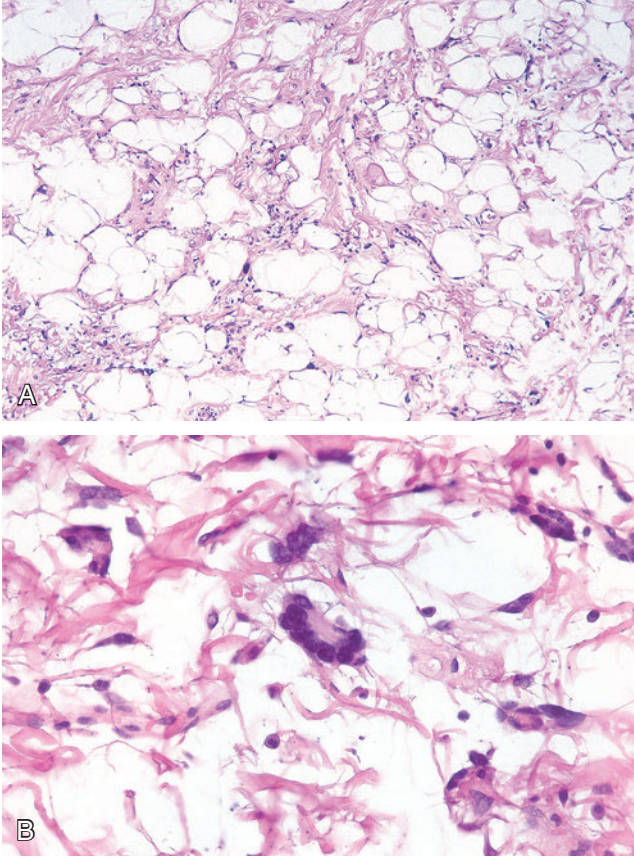


Fig. 13-15. Pleomorphic lipoma, posterior neck.

A and B, This variant of lipoma is characterized by an admixture of fat, bundles of collagen, spindle and rounded hyperchromatic cells, and the presence of multinucleated “floret-like” giant cells.

- Rarely, multiple lesions may occur; may be associated with conventional (ordinary) lipoma
- Familial occurrence has been reported.

Pathology

Gross

- Circumscribed, yellow mass usually measuring less than 5 cm but may attain large size, measuring up to 20 cm

Histology

- Characterized by an admixture of fat, thick bundles of birefringent collagen, spindle and rounded hyperchromatic stromal cells, and the presence of multinucleated “floret-like” giant cells
- Giant cells are:
 - A cardinal feature
 - Seen in most but not pleomorphic adenomas
 - Vary from sparse to numerous
 - Composed of cells with multiple marginally placed, overlapping nuclei radially arranged in a

“floret-like pattern” reminiscent of the petals of a flower, and eosinophilic cytoplasm

- Absence of pleomorphic lipoblasts
- Approximately 25% of cases associated with areas typical for spindle cell lipoma (see later):
 - WHO classification is that of spindle cell lipoma/pleomorphic lipoma with an indication that these tumor types represent a common histologic spectrum.
 - Cases with features intermediate between spindle cell lipoma and pleomorphic lipoma occur fairly often.
- Additional findings may include foci of lymphocytes, mast cells, fat necrosis, and dystrophic calcification.
- Immunohistochemistry:
 - Spindle cells and multinucleated cells are CD34 and vimentin positive; may rarely be positive for S100 protein and occasionally desmin
 - Negative for *MDM2* and *CDK4*
- Cytogenetics and molecular genetics:
 - Karyotypes more complicated than those of conventional lipomas:
 - Frequently hypodiploid with multiple partial losses
 - Loss of 16q and 13q material:
 - Loss of 16q13-qter
 - Loss of 13q12 and 13q14-q22
 - Loss of material from 16q more often seen than loss of material from 13q
 - No aberrant *HMG2* expression

Differential Diagnosis

- Liposarcoma, sclerosing

Treatment and Prognosis

- Surgical resection is the preferred treatment and is curative.

Spindle Cell Lipoma (Fig. 13-16)

Clinical

- Many findings similar to those of pleomorphic lipoma
- More common in men than in women; occurs over a wide age range from fifth to eighth decades of life
- Majority of cases occurs on the shoulder or back and posterior neck; other less common sites of occurrence include the extremities, trunk, head, forehead, oral cavity (floor of mouth, hard palate), face, orbit, and nasolabial fold.
- Typically presents as an asymptomatic, slowly enlarging mass:
 - Freely mobile dermal or subcutaneous mass
 - Often, history is that of a long-standing lesion.

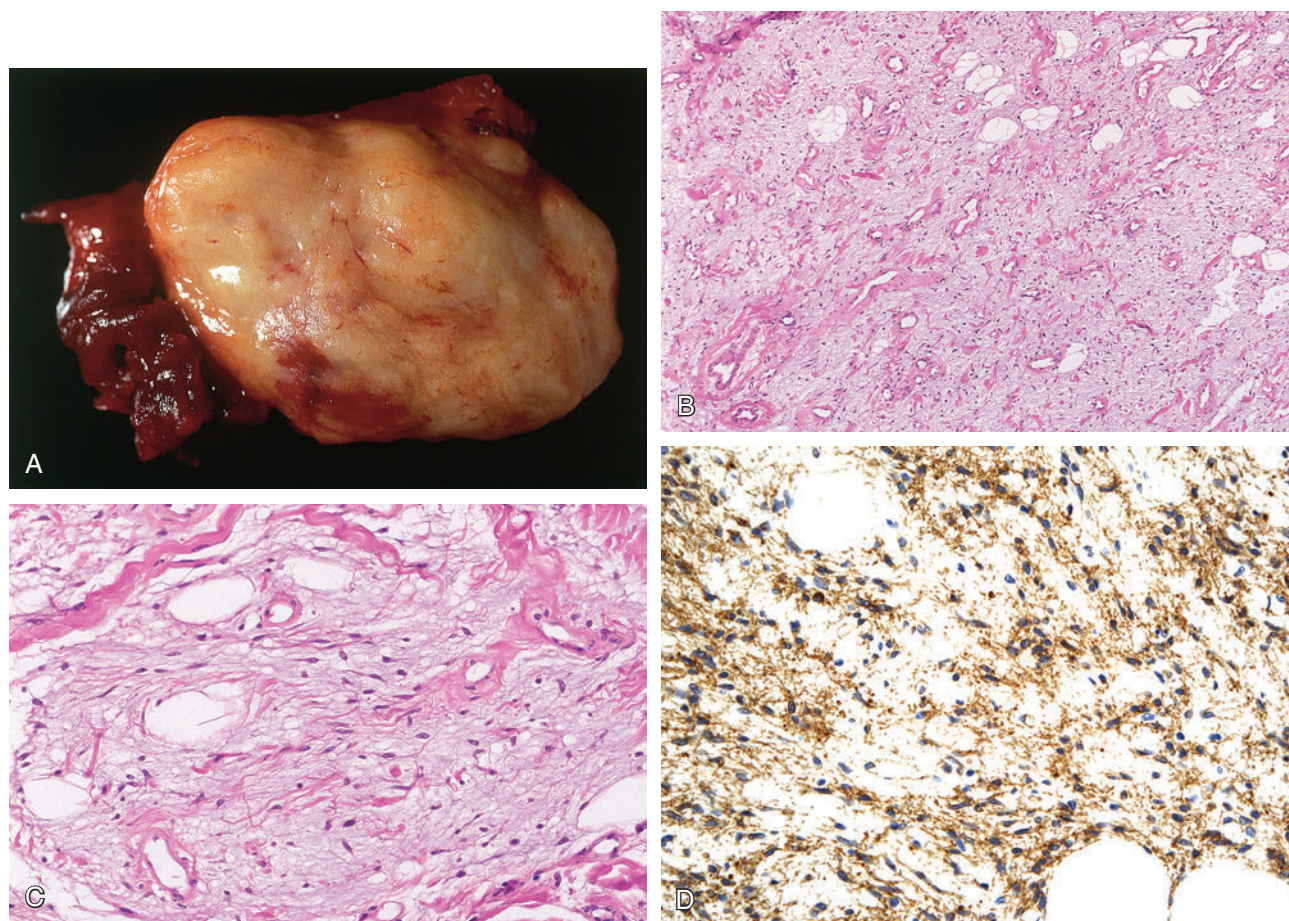


Fig. 13-16. Spindle cell lipoma.

A, Circumscribed, yellow, and glistening mass. **B** and **C**, Histologically, this variant of lipoma is characterized by an admixture of small, uniform spindle-shaped cells with associated mature fat cells, ropey-type collagen, and myxoid-appearing stroma. **D**, Spindle cells are CD34 positive.

- Usually are solitary lesions but may be multiple; may be associated with conventional (ordinary) lipomas in other sites

Pathology

Gross

- Usually well-circumscribed, yellow and soft to grayish and rubbery mass measuring less than 5 cm in greatest dimension; a gelatinous or glistening appearance on cut section may be identified.
- May be poorly delineated with extension into the dermis or deeper soft tissues (e.g., subjacent skeletal muscle)

Histology

- Composed of spindle-shaped cells arranged in parallel between univacuolar adipocytes and associated thick rosy collagen:
 - Spindle cell component may be focal or diffuse
 - Sparse to absent mitotic figures

- Myxoid or mucinous-appearing stroma is often present; stromal changes may also include the presence of slit-like cleavage spaces resembling vascular slits (pseudoangiomatous).
- Additional findings include the presence of large numbers in between the spindle-shaped cells; lymphocytes and plasma cells may be present.
- Associated with areas typical for pleomorphic lipoma (see above):
 - WHO classification is that of spindle cell lipoma/pleomorphic lipoma with an indication that these tumor types represent a common histologic spectrum
 - Examples with features intermediate between spindle cell lipoma and pleomorphic lipoma occur fairly often.
- Vascular pattern generally is inconspicuous and composed of small to intermediate-sized thick-walled vessels; a prominent plexiform vascular pattern similar to that seen in myxoid liposarcomas can be found.

- Immunohistochemistry:
 - Spindle cells are CD34 and vimentin positive; may rarely be positive for S100 protein and occasionally desmin
 - Negative for MDM2 and CDK4
 - Absence, actins (smooth muscle and muscle specific) macrophage/histiocytic markers
- Electron microscopy:
 - Abundant rough endoplasmic reticulum, well-formed Golgi apparatus, and non-membrane-bound lipid vacuoles
- Cytogenetics and molecular genetics:
 - Karyotypes more complicated than those of conventional lipomas:
 - Frequently hypodiploid with multiple partial losses
 - Loss of 16q and 13q material:
 - Loss of 16q13-qter
 - Loss of 13q12 and 13q14-q22
 - Loss of material from 16q more often seen than loss of material from 13q
 - No aberrant *HMG A2* expression

Differential Diagnosis

- Peripheral nerve sheath tumor(s)
- Nodular fasciitis
- Dermatofibrosarcoma protuberans
- Liposarcomas, including myxoid and spindle cell types

Treatment and Prognosis

- Surgical resection is the preferred treatment and is curative.

Hibernoma (Fig. 13-17)

Definition: Benign adipose tissue tumor composed at least in part of brown fat cells.

Synonyms: Fetal lipoma; lipoma of embryonic fat; lipoma of immature adipose tissue

Clinical

- Rare tumor
- No gender predilection; may occur over a wide age range but most often occurs in the third decade of life
- Sites of occurrence parallel normal anatomical distribution of brown fat:
 - Typically a subcutaneous mass predilecting to the thigh, scapular and interscapular regions, mediastinum, and upper thorax
 - In the head and neck the most common site of occurrence is the neck.
 - Less common sites of occurrence include the axilla, intrathorax, chest wall, abdominal wall, retroperitoneum, and inguinal region:

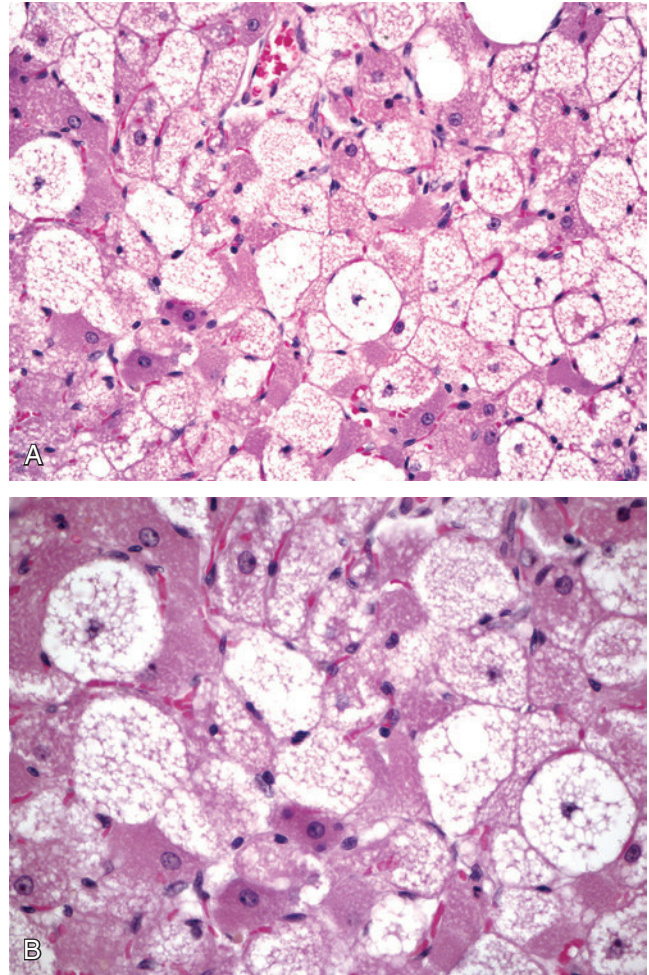


Fig. 13-17. Hibernoma.

A and B, This tumor shows an admixture of uniform, round to ovoid, granular eosinophilic cells with distinct cellular membrane and multivacuolated cells with central nuclei and multiple small lipid droplets.

- Myxoid and spindle cell variants tend to be located at the posterior neck and shoulders
 - Approximately 10% are intramuscular.
- Presents as a solitary, slow-growing, painless mass (similar to lipomas)

Pathology

Gross

- Well-defined, mobile, soft mass with a yellow to tan to deep red-brown color; usually measuring between 5 and 10 cm in greatest dimension

Histology

- Lobulated pattern composed of cells showing varying degrees of differentiation:
 - Uniform, round to ovoid, granular eosinophilic cells with distinct cellular membrane

- Multivacuolated cells with central nuclei and multiple small lipid droplets that are oil red-O positive
- Intermixed univacuolar cells with lipid droplets and peripherally displaced nuclei can be identified.
- Prominent vascularity is identified.
- Myxoid variant characterized by the presence of myxoid stroma
- Spindle cell variant characterized by the presence of a spindle cell component with thick collagen bundles, scattered mast cells, and mature adipose tissue:
 - Hybrid lesions with admixture of hibernoma and spindle cell lipoma may be identified.
- Infiltration of underlying muscle can be found.
- Immunohistochemistry:
 - S100 protein positive
 - Typically CD34 negative except for the spindle cell variant, which is CD34 positive (similar to spindle cell lipoma)
 - Uncoupling protein 1 (UCP1) positive
- Cytogenetics and molecular genetics:
 - Abnormalities of the long arm of chromosome 11 (11q13-21)

Differential Diagnosis

- Rhabdomyoma, adult type
- Granular cell tumor

Treatment and Prognosis

- Surgical excision is curative.
- No recurrence following complete excision:
 - All histologic types share similar treatment and prognosis.

Lipoblastoma and Lipoblastomatosis (Fig. 13-18)

Definition: Rare lobulated variant of lipoma occurring almost exclusively during infancy and early childhood, resembling fetal adipose tissue, and occurring in two forms:

- Localized/circumscribed (lipoblastoma)
- Diffuse infiltrating (lipoblastomatosis)

Synonyms: Embryonic lipoma; infantile lipoma

Clinical

- More common in males than females; tumor of infancy usually (>90%) occurring during the first 3 years of life:
 - Some cases occur at birth or in older children.
- Most common in the upper and lower extremities; less common sites of occurrence include the neck, as well as the trunk, mediastinum, mesentery, and retroperitoneum:

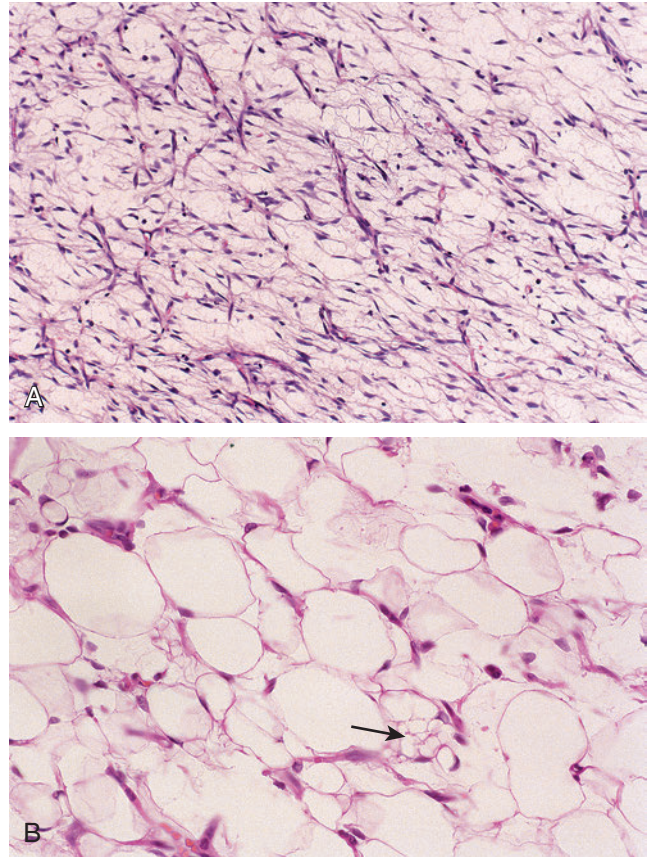


Fig. 13-18. Lipoblastoma.

A, The lesion is composed of lipoblasts with myxoid stroma and prominent plexiform vascular pattern. **B,** A multivacuolated lipoblast-like cell is present. This combination of features resembles those associated with myxoid liposarcoma with which lipoblastoma can be confused. Features of lipoblastoma, including occurrence in the first decade of life and absence of nuclear atypia, assist in differentiating it from (myxoid) liposarcoma.

- Other than the neck region, other head and neck sites of occurrence include:
 - Scalp, face, eyelid, cheek, parotid gland, and parapharyngeal region
- Slow-growing, well-circumscribed soft tissue nodule or mass:
 - Lipoblastoma: confined to subcutis or superficial soft tissues resembling a lipoma
 - Lipoblastomatosis: infiltrative growth not only the subcutis but also deeper muscle
- Larger tumors particularly of the head and neck may result in compression of adjacent structures (e.g., airway obstruction and respiratory insufficiency).
- Radiology:
 - Well-delineated soft tissue mass with density of adipose tissue

Pathology

Gross

- Most tumors measure 2 to 5 cm in greatest dimension with a pale yellow color and a myxoid or gelatinous appearance on cut section.

Histology

- Characteristic (multi)lobulated pattern separated by connective tissue septa and mesenchymal areas with loose myxoid appearance:
 - Lobulation less prominent in lipoblastomatosis
 - Entrapped muscle fibers frequently identified in lipoblastomatosis
- Lobules composed of lipoblasts in different stages of development ranging from primitive, stellate, and spindle-shaped mesenchymal cells (so-called preadipocytes) to lipoblasts with univacuolar “signet ring” appearance of mature fat cells:
 - Degree of cellular differentiation may be the same throughout the tumor or vary in different tumor lobules.
- Myxoid or mucoid matrix surround the lipoblasts and prominent plexiform vascular pattern is identified:
 - These features resemble those of myxoid liposarcoma.
- Extramedullary hematopoiesis and cells resembling brown fat may occasionally be identified.
- Cellular maturation with a lipoma-like appearance can be found.
- Adipocytes are S100 protein and CD34 positive.
- Primitive mesenchymal cells are often desmin positive.
- Electron microscopy:
 - Wide morphologic spectrum, including:
 - Immature mesenchymal cells and preadipocytes:
 - Prominent rough endoplasmic reticulum
 - Multivacuolated lipoblasts:
 - Contain numerous vesicles, round to oval mitochondria, and well-developed Golgi apparatus
 - Univacuolated mature lipocytes
- Cytogenetics and molecular genetics:
 - Characteristic cytogenetic abnormality found in the majority of cases is rearrangement of 8q11-13
 - Fusion genes resulting from chromosomal rearrangements include *PLAG1*, a developmentally regulated zinc finger gene, hyaluronic acid synthase 2 (*HAS2*), or collagen 1 alpha 2 (*COL1A2*):
 - *HAS2/PLAG1*
 - *COL1A2/PLAG1*
 - Rearrangement of *HMGA2* rarely reported

Differential Diagnosis

- Myxoid liposarcoma:
 - Rare tumor in the first decade of life
 - Presence of nuclear atypia and absence of pronounced lobular pattern seen in myxoid liposarcoma assist in differentiating it from lipoblastoma/lipoblastomatosis.
- Conventional lipoma
- Hibernoma
- Lipomatosis:
 - Diffuse overgrowth of mature adipose tissue occurring in a variety of clinical settings and affecting different anatomic regions, including:
 - Benign (multiple) symmetric lipomatosis:
 - Rare, idiopathic condition of massive symmetric enlargement of the neck region as a result of fat deposition
 - Synonyms include Madelung disease; Launois-Bensaude syndrome
 - Occurs in middle-aged men often of (but not exclusive to) Mediterranean descent
 - Distribution of fat in the neck region may include cervical neck, preauricular and postauricular, and supraclavicular; non-head and neck areas of involvement may include the axilla and inguinal regions.
 - Not associated with fat deposition elsewhere in the body
 - Presentation is that of nonpainful deformity of involved area:
 - ◻ In the neck the deposition may result in so-called horse collar deformity.
 - ◻ Symptoms associated with fat deposition result from compression of adjacent structures that may include tracheal compression with airway obstruction, and compression on the great vessels of the neck, resulting in signs and symptoms of superior vena caval syndrome.
 - ◻ Patients seek medical attention for cosmetic reasons and/or for relief of symptoms associated with fatty deposition.
 - Cause is unknown but patients may have a history of liver disease and/or excessive alcohol consumption; also may be associated with concomitant diabetes mellitus, gout, and hyperlipidemia.
 - No known genetic or hereditary abnormality
 - Histology includes the presence of nonencapsulated normal-appearing adipose tissue that may include fatty infiltration of adjacent structures.
 - Laboratory (chemical) analysis includes the presence of increased lipid content (as

TABLE 13-4 Benign Peripheral Nerve Sheath Tumors: Clinicopathologic Comparison

	Conventional Schwannoma	Neurofibroma Unassociated with NF1	Neurofibroma in Association with NF1
Gender/age	M = F; 3rd-6th decades	M = F; 3rd-5th decades	M = F; occurs at much younger ages
Common sites	Head and neck; extremities (flexor surfaces), mediastinum, retroperitoneum	Skin and subcutaneous	Cutaneous, deep nerves and viscera
Head and neck sites	Lateral neck, middle ear; less common, oral cavity, SNT, nasopharynx, larynx	Occasionally can be seen in all upper aerodigestive tract sites	Neck, scalp, oral cavity (tongue), and major nerves; other sites of occurrence may include the sinonasal tract, larynx, and salivary glands
Gross	Encapsulated solitary mass; often seen attached to parent nerve	Unencapsulated solitary mass; associated nerve infrequently identified	Unencapsulated, multiple mass lesions; marked distortion of nerve may occur
Histology	Spindle cells seen in cellular (Antoni A) and hypocellular (Antoni B) areas; palisading nuclei (Verocay bodies); prominent thick-walled vessels; degenerative changes are common; scant to no stromal myxoid matrix	Interlacing bundles of spindle cells with wavy or buckled nuclei associated with collagen strands and separated by a myxomatous stroma containing mast cells and lymphocytes	Plexiform type is typical of the disease; proliferation of spindle cells with increase in the endoneurial matrix and separation of the nerve fascicles with associated thick collagen fibers
IHC	Diffuse and intense S100 protein positive	Variable S100 protein staining	Variable S100 protein staining
Association with NF	Uncommon usually occurs sporadically; may be associated with NF2 (especially bilateral acoustic neuromas); rarely associated with NF1	Uncommon	Plexiform (and a lesser degree diffuse) type typical of NF1
Malignant transformation	Rare	Rare	Uncommon, occurring in approximately 2% to 3%

IHC, Immunohistochemistry; NF, neurofibromatosis; SNT, sinonasal tract.

compared with normal fat), in particular, triglycerides

- No effective medical treatment
- Conservative surgical debulking for cosmetic purposes and/or to relief symptoms associated with fatty deposition
 - Asymmetric lipomatosis
 - Pelvic lipomatosis
 - Mediastinoabdominal lipomatosis

Treatment and Prognosis

- Wide surgical excision is the preferred treatment.
- Recurrence reported in 9% to 25%
- Restricted to patients with the diffuse infiltrating type (i.e., lipoblastomatosis)
- Malignant transformation or metastasis does not occur.

BENIGN NERVE SHEATH NEOPLASMS (Table 13-4)

General Considerations

Benign nerve sheath tumors include schwannoma (neu-rilemoma) and neurofibromas.

- Other benign tumors of nerve sheath or presumed peripheral nerve sheath origin include:
 - Granular cell tumor
 - Solitary circumscribed neuroma (palisaded encapsulated neuroma)
 - Dermal nerve sheath myxoma (neurothekeoma)
 - Perineurioma
- Benign nerve sheath tumors of the head and neck are common, perhaps accounting for as many as 45% of all cases:

- Most common site of occurrence is the neck
- Benign nerve sheath tumors of the oral cavity, oropharynx, and nasopharynx are uncommon, accounting for less than 4% of such tumors.
- In the head and neck, schwannomas are more common than neurofibromas.
- Some benign nerve sheath tumors occur in association with neurofibromatosis (see later).
- Represent tumors of neural crest origin or with neuroectodermal differentiation arising in soft tissues including those with nerve sheath differentiation and those arising in association with nerve

Schwannoma

(Figs. 13-19 through 13-21)

Definition: Benign (usually encapsulated) nerve sheath tumor composed of differentiated neoplastic Schwann cells and characterized by cellular component (Antoni A) and loose myxoid component (Antoni B) and presence of diffuse S100 protein immunoreactivity.

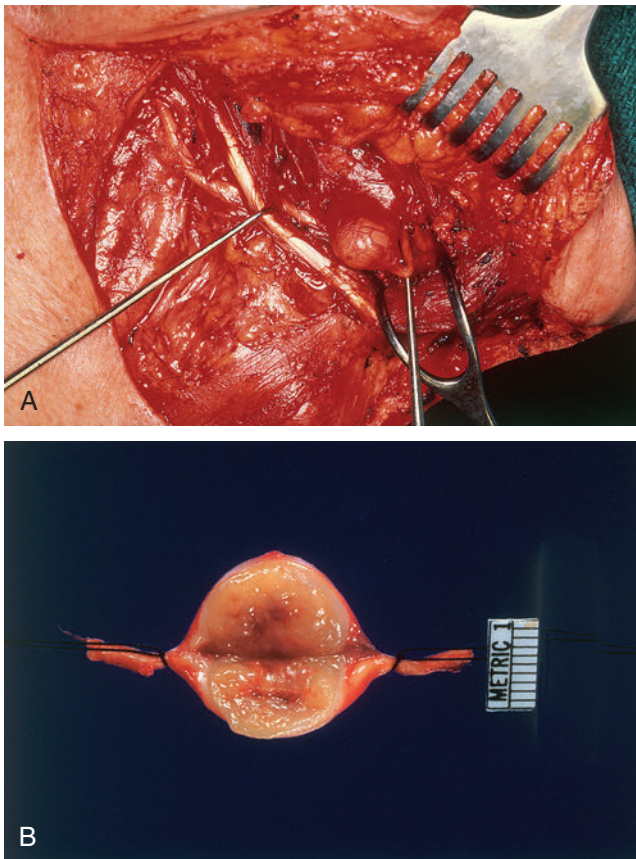


Fig. 13-19. Schwannoma.

A, Intraoperatively, the tumor is encapsulated and is attached to the hypoglossal (XII) nerve. **B,** Resected specimen appearing as an encapsulated, tan-white, solid to partly cystic mass attached to an identifiable nerve.

Synonyms: Neurilemoma; benign schwannoma; neurinoma; conventional schwannoma

- 2 clinical, morphologic, and genetically different entities recognized, including:
 - Conventional schwannoma
 - Melanotic schwannoma
- Cellular schwannoma and plexiform schwannoma represent histologic and clinically significant variants.

Clinical

- Most common tumor of peripheral nerves
- Majority (approximately 90%) are solitary and sporadic and not related to neurofibromatosis
- No gender predilection; occur in all ages but most common in the third to sixth decades of life
- Can arise anywhere in the body but predilects to head and neck region, extremities (flexor aspects), as well as mediastinum (posterior; may be referred to as dumbbell tumors as a result of its configuration due to extension into vertebral canal) and retroperitoneum
- Up to 45% of schwannomas present in the head and neck:
 - May occur anywhere but the most common site of occurrence is the neck (lateral aspect) in relation to spinal roots and cervical, sympathetic, and vagus nerves:
 - Sensory nerves are preferred sites of origin but may originate from motor and autonomic nerves.
 - Visceral involvement is rare.
 - Other sites of involvement include the middle ear (referred to as acoustic neuroma, see Section 7 for a more complete discussion) and sinonasal cavity
 - Oral cavity, pharyngeal (oropharynx and nasopharynx) involvement is uncommon:
 - The tongue is the most common site in the oral cavity.
 - May arise in the parapharyngeal space
- Symptoms vary according to site:
 - Neck: solitary, painless mass:
 - Typically, slow-growing neoplasm present for several years prior to diagnosis
 - Oral cavity and pharynx: airway obstruction and dysphagia
 - Pain, paresthesia, or other neurologic symptoms are uncommon.
 - Motor symptoms are uncommon because origin from sensory nerve roots is most common.
- Radiology:
 - MRI:
 - Well-circumscribed heterogeneously enhancing mass
 - May be cystic

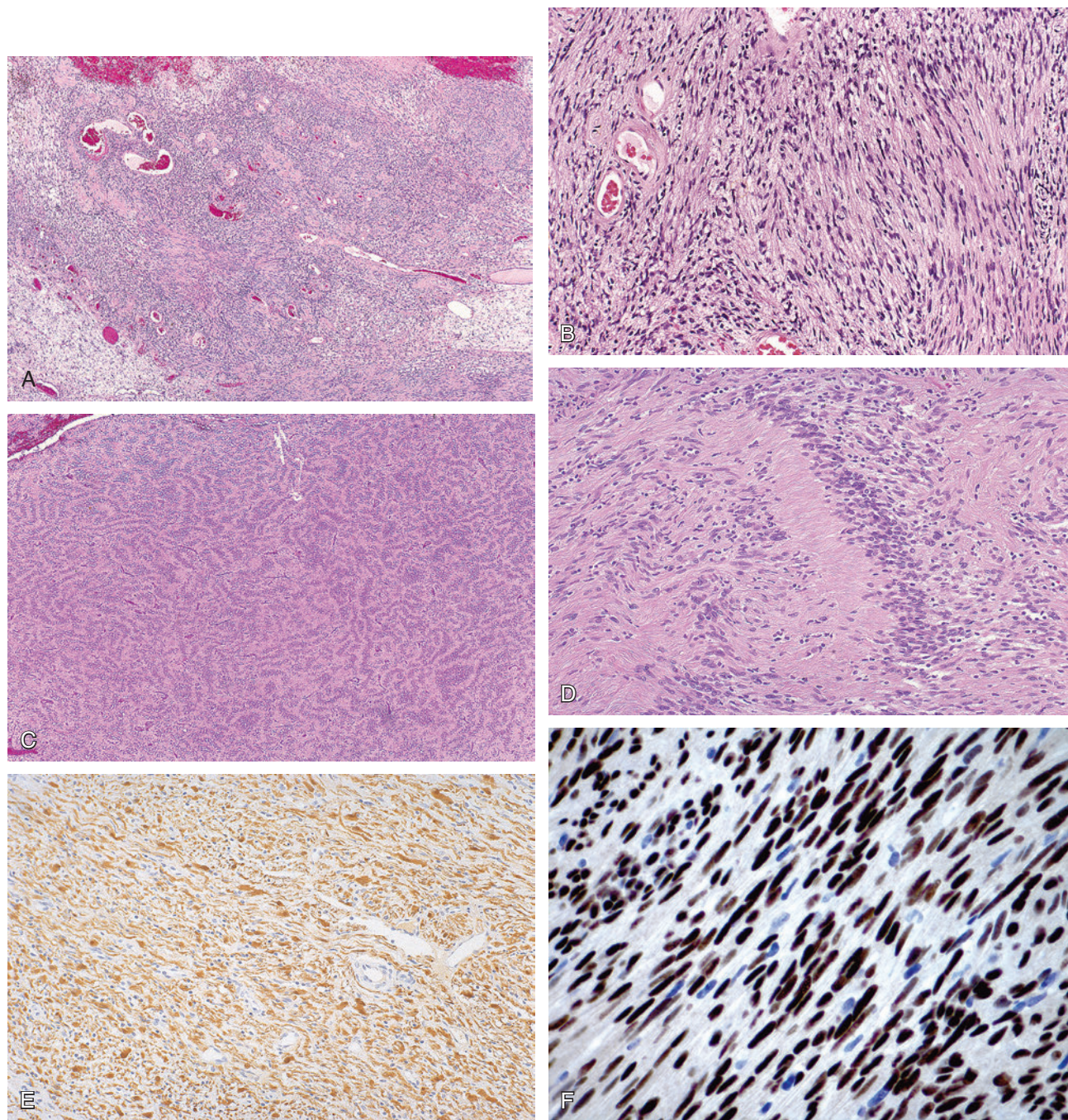


Fig. 13-20. Schwannoma.

Typical histology includes **(A)** alternating regions consisting of compact spindle cells (Antoni A areas) arranged in short, interlacing fascicles and loose, hypocellular zones (Antoni B areas). **B**, Hyperchromatic nuclei with elongated and twisted appearance, indistinct cytoplasmic borders, and hyalinized vasculature. **C** and **D**, Nuclear whorling, palisading, or alignment in rows (Verocay bodies). **E**, Diffuse and intense S100 protein immunoreactivity. **F**, Sox10 (nuclear) reactivity.

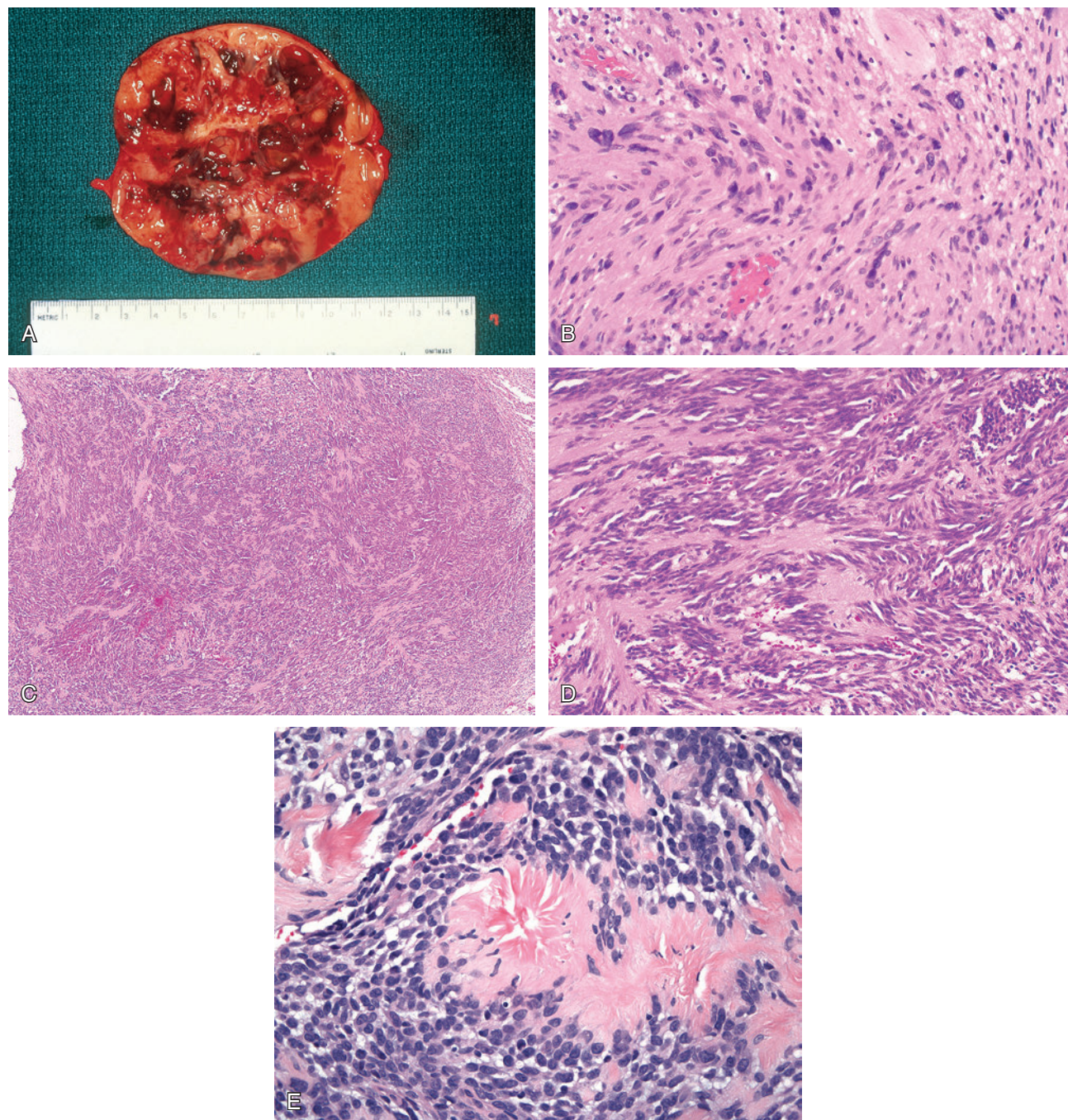


Fig. 13-21. Schwannoma with degenerative changes (ancient schwannoma).

A, Encapsulated tumor with cystic degeneration and hemorrhage. **B**, Histologically, degenerative changes may include the presence of bizarre-appearing nuclei. **C** and **D**, Schwannoma with increased cellularity (cellular schwannoma); despite increased cellularity there are no features of malignancy. **E**, Neuroblastoma-like schwannoma characterized by the presence of small rounded or spindle-shaped cells with hyperchromatic nuclei and scant cytoplasm, as well as rosette-like structures.

- Etiology:
 - Most conventional schwannomas are sporadic in occurrence with no known cause.
 - Approximately 2% of schwannomas are associated with neurofibromatosis type 2 (NF2 syndrome):
 - Autosomal-dominant disorder caused by germline loss of function of the *NF2* gene located on chromosome 22q12
 - Characterized by multiple conventional schwannomas, meningiomas, and ependymomas
 - In this setting schwannomas often are multiple and/or multifocal
 - Bilateral acoustic neuromas are pathognomonic/ diagnostic feature of NF2 (see later)
 - NF2-associated schwannoma commonly present before 30 years of age
 - In the absence of NF2, multiple conventional schwannoma may be indicative of schwannomatosis:
 - Second most frequent schwannoma-associated disorder
 - Definitive diagnosis predicated on the presence of two or more histopathologically proven conventional or less often plexiform schwannomas and absence of radiographic evidence of vestibular nerve involvement in patients over 18 years of age
 - Presumptive diagnosis made in the presence of two or more histopathologically proven schwannomas:
 - Without symptoms of VIII (vestibular) nerve dysfunction in patients over 30 years of age
 - In an anatomically limited distribution (e.g., single limb or segment of spine) without symptoms of VIII (vestibular) nerve dysfunction in patients of any age
 - Considered to represent a rare genetically distinct disorder
 - No gender predilection
 - Multiple painful cutaneous/subcutaneous or soft tissue nodules
 - May have striking segmental distribution
 - In contrast to NF2 patients, approximately 15% of schwannomatosis cases are familial.
 - Somatic (in tumor) but not germline (normal tissues) mutations of *NF2* gene
 - Identification of *SMARCB1* (*INI1*) gene located centromeric to NF2 on chromosome 22:
 - When mutated predisposes individuals to schwannomatosis
 - Gorlin-Koutlas syndrome:
 - Autosomal-dominant pattern of inheritance:
 - At present, precise genetic defect underlying this syndrome unknown
 - Multiple conventional schwannomas in extended family who also develop multiple nevocytic nevi and vaginal leiomyomas
 - Nevi are congenital, representing earliest manifestations of syndrome
 - Schwannomas and leiomyomas do not appear until adulthood.
 - Radiation induced:
 - Rare occurrence
 - Mean latency of approximately 20 years from time of radiation to development of tumor

Pathology

Gross

- Encapsulated mass often seen attached to an identifiable nerve with a tan-white color, rubbery to firm consistency, and a solid to partly cystic appearance; vary in size but generally measure less than 5 cm in diameter
- Myxoid change may be prominent.

Histology

- Majority of schwannomas of the neck are encapsulated:
 - As a result of these tumors arising in the nerve sheath, the epineurium or perineurium envelops the tumor, creating a true capsule.
- Unlike their soft tissue counterparts, schwannomas of mucosae of the upper aerodigestive tract mucosa, as well as the middle ear, are unencapsulated.
- Composed of alternating regions of compact spindle cells called Antoni A areas, and loose, hypocellular zones called Antoni B areas; in a given tumor, the proportion of these components varies.
- Nuclei are vesicular to hyperchromatic, elongated, and twisted with relatively abundant, slightly eosinophilic cytoplasm with indistinct cytoplasmic borders.
- Cells are arranged in short, interlacing fascicles and whorling or palisading of nuclei may be seen; nuclear palisading with nuclear alignment in rows called Verocay bodies.
- Antoni B areas display a disorderly cellular arrangement, myxoid stroma, and a chronic inflammatory cell infiltrate.
- Increased vascularity is prominent, composed of large vessels with thickened (hyalinized) walls.
- Scattered mitotic figures may be present, but the mitotic rate is low and atypical mitoses are not present.
- Cellular pleomorphism with hyperchromasia can be identified but are not indicative of malignancy.
- Immunohistochemistry:
 - Diffuse and intense S100 protein immunoreactivity (cytoplasmic and nuclear pattern)
 - Leu-7 and glial fibrillary acidic protein (GFAP) may be positive.

- Sox10 (nuclear) staining seen in nearly all schwannomas
- Cytokeratin, actins, desmin, CD34, and epithelial membrane antigen staining are absent.
- Proliferation rate (i.e., MIB-1 staining) is low with staining of 1% to 5% of tumor cell nuclei stain:
 - Low proliferation rates also seen in cellular schwannomas.
- Electron microscopy:
 - Single cell type that includes:
 - Convoluted, relatively thin cytoplasmic processes essentially devoid of pinocytotic vesicles lined by a continuous basal lamina
 - Stromal long-spacing collagen, referred to as Luse body, is commonly identified.
- Cytogenetics and molecular genetics:
 - Loss of expression of neurofibromatosis type 2 (NF2) tumor suppressor gene product termed merlin protein (schwannomin) consistent finding in schwannomas, suggesting a key role in tumorigenesis
 - Underlying loss of merlin expression is inactivation of NF2 tumor suppressor gene located at 22q12
 - Other consistent genetic alterations not identified
- Histologic variants of conventional schwannoma include:
 - Ancient
 - Cellular
 - Plexiform
 - Epithelioid
 - Hybrid schwannoma/perineurioma
 - Microcystic/reticular schwannoma
 - Glandular
 - Neuroblastoma-like

Ancient Schwannoma

- Benign schwannoma with degenerative/retrogressive changes, including cystic degeneration, necrosis, hyalinization, calcification, and hemorrhage may be seen:
 - Pronounced degenerative changes may include bizarre-appearing nuclei characterized by nuclear hyperchromasia and coarse-appearing chromatin
 - Mitoses are generally absent.
 - May occur at any location but tend to be deep seated

Cellular Schwannoma

- Cellularity may vary and some tumors can be very cellular, conferring the designation cellular schwannoma:
 - Composed almost exclusively of Antoni A areas with absence of Verocay bodies

- Demonstrates fascicular growth
- Increased mitotic activity may be present, ranging from one to four mitoses per 10 high-power fields.
- Nuclear hyperchromasia and atypia may be present.
- Strong, diffuse S100 protein staining
- GFAP and Leu-7 may be positive:
 - GFAP may be strong and present in nearly 50% of cases
 - Leu-7 often irregular and patchy and seen in approximately one third of cases
- Rarely may have striking plexiform appearance (plexiform cellular schwannoma)
- Clinical features:
 - Slow growing
 - Tends to occur in retroperitoneum, paravertebral region of mediastinum, pelvis, or intraspinal space:
 - May also occur frequently in the head and neck and extremities
 - Often arises from major nerve
 - Usually encapsulated but may be focally infiltrative, including erosion of bone
 - Typically lacks association with NF1, although occasionally associated with neurofibromatosis
 - May recur if incompletely excised but do not metastasize

Plexiform Schwannoma

- Histologic variant characterized by:
 - Plexiform or multinodular growth pattern
 - Each nodule is encapsulated.
 - Composed mainly of Antoni A areas; mitoses may be present
 - Infrequently multicentric
 - Clinical features:
 - Predilection in skin or subcutaneous tissue of the extremity, head and neck, and trunk
 - Tend to affect younger patients than conventional schwannoma
 - With rare exceptions not associated with NF1 and NF2:
 - Contrasts with plexiform neurofibroma
 - In approximately 5% of cases associated with NF2; occasional cases reported in schwannomatosis
 - Congenital/childhood plexiform cellular schwannoma:
 - Recently described
 - Initially thought to possibly be a congenital neural hamartoma
 - No gender predilection
 - >50% present in infancy; >40% congenital
 - Most involve skin and subcutaneous tissue; may also occur in retro-orbit and pelvis

- May be large (>5 cm)
- Histologic findings:
 - Hypercellular, variably hyperchromatic spindle-shaped proliferation
 - Arranged in fascicles, sheets, micronodules, or lobules
 - Mitoses commonly identified:
 - Some reported cases with more than 30 mitoses per 10 high-power fields
 - Atypical mitoses not seen
 - May be well circumscribed but may also show pushing and/or infiltrative margins
 - Lack of epithelioid morphology, anaplasia, and necrosis
- Immunohistochemistry:
 - Cells uniformly S100 protein positive
 - EMA may be positive in peripheral lining cells
 - Increased proliferation rate by Ki67 (MIB1) staining may be present:
 - Some reported cases with greater than 30% proliferation rate
- Tend to recur or persist
- Do not metastasize

Epithelioid Schwannoma

- Mainly occur in adults in deep dermis and subcutis of the limbs:
 - May occur in viscera (gastrointestinal tract [colon] and genitourinary tract [bladder])
 - Rare in head and neck
- Typically encapsulated:
 - Lack Antoni A or B zonation or hyaline vessels
 - Consists of nests or trabeculae of eosinophilic epithelioid cells
 - Cells have uniform round to oval nuclei with frequent intranuclear pseudoinclusions and eosinophilic fibrillary cytoplasm.
 - Mitoses are not seen.
 - Diffusely S100 protein positive; CD34 reactivity may be identified
 - Cytokeratins and EMA negative

Hybrid Schwannoma/Perineurioma

- Represents the most common type of hybrid peripheral nerve sheath tumor:
 - Defined as one of the major benign peripheral nerve sheath tumors (BPNST) containing a histologic component typical of another
 - Other less common hybrid PNSTs include:
 - Hybrid neurofibroma/perineurioma
 - Hybrid neurofibroma/schwannoma
- Hybrid schwannoma/perineurioma represents a BPNST mainly consisting of Antoni A areas (without palisading or hyaline vessels) and a marked whorled growth pattern

- Primarily occurs in adults
- Usually occurs in somatic soft tissue
- Immunoreactivity for S100 protein and EMA

Microcystic/Reticular Schwannoma

- Rare morphologic variant
- Primarily occurs in adults
- Predilection to arise in gastrointestinal tract
- Characterized by anastomosing and intersecting strands of eosinophilic spindle-shaped cells arranged in islands of myxoid or collagenous stroma

Glandular Schwannoma

- Nerve sheath tumor with focal glandular differentiation
- Controversial entity as most nerve sheath tumors with glandular differentiation are malignant (malignant peripheral nerve sheath tumor):
 - Appears that rare benign peripheral nerve sheath tumors with glandular differentiation reported but the glandular component may represent entrapped nonlesional, normal structures

Neuroblastoma-Like Schwannoma

- Predilects to the superficial soft tissues of the neck, palm, and flank
- Histologically, has a fibrous capsule with areas of typical neurilemoma as well as neuroblastoma-like areas:
 - Neuroblastoma-like areas are composed of sheets or nests of small rounded or spindle-shaped cells with central hyperchromatic nuclei and scant cytoplasm
 - Rosettes and pseudorosettes are identified:
 - Rosettes are perivascular or surround central cores of radiating spokes of collagen
 - Focal areas of conventional schwannoma can be found.
 - Scarce mitotic activity; necrosis and hemorrhage are absent

Melanotic Schwannoma (MS)

- Otherwise typical schwannoma but uniquely characterized by presence of intracytoplasmic melanin pigment:
 - Tend to occur in patients a decade younger than conventional schwannomas
 - Tumors tend to be cellular and unencapsulated.
 - Composed of closely packed, pigmented, spindle-shaped, and epithelioid cells arranged in short fascicles or nests:
 - Tumor cells with round nuclei, distinct small nucleoli, striking nuclear grooves, and eosinophilic to amphophilic cytoplasm
 - Multinucleated cells may occasionally be present.

- Schwann cells contain intracytoplasmic brown to black melanin pigment.
- Fontana positive
- Immunoreactivity for S100 protein, HMB45, and melan-A
- Melanosomes identified ultrastructurally
- May be divided into non-psammomatous and psammomatous variants:
 - 50% contain psammoma bodies (psammomatous melanotic schwannomas)
 - Approximately 50% of patients with psammomatous melanotic schwannomas have Carney complex, which is an autosomal-dominant multiple endocrine and lentiginous syndrome characterized by:
 - Cardiac myxoma as well as myxomas of the skin and breast
 - Lentiginous (spotty) pigmentation
 - Endocrine abnormalities including Cushing syndrome associated with multinodular adrenal hyperplasia and acromegaly due to pituitary adenoma
 - Congenital osteochondromyxoma
 - Two genetic loci identified:
 - One on chromosome 17q22-24 (CNC1) at the site of *PRKAR1A* gene, the tumor suppressor gene mutated in about 50% of CNC kindreds
 - One on chromosome 2p16 (CNC2)
- A small proportion of melanotic schwannomas (with or without psammoma bodies) have low-grade malignant potential with metastases:
 - May metastasize to:
 - Lung, stomach, liver, adrenal gland, and brain
 - Brain metastases often fatal
 - Metastases usually occur after initial local recurrence.
 - Often arise from sympathetic chain or nonaxial locations
 - No pathognomonic features of malignancy but malignant ones tend to have:
 - Large vesicular nuclei with scant chromatin
 - Prominent eosinophilic or violaceous (macro) nucleoli
 - Increase mitoses including atypical mitoses
 - Broad zones of necrosis
 - Histology of primary tumor may appear deceptively bland.
 - Distinction from metastatic melanoma may be difficult.
 - Surgical excision to include tumor-free margins is treatment for melanocytic schwannomas.
 - Recent evidence purports that melanotic schwannomas are distinctive malignant tumors rather than benign neoplasms with occasion-

ally unpredictable behavior proposing reclassification as malignant melanotic schwannian tumor:

- 26 of 40 cases reported with adequate follow-up included:
 - 35% recurred and 44% metastasized
 - 54% alive without disease, 19% alive with disease, and 27% died of disease
- Gene expression profiling showed significant differences between MS, melanoma, and conventional schwannoma.
- Loss of *PRKAR1A* expression suggested link to Carney complex even when this history was absent.

Differential Diagnosis

- For conventional schwannoma:
 - Neurofibroma (see later and [Table 13-4](#))
 - Leiomyoma
 - Meningioma
 - Solitary fibrous tumor
 - Fibrous histiocytoma
 - Synovial sarcoma, monophasic
- For cellular schwannoma:
 - Malignant peripheral nerve sheath tumor
 - Leiomyosarcoma
 - Fibrosarcoma
- For melanotic schwannoma:
 - Malignant melanoma
- For glandular schwannoma:
 - Malignant peripheral nerve sheath tumor
- For neuroblastoma-like schwannoma:
 - Neuroblastoma
 - Primitive neuroectodermal tumor

Treatment and Prognosis for Conventional Schwannoma and Histologic Variants (Except for Melanotic Schwannoma)

- Surgical excision is the preferred treatment:
 - Every effort should be made to preserve the integrity of the nerve from which the tumor arises.
 - In cases in which the complete excision would result in damage or sacrifice of the parent nerve, incomplete excision can be performed.
- Local recurrences are infrequent.
- Prognosis is excellent following surgical removal:
 - Malignant transformation is extremely rare.

Neurofibroma

Definition: Well-demarcated but unencapsulated intra-neural or diffusely infiltrative extraneural tumor consisting of an admixture of Schwann cells, perineurial cells, and fibroblasts; residual interspersed myelinated and unmyelinated axons embedded in extracellular matrix.

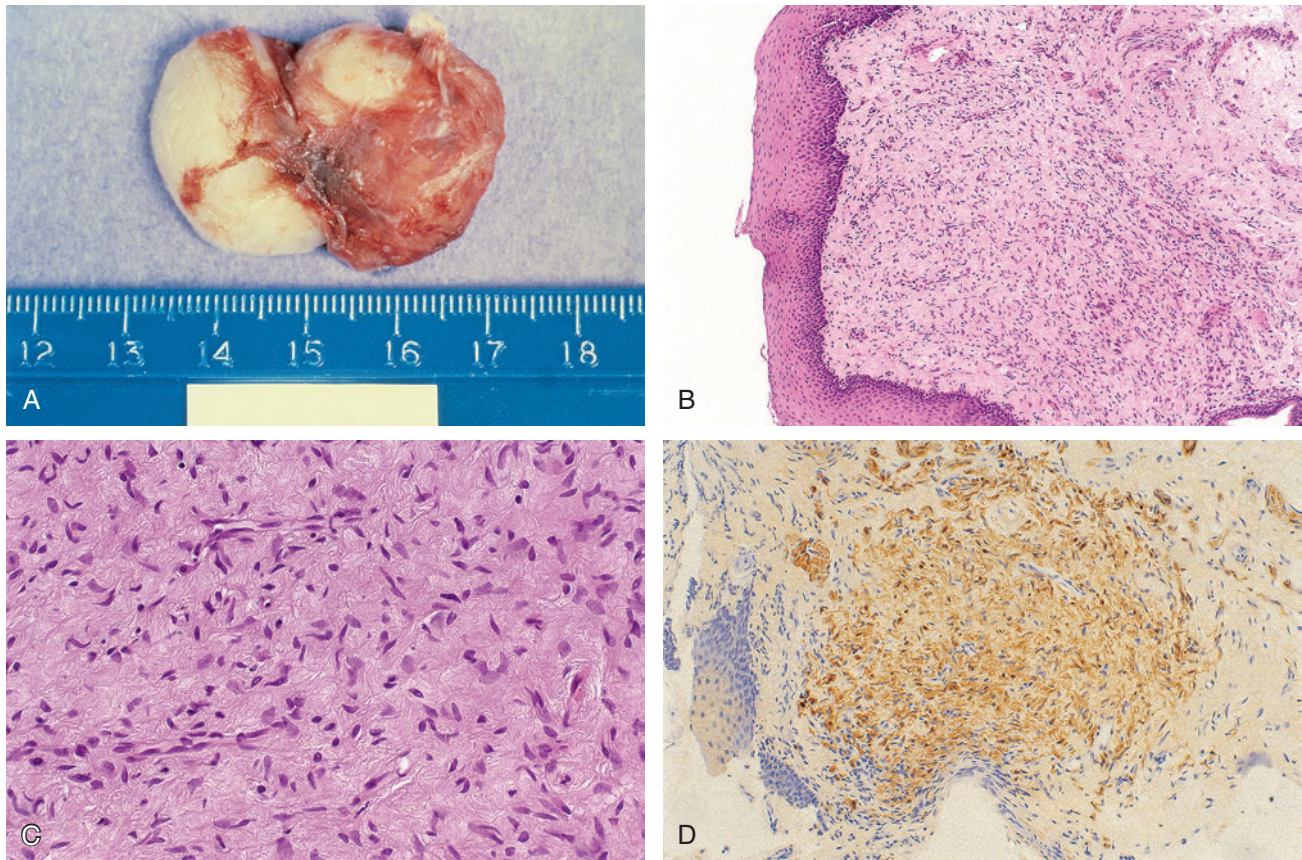


Fig. 13-22. Solitary neurofibroma.

A, Neurofibroma appearing as a circumscribed, unencapsulated, tan-white to gray mass. **B**, Histologically, the neoplasm is submucosal and unencapsulated, composed of interlacing bundles and haphazardly arranged spindle-shaped cells. **C**, At higher magnification, the nuclei appear wavy or buckled and are loosely arranged in a collagenized to myxomatous stroma; wire-like strands of collagen ("shredded carrots") are present; stromal inflammatory cells including lymphocytes and mast cells are present. **D**, S100 protein positive but reactivity tends to be less striking as compared with schwannomas.

NOTE: In mucosal sites, schwannomas may also be unencapsulated.

- Occurs as solitary, diffuse, or plexiform lesions with varying clinical and pathologic findings

Solitary Neurofibroma

(Table 13-4, Fig. 13-22)

Definition: Localized, benign peripheral nerve sheath tumor composed principally of Schwann cells:

- Appear to originate within endoneurium:
 - Presence of mixed cell population in conjunction with apparent endoneurial origin raise doubts relative to its being a neoplasm and perhaps better considered a hamartomatous lesion
- Small subset entirely intraneural

Synonym: Localized (sporadic) neurofibroma

Clinical

- Is more common than diffuse or plexiform neurofibromas

- No gender predilection; most commonly occurs in the third to fourth decades of life
- May affect any part of the body but are found most commonly in the skin and subcutaneous tissue
 - Occasionally, can be seen in all upper aerodigestive tract mucosal sites
 - Rarely may occur in deep soft tissue often in axial location
- Presentation is most often that of a solitary, painless (cutaneous) mass; usually slow-growing, developing over years
- Occurs sporadically; not associated with neurofibromatosis (NF):
 - Multiple neurofibromas typically are associated with NF1 (see Neurofibromatosis later in chapter)
 - Solitary neurofibromas of deep soft tissues more often associated with NF1 and have a small risk of undergoing malignant transformation

- Multiple NFs:
 - Presence of small number of cutaneous NFs:
 - May occur in patients without stigmata of NF1 but in this situation a diagnosis of NF1 should be excluded

Pathology

Gross

- Circumscribed but unencapsulated, nodular to polypoid, rubbery to firm, tan-white to gray-appearing glistening mass:
 - Neurofibromas result from a diffuse increase in the endoneurial matrix with proliferation and distortion of Schwann cells and axons, resulting in an unencapsulated neoplasm.
- Involved nerve occasionally may be identified entering and exiting from the tumor, which expands the nerve in a fusiform manner:
 - In this setting, confinement to within the endoneurium results in an encapsulated tumor.

Histology

- Nonencapsulated lesion composed of interlacing bundles of spindle-shaped cells with hyperchromatic nuclei having a wavy or buckled appearance loosely arranged in a variable fibromyxoid stroma:
 - Myxomatous stroma may be:
 - Focal and limited in extent
 - Extensive and diffuse:
 - Typically occurs in extremities and histochemically contains abundant pools of acid mucopolysaccharides
 - May be so prominent as to suggest a diagnosis of myxoma:
 - Presence of S100 protein would differentiate it from myxoma
 - Collagenized stroma may include:
 - Wire-like strands of collagen (likened to “shredded carrots”)
 - Dense collagen bundles
- Stromal inflammatory cells include mast cells and lymphocytes; xanthomatous cells can be identified.
- Cellularity varies, including hypercellular tumors (cellular neurofibromas) and hypocellular tumors with a prominent myxoid change.
- Some tumors may have atypical nuclei and may be referred to as neurofibroma with atypical features:
 - Include nuclear pleomorphism with marked hyperchromasia (similar to nuclei seen in ancient schwannoma)
 - Usually atypical features are focally identified
 - Insufficient features (i.e., increased cellularity and mitotic activity) for a diagnosis of a low-grade malignant peripheral nerve sheath tumor

- Similar atypia in patients with NF1 should seriously raise concern for the possibility of malignant change:
 - Presence of mitoses as well as nuclear atypia and increased cellularity in this setting considered by some authorities as evidence of malignancy
 - Molecular analysis suggests that such lesions in patients with NF1 are premalignant.
- Mitotic activity is rare to absent; necrosis and hemorrhage not identified
- In contrast to schwannomas blood vessels lack hyalinization.
- Immunohistochemistry:
 - S100 protein positive but less striking as compared with benign schwannomas:
 - In NF proportion of S100 protein-positive cells ranges from 30% to 50%
 - S100 protein in benign schwannomas is almost 100% positive.
 - Epithelial membrane antigen (EMA) negative (except in residual perineurium)
 - Sox10 (nuclear) staining seen in more than 90% of cases
 - Perineurial cells are immunoreactive for EMA, glucose transporter 1 (GLUT1), and claudin-1
 - Stromal cells are CD34 positive.
- Electron microscopy:
 - Mixture of cell types:
 - Spindle (perineurial-like) cells: thin, long, attenuated bipolar cytoplasmic processes, pinocytotic vesicles, and discontinuous basal lamina
 - Cells with features characteristic of Schwann cells, including convoluted, cytoplasmic processes essentially devoid of pinocytotic vesicles lined by a continuous basal lamina
- Histologic variants of solitary NF considered rare and include:
 - Epithelioid NF:
 - Round cells with eosinophilic cytoplasm
 - Granular cell NF:
 - Cells with granular eosinophilic cytoplasm:
 - Intracytoplasmic diastase-resistant, PAS-positive material
 - Pigmented NF:
 - Rare tumor type that can be associated with NF1
 - Most often are of the diffuse-type neurofibroma but some tumors may have features of diffuse and plexiform neurofibromas
 - Pigmented cells dispersed throughout the lesion but with a tendency to cluster in more superficial aspects
 - Pigmented cells are immunoreactive for S100 protein and melanocytic markers

Differential Diagnosis

- Schwannoma (see above and Table 13-4)
- Myxoma:
 - In contrast to myxoma, myxomatous neurofibromas have a greater degree of cellular orientation, a more prominent vascular pattern, and S100 protein immunoreactivity.
- Perineurioma (see later)

Treatment and Prognosis

- Simple surgical excision is the preferred treatment and is curative.
- Risk for malignant transformation is extremely low.

Plexiform Neurofibroma

(Figs. 13-23 and 13-24)

Definition: Benign peripheral nerve sheath neoplasm with characteristic clinical and pathologic features found almost exclusively in patients with neurofibromatosis 1 (NF1):

- Generally regarded as pathognomonic for NF1 even in the absence of other stigmata at time of presentation

Clinical

- No gender predilection; generally occurs early in childhood
- May occur in any location but tendency to occur in the head and neck, back, and inguinal region:
 - In the head and neck, common sites of occurrence include:
 - Neck, scalp, oral cavity (tongue), and major nerves
 - Other sites of occurrence may include the sino-nasal tract, larynx, and salivary glands.
- Presentation includes cosmetic deformity, enlarging mass lesion, and functional impairments of the site of involvement:
 - Lingual involvement:
 - May produce macroglossia with functional impairment
 - Usually occurs in children under 3 years of age
- Involvement of major nerves leads to nodular or fusiform enlargement that is poorly circumscribed, forming a tortuous appearance along segments of the nerve; a characteristic appearance termed “bag of worms” or “string of beads” results:
 - Involvement of the entire extremity termed “elephantiasis neuromatosa”
- Radiology:
 - CT scan:
 - Well-defined oval to spheric to fusiform lesion centered at the anatomic location on a peripheral nerve, cranial nerve, or other nerves

- Often, there is a family history of NF1:
 - Presence of plexiform neurofibroma strictly correlates to and is virtually pathognomonic of NF1 (see neurofibromatosis later in this section)
 - Some patients with plexiform neurofibromas may have NF2.
 - Some patients with small solitary plexiform neurofibromas may not have neurofibromatosis.

Pathology

Gross

- Ill-defined, elongated, nodular, or multinodular growth or cylindric enlargement of the involved nerve:
 - Due to containment within the perineurium the appearance has been likened to a bag of worms or string of beads
 - Alternative appearance, especially when a large nerve trunk is involved, may be that of ropey enlargement of the involved nerve

Histology

- Tortuous expansion of the nerve with:
 - Increase in the endoneurial matrix with separation of the nerve fascicles
 - Disorderly proliferation of Schwann cells, fibroblasts, and axons with associated thick collagen fiber
 - Perineurial fibrous thickening
- With continued growth, cellular extension into adjacent soft tissues may occur, resulting in a lesion with mixed plexiform and diffuse areas.
- Hybrid lesions with clinicopathologic features of plexiform NF and diffuse NF not uncommon
- Hybrid lesions of plexiform NF and schwannoma occasionally occur.
- Mitotic activity:
 - Presence of mitotic activity generally in association with increased cellularity and nuclear atypia felt to be indicative of malignant transformation (i.e., malignant peripheral nerve sheath tumor)
- Immunohistochemistry:
 - Variably S100 protein and Leu-7 positive
- Electron microscopy:
 - Mixture of cell types:
 - Predominant cell has features characteristic of Schwann cells, including convoluted, cytoplasmic processes essentially devoid of pinocytotic vesicles lined by a continuous basal lamina
 - Fibroblastic cells are numerous, characterized by prominent endoplasmic reticulum lacking basal lamina.

Differential Diagnosis

- Schwannoma conventional and plexiform types (see Table 13-4)

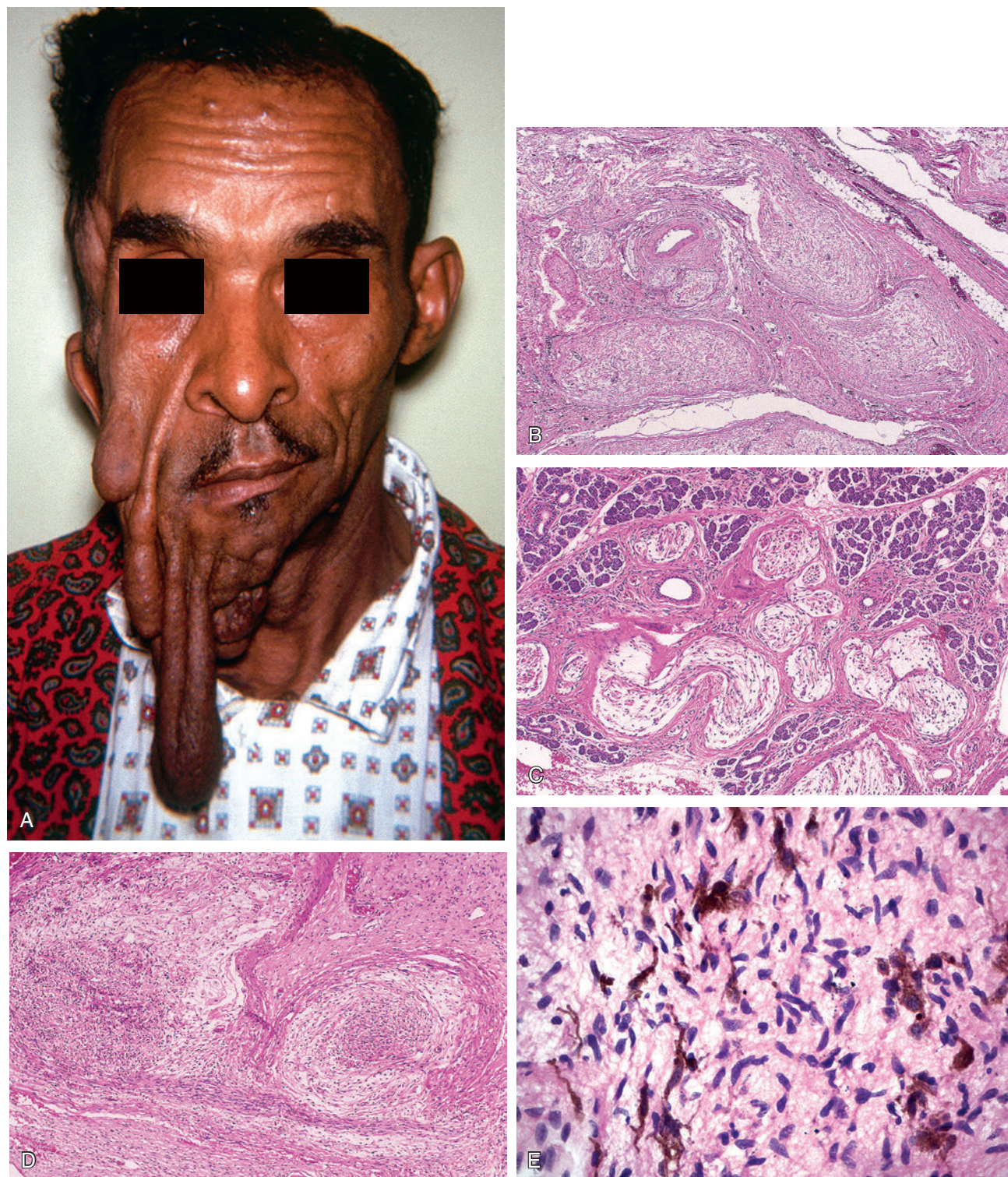


Fig. 13-23. Plexiform neurofibroma.

A, Marked facial deformity due to plexiform neurofibromas in this man with neurofibromatosis. **B** through **D**, Histology of soft tissue and intraparotid plexiform neurofibromas showing tortuous expansion of the nerves with increase in the endoneurial matrix with separation of the nerve fascicles, disorderly proliferation of Schwann cells, fibroblasts, and axons with associated thick collagen fiber and perineurial fibrous thickening. **E**, Pigmented neurofibroma is characterized by the presence of melanin containing cells (S100 protein and melanocytic markers positive, not shown); pigmented cells are dispersed throughout the lesion but tend to cluster in more superficial aspects. Pigmented neurofibromas most often occur in the diffuse-type neurofibroma, but in some tumors there may be features of both diffuse and plexiform neurofibromas.

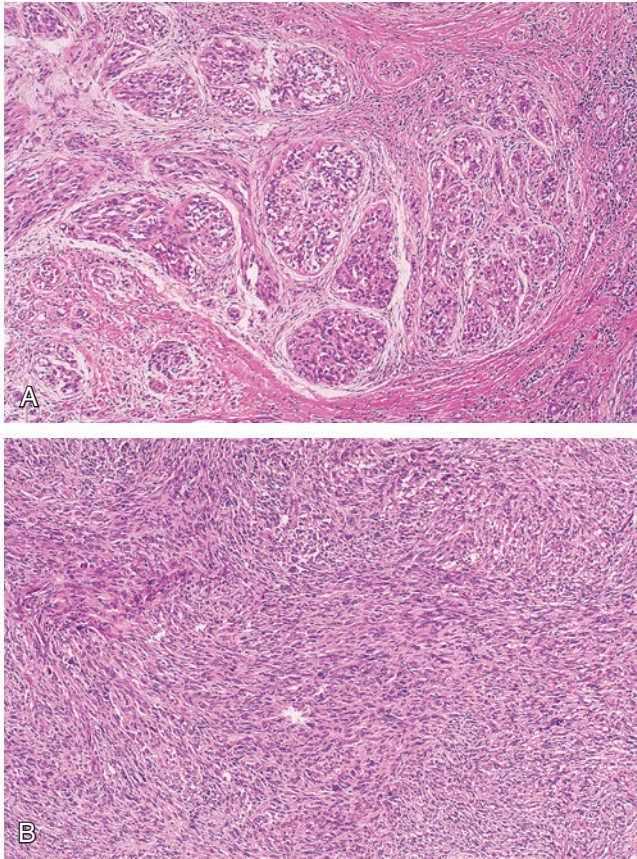


Fig. 13-24. Malignant transformation.

Malignant transformation of plexiform neurofibroma in neurofibromatosis. **A**, Intraneural and **(B)** infiltrative growth. Malignant transformation includes the presence of hypercellularity, cellular atypia, and increased mitotic activity.

- Mucosal neuroma (see later)
- Neurothekeoma (see later)

Treatment and Prognosis

- Surgery is the preferred treatment:
 - Conservative surgical resection for cosmesis, as well as preservation of nerve function, is advocated, if possible
 - Complete tumor resection is possible in patients with small tumors (measuring less than 5 cm)
 - Management compromised in patients with larger tumors (measuring greater than 5 cm) given tendency to local recurrence due to diffuse spread of the lesion along the course of the nerve
- Patients with head and neck plexiform neurofibroma are more likely to benefit from surgery for one (or more) of the following indications:
 - Exclude malignancy in a rapidly enlarging mass

- Provide relief from neurogenic pain or motor weakness
- Improve symptoms caused by airway compression
- Enhance cosmesis in those with disfiguring disease
- Metastatic disease generally does not occur.
- Increased morbidity related to local recurrence
- Malignant transformation:
 - Occurs in plexiform neurofibromas associated with NF1
 - Occurs in approximately 2% to 3% of NF1 patients
 - Peak incidence in third decade of life
 - Occurs most often in deep-seated, large centrally located tumors
 - Malignant transformation would necessitate radical surgical extirpation.

Diffuse Neurofibroma

Definition: Uncommon, histologically distinct form of neurofibroma generally not associated with neurofibromatosis.

Synonym: Paraneurofibroma

Clinical

- No gender predilection; occurs principally in children and young adults (second and third decades)
- Primarily occurs in the trunk and skin of the head and neck:
 - Other less frequent sites of occurrence include the orbit and gastrointestinal and genitourinary tract.
- Presents as a solitary, ill-defined, plaquelike subcutaneous mass
- Majority of patients with diffuse neurofibroma do not have neurofibromatosis:
 - 10% of patients have NF1.

Pathology

Gross

- Poorly defined, glistening to gelatinous-appearing nodular mass ranging in size from 0.5 to greater than 6 cm.

Histology

- Infiltrative (but not destructive) lesion with extension throughout soft tissues enveloping structures such as nerves and cutaneous adnexal structures:
 - Infiltrates along connective tissue septa and envelops rather than destroys normal structures
- Shares histologic features of conventional neurofibroma but differs in that:
 - Schwann cells are less elongated with fusiform or round contours with indistinct cytoplasm
 - Has a uniform matrix of fine fibrillary collagen

- Has presence of meissnerian differentiation, a characteristic finding of this lesion
- Constituent nerves appear markedly hypertrophic and edematous.
- Pigmented (melanin-containing) dendritic cells not uncommonly present
- Multinucleated giant cells may be present.
- Other mesenchymal components including mature fat and large ectatic blood vessels may be prominently identified; lesions with these findings tend to be more commonly seen in association with NF1.
- Nuclear palisading may rarely be present.
- Immunohistochemistry:
 - S100 protein positive in many but not all cells
 - CD34 negative

Differential Diagnosis

- Spindle cell lipoma
- Dermatofibrosarcoma protuberans (DFSP), including pigmented form (also referred to as Bednar tumor), differs from diffuse neurofibroma (nonpigmented and pigmented types) by:
 - Presence of storiform growth with uniform fibroblastic cells
 - Expression of CD34 but absence of S100 protein staining

Treatment and Prognosis

- Surgical excision is the preferred treatment:
 - Due to infiltrative type growth, may be difficult to completely excise
- Tendency to local recurrence as a result of difficulties in complete surgical resection
- Rarely undergoes malignant transformation

Granular Cell Tumor

Definition: Benign tumor showing neuroectodermal differentiation composed of large oval to round cells with abundant eosinophilic granular cytoplasm.

Synonyms: Granular cell myoblastoma; granular cell neuroma; granular cell schwannoma; granular cell neurofibroma; Abrikossoff tumor; granular cell schwannoma

- Two forms can occur:
 - Mucosal granular cell tumor
 - Congenital granular cell epulis

Mucosal Granular Cell Tumor

- See Section 4, Larynx, for a more complete discussion, including illustrations.

Congenital Granular Cell Epulis

- See Section 5, Oral Cavity, for a more complete discussion, including illustrations.

Solitary Circumscribed Neuroma (Palisaded Encapsulated Neuroma)

- Benign peripheral nerve sheath tumor composed of Schwann cells, axons, and perineurial fibroblasts
- See Section 2, Oral Cavity, for a more complete discussion, including illustrations.

Mucosal Neuroma

- Benign lesion of nerve sheath origin involving mucosal surfaces of the oral cavity, eyelids, and intestines occurring associated with multiple endocrine neoplasia (MEN) syndrome type 2B
- See Section 2, Oral Cavity, for a more complete discussion, including illustrations.

Nerve Sheath Myxoma (Fig. 13-25)

Definition: Benign, usually cutaneous, histologically distinctive predominantly myxoid neoplasm presumably of nerve sheath (Schwann cell) origin.

Clinical

- No gender predilection; occur over a wide age range (first to eighth decades) but primarily occur in young and middle-age adults
- Predilection for the distal extremities (85% of cases)
 - Hands and fingers more common
 - Other common sites include knee, lower leg, ankle, and foot.

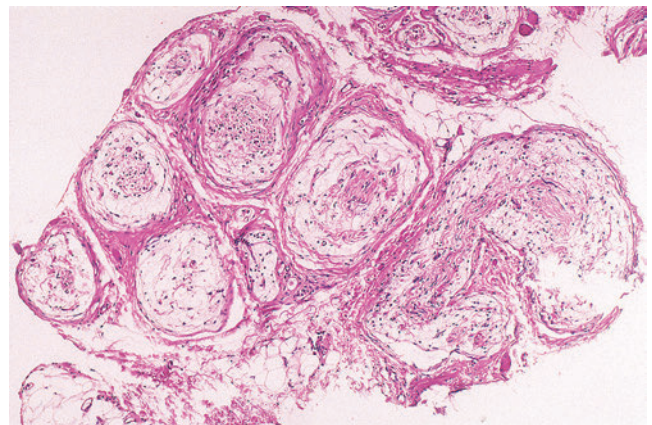


Fig. 13-25. Neurothekeoma.

Dermal nerve sheath myxoma (myxoid classic neurothekeoma) characterized by a lobular, well-circumscribed proliferation of spindle-shaped or rounded (epithelioid) cells in abundant myxoid matrix. S100 protein immunoreactivity was present (not shown).

- Trunk and head and neck involvement infrequent:
 - Rarely, seen in the oral cavity (tongue, lip) and external auditory canal
- Presentation is that of a solitary, slowly growing mass.
- No known association with neurofibromatosis
- Previously, nerve sheath myxoma and neurothekeoma were considered related lesions; however:
 - Distinct gene expression profiles for nerve sheath myxomas and neurothekeomas substantiate that these are separate entities.
 - Molecular data confirm that dermal nerve sheath myxomas are of peripheral nerve sheath origin and suggest that neurothekeomas may be a variant of fibrous histiocytomas.

Pathology

Histology

- Characterized by a lobular or multinodular, well-circumscribed but unencapsulated proliferation of admixed spindle-shaped or rounded (epithelioid) cells separated by scant collagen set in abundant myxoid matrix:
 - Spindle neoplastic cells arranged in nests, cords, and syncytial-like aggregates in fascicles or whorls
 - Composed of spindle-shaped, epithelioid, ring-like, and stellate cells
 - Nuclei tend to have vesicular chromatin but may be hyperchromatic or pleomorphic with eosinophilic cytoplasm:
 - Some cells may be multivacuolated and have spider-like processes.
 - Usually no significant increase in mitotic activity but occasional cases may have increased mitotic activity; atypical mitoses are not present
 - Myxoid matrix is composed of hyaluronic acid or sulfated acid mucins.
- Immunohistochemistry:
 - Diffusely S100 protein positive
 - GFAP, CD57 (Leu-7), and NSE reactive
 - Vimentin positive
 - Collagen type IV present around tumor cells
 - EMA-positive perineurial cells can be found in fibrous capsule.
 - Occasional CD34-positive intraneural fibroblasts may be present.
- Electron microscopy:
 - Spindle-shaped cells have features supportive of Schwann cells:
 - Cells with convoluted, cytoplasmic processes essentially devoid of pinocytotic vesicles lined by a continuous basal lamina

Differential Diagnosis

- (Cellular) neurothekeoma
 - Unrelated to nerve sheath myxoma
 - Although not completely proven, increasing evidence supports tumor within the spectrum of fibrohistiocytic tumors.
 - In contrast to nerve sheath myxoma:
 - More common in women than in men
 - Occurs primarily in children and young adults:
 - Wide age range but majority of cases occurs in the first two decades of life
 - Cutaneous (dermal and subcutaneous)-based tumors
 - Commonly involves head and neck, upper extremities, and shoulder region
 - Histology:
 - Multilobular, micronodular, or plexiform growth consisting of tumor nests circumscribed by bands of densely hyalinized collagen; whorling growth pattern frequently presents within individual tumor nests
 - Composed of epithelioid to slightly spindle-shaped cells with ovoid nuclei, indistinct nucleoli, and ample amount of slightly eosinophilic cytoplasm
 - Generally lack significant nuclear pleomorphism but rarely may have focal marked cytologic atypia
 - Increased mitotic activity may be present but usually less than 5 mitoses per 10 high-power fields; atypical mitoses usually absent
 - Myxoid stromal change frequently present and may be prominent:
 - When myxoid stroma is prominent, it may suggest a diagnosis of nerve sheath myxoma.
 - Immunohistochemistry:
 - S100 protein negative
 - GFAP usually but not always negative
 - MITF1 positive
 - Treatment includes complete excision.
 - May recur if incompletely excised
- Neurilemoma
- Neurofibroma
- Leiomyoma
- Myxoma
- Fibrohistiocytic lesions
- Neuroid nevus

Treatment and Prognosis

- Conservative but complete surgical resection is the preferred treatment.
- Local recurrence occurs because of inadequate excision.
- No malignant potential

Perineurioma (Fig. 13-26)

Definition: Benign tumor composed of perineurial cells occurring intraneurally and as a soft tissue lesion, the latter unassociated with a nerve.

Clinical

- Rare tumor(s) of all sites
- All perineuriomas are rare in head and neck sites.
- Most common genetic abnormality involves chromosome 22 but no known association with neurofibromatosis, although very rare examples reported in patients with NF1 or NF2
- Several forms are recognized, including:
 - Soft tissue (extraneural) perineurioma
 - Intraneural perineurioma
 - Sclerosing perineurioma
 - Reticular perineurioma
- Soft tissue perineurioma:
 - Previously referred to as storiform perineurial fibroma
 - Recognized as a distinctive type of nerve sheath tumor
 - More common than intraneural perineurioma
 - More common in women than men; occurs in adults:
 - Primarily affects soft tissues of the extremities and shoulder girdles:
 - Approximately 30% occur in deep soft tissue
 - Rarely occur in visceral sites
 - Present as a discrete, solitary, painless superficial nodule
- Intraneural perineurioma:
 - Benign neoplasm previously referred to as localized hypertrophic neuropathy
 - No gender predilection; adolescence and early adulthood
 - Primarily affects peripheral nerves of the extremities
 - Associated with motor neurologic deficits including progressive muscle weakness with or without atrophy; sensory disturbances are less common.
- Sclerosing perineurioma:
 - Benign nonrecurring neoplasm
 - No gender predilection for males; young adults
 - Typically affects skin of hand (finger and palm)
- Reticular perineurioma:
 - Predilection for women; adults (fourth to seventh decades; mean, 23 years)

Pathology

Gross

- Soft tissue perineurioma:
 - Well-circumscribed but not encapsulated, lobulated, firm, gray-white-appearing mass usually

measuring between 1 and 7 cm in greatest dimension but also may attain larger sizes

- Usually solitary but multinodular examples occur
- No apparent nerve association
- Intraneural perineurioma:
 - Segmental, sausage-shaped, tubular enlargement of an often but not always affected nerve
 - Usually measures less than 10 cm in greatest dimension but may reach large sizes
 - Appearance similar to plexiform neurofibroma (i.e., “bag of worms”) is not identified.
- Sclerosing perineurioma:
 - Circumscribed but not encapsulated solitary small nodule usually located in dermis

Histology and Immunohistochemistry

- Soft tissue (extraneural) perineurioma:
 - Composed of elongated, slender, spindle-shaped, or wavy cells arranged in short bundles, fascicles, or lamellae to looser whorls or storiform patterns embedded in collagen fibers
 - Cells have elongated, wavy-appearing nuclei with tapered ends, inconspicuous nucleoli, and elongated bipolar cytoplasmic processes
 - Aggregates of collagen fibers can be seen to be encircled by elongated tumor cell processes
 - Myxoid matrix often present (focal > diffuse)
 - Rare to absent mitoses; pleomorphism and necrosis are absent
 - Entrapment or infiltration of surrounding fat and skeletal muscle may occur.
 - Immunohistochemistry:
 - Epithelial membrane antigen (EMA) positive
 - Claudin-1 and GLUT1 often positive
 - CD34 positive in approximately 50% to 60% of cases often more diffuse than EMA
 - S100 protein negative (may focally be present)
 - Collagen 4 and laminin positive
- Intraneural perineurioma:
 - Proliferation of perineurial cells throughout the endoneurium forming concentric multiple layers around nerve fibers referred to as pseudo-onion bulbs:
 - Distinctive architectural feature best seen on cross-section
 - Large whorls may envelop large nerve fibers.
 - Mitotic activity is rare.
 - Immunohistochemistry:
 - EMA positive (membranous and diffuse)
 - Claudin-1 and GLUT1 often positive
 - S100 protein negative
 - Collagen 4 and laminin positive
- Sclerosing perineurioma:
 - Histologic variant characterized by increased sclerosis

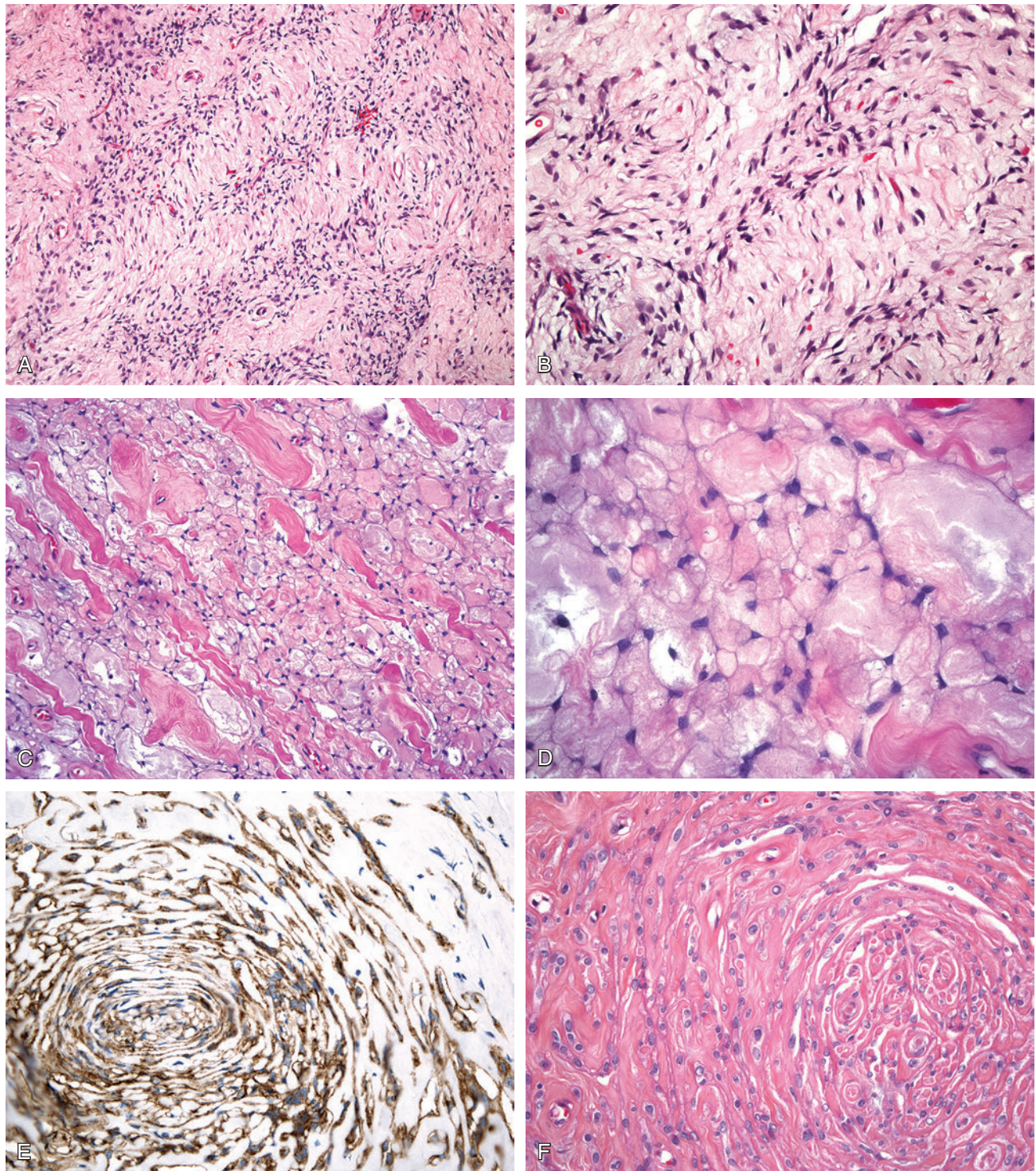


Fig. 13-26. Perineurioma.

A, Soft tissue (extraneural) perineurioma composed of elongated, slender, spindle-shaped, or wavy cells arranged in short fascicles within a collagenized stroma. **B**, Cells have elongated, wavy-appearing nuclei with tapered ends, inconspicuous nucleoli, and elongated cytoplasmic processes. **C** and **D**, Soft tissue (extraneural) reticular perineurioma showing tumor cells arranged in a net-like fashion around ground substance; slender cell processes can be seen. **E**, Neoplastic cells are EMA positive characterized by membranous staining pattern. **F**, Intraneural perineurioma in which there is a proliferation of perineurial cells throughout the endoneurium forming concentric multiple layers around nerve fibers (pseudo-onion bulb).

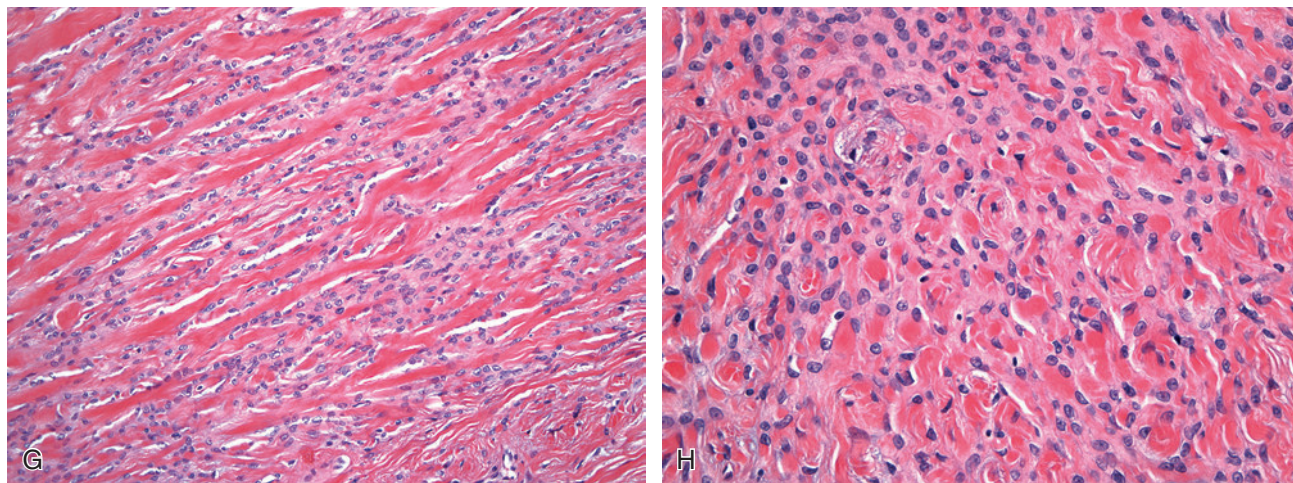


Fig. 13-26, cont'd

G and **H**, Sclerosing perineurioma is a histologic variant characterized by increased sclerosis; cells are arranged in cords and trabeculae and have a rounded appearance.

- Cells are arranged in cords and trabeculae and have a spindle-shaped to rounded (epithelioid) appearance.
- EMA positive; actins and keratins may be positive.
- S100 protein negative
- Reticular perineurioma
 - Net-like or lace-like pattern arrangement of cells of growth
 - Results in formation of prominent cystic or microcystic change
 - Most reticular tumors have foci of “conventional” perineurioma.
 - Aside from this appearance shares similar findings to “conventional” perineurioma
- Cytogenetics and molecular genetics:
 - Abnormalities of chromosome 22 (deletion, partial or complete):
 - Not considered diagnostically specific as found in other soft tissue tumors, including benign schwannomas
- For sclerosing perineurioma
 - Sclerosing adnexal tumor
 - Epithelioid neurofibroma and schwannoma
 - Epithelioid hemangioendothelioma
 - Epithelioid sarcoma
- For reticular perineurioma
 - Myoepithelial tumors of soft tissue
 - Dermatofibrosarcoma protuberans

Treatment and Prognosis

- Surgical resection is the preferred treatment and is curative.
- Rarely recur
- Rare malignant perineuriomas exist (perineurial malignant peripheral nerve sheath tumor):
 - Show features similar to soft tissue perineurioma but with hypercellularity, nuclear atypia, hyperchromasia, and high mitotic rate
 - May recur and/or metastasize but appear to behave less aggressively than conventional peripheral nerve sheath tumor
 - Not associated with neurofibroma or occurring in patients with NF1

Differential Diagnosis

- For dermal soft tissue perineurioma
 - Neurofibroma
 - Dermatofibrosarcoma protuberans
 - Extracranial meningioma
- For deep soft tissue perineurioma
 - Solitary fibrous tumor
 - Fibromatosis
 - Cellular myxoma
 - Low-grade fibromyxoid sarcoma
 - Low-grade myxofibrosarcoma

Neurofibromatoses

Definition: Two clinically distinct autosomal-dominant inherited disorders caused by two separate abnormal genes characterized by a variety of lesions, including those of the nervous system:

- Two disorders include neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2).

Neurofibromatosis 1 (NF1)

Definition: Autosomal-dominant disorder characterized by multiple neurofibromas, malignant peripheral nerve sheath tumor, optic nerve glioma, multiple café-au-lait spots, axillary and inguinal freckling, pigmented hamartomas of the iris (Lisch nodule), and various osseous lesions.

Synonyms: von Recklinghausen disease; peripheral neurofibromatosis

Clinical

- Most common type with incidence reported to be 1/2500 to 3000 live births and a prevalence of 1 per 4000
- Autosomal dominant:
 - Gene localized to chromosome 17q11.2 codes a protein called neurofibromin thought to function as a tumor suppressor by acting as a negative regulator of RAS signaling pathway
 - About 50% of NF1 cases are caused by new (spontaneous) germline mutations, which with few exceptions occur in the paternal germline.
- No gender predilection; 40% of patients have the onset of disease before the first year of life, and onset of disease is uncommon after 25 years of age.
- Severity of disease varies from patient to patient and from family to family.
- Diagnostic criteria are detailed in [Box 13-4](#).
- Café-au-lait spots are often the first sign of disease:
 - Appear in newborns
 - Number and size increase during infancy.
 - May remain stable or regress in adults
- Pigmented hamartomas of the iris also referred to as Lisch nodules represent small, elevated clumps of pigment that appear on the surface of the iris (colored part of the eye)
 - Usually appear at around 6 to 10 years of age
 - Cause no vision problems
- Head and neck manifestations seen in up to approximately 35% of patients:

BOX 13-4 Neurofibromatosis 1: Diagnostic Criteria

Two or more of the following criteria are diagnostic for NF1:

- Six or more café-au-lait spots:
 - Greater than 5 mm in diameter in prepubertal patients
 - Greater than 15 mm in diameter in postpubertal patients
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Axillary and/or inguinal freckling
- Optic nerve glioma
- A distinctive osseous lesion such as dysplasia of the sphenoid wing, thinning of long bone cortex with or without pseudoarthritis
- A first-degree relative (e.g., parent, sibling, or offspring) with NF1 according to the above criteria

- Peripheral nerve sheath tumors are slow-growing, found in virtually any location with the most common head and neck sites, including:
 - Skin, subcutaneous tissues, and soft tissues of the neck
 - Oral cavity affected in approximately 5% of cases and may include involvement of the lips, buccal mucosa, gingiva, and floor of mouth
- Accelerated growth noted during pregnancy and at puberty
- Sudden increase in size raises concern for possible malignant transformation
- Gliomas:
 - Majority are pilocytic astrocytomas within the optic nerve
 - Other gliomas in NF1 include diffuse astrocytoma and glioblastoma.
- NF1 patients are at increased risk of developing other tumors, including:
 - Malignant peripheral nerve sheath tumor (MPNST); see later
 - Pheochromocytoma
 - Duodenal carcinoid tumor
 - Rhabdomyosarcoma
 - Childhood chronic myeloid leukemia (often associated with cutaneous xanthogranulomas)
- Osseous lesions occur in approximately 40% of NF1 patients and may include:
 - Sphenoid wing dysplasia
 - Scoliosis
 - Height reduction
 - Macrocephaly
 - Pseudoarthritis usually of long bones, especially the tibia
- Vascular lesions include fibromuscular hyperplasia of renal artery and other arteries
- Genetics:
 - Associated with deletions, insertions, or mutations of *NF1* gene
 - *NF1* gene is a tumor suppressor gene located in the pericentromeric region of chromosome 17
 - *NF1* gene encodes a cytoplasmic protein known as neurofibromin ubiquitously distributed in all tissues but highest levels found in central and peripheral nervous system and in the adrenal gland

Pathology

- Neurofibromas include plexiform, diffuse, and dermal types.
- Malignant transformation of neurofibroma may occur:
 - Include rhabdomyoblastic or other heterologous elements (Triton tumors):
 - Highly characteristic of NF1

- May include the glandular variant of malignant peripheral nerve sheath tumor:
 - Another lesion indicative of NF1

Treatment and Prognosis

- There are no treatment modalities that alter the course of NF1.
- Management depends on specific manifestations and often requires multidisciplinary collaboration.
- Complete surgical excision relative to the neurofibromas is problematic given their increased numbers as well as the tendency to infiltrative and ill-defined growth.
- Surgery is indicated for:
 - Tumors located in areas where compromise of function or involvement of vital structures may occur
 - Large tumors
 - Painful tumors
 - For cosmetic deformities
 - Tumors that have become malignant
- Optic gliomas that affect vision can be treated with surgery and/or radiation.
- Most serious complication is malignant transformation of a peripheral nerve sheath tumor:
 - Lifetime risk of NF1 patients developing malignant peripheral nerve sheath tumor is 5% to 10%
 - Usually occurs at a younger age
 - Usually seen in long-standing, deep-seated, large central, plexiform-type neurofibroma
 - Presents with a rapidly enlarging or painful (pre-existing) lesion
 - Should always be biopsied
 - Requires radical excision or amputation
 - May benefit from radiotherapy
 - Associated with a poor prognosis with <20% 5-year survival rates

Neurofibromatosis 2 (NF2)

Definition: Autosomal-dominant disorder characterized by neoplastic or dysplastic lesions of Schwann cells, meningeal cells, and glial cells; bilateral vestibular (acoustic) schwannomas are diagnostic.

Synonyms: Central neurofibromatosis; bilateral acoustic neurofibromatosis

Clinical

- Less common type with incidence reported to be 1/25,000 to 40,000 live births
- Autosomal dominant with a high rate of penetrance (95%); gene localized to chromosome 22q12.2:
 - About 50% of NF2 cases are caused by new (spontaneous or de novo) germline mutations
- No gender predilection; affects young patients with a mean age of presentation of 28 years of age

BOX 13-5 Neurofibromatosis 2: Diagnostic Criteria

The following criteria are diagnostic for NF2:

- Bilateral vestibular schwannomas
 - A first-degree relative (e.g., parent, sibling, or offspring) with NF2, and either
 - A vestibular schwannoma or
 - Two of the following: meningioma, schwannoma, glioma, posterior subcapsular lens opacity, or cerebral calcification or
 - Two of the following:
 - Unilateral vestibular schwannoma
 - Multiple meningiomas
 - Either schwannoma, glioma, neurofibroma, posterior subcapsular lens opacity, or cerebral calcification
- Diagnostic criteria are detailed in [Box 13-5](#).
 - Schwann cell tumors/lesions in NF2 include:
 - Schwannoma and schwannomatosis
 - Hallmark of NF2 is bilateral vestibular (acoustic) neuromas:
 - Seen in more than 90% of patients with NF2
 - Accounts for approximately 5% of all vestibular neuromas
 - Symptoms usually occur in teenage years or early third decade of life
 - Symptoms include:
 - Early: hearing (sensorineural) loss, tinnitus, dizziness
 - Late: headache, facial pain and/or weakness, others
 - Both tumors may not occur at the same time; therefore occurrence of an acoustic neuroma in a patient under 30 years of age should raise suspicion for a possible diagnosis of NF2.
 - Occasionally, unilateral vestibular (acoustic) neuroma may occur in patients with NF2 in the absence of other criteria necessary for a diagnosis of NF2.
 - Approximately 50% to 67% of patients with NF2 develop cutaneous schwannomas.
 - Schwannomatosis (multiple schwannomas):
 - Distinct clinicopathologic entity representing a third major form of neurofibromatosis that causes multiple schwannomas without vestibular tumors diagnostic of NF2:
 - Previously but no longer considered an attenuated form of NF2
 - Represent 2.4% to 5% of all patients requiring schwannoma resection
 - Approximately one third of patients with schwannomatosis have anatomically localized disease with tumors limited to a single limb or segment of spine
 - Epidemiologic studies suggest that schwannomatosis is as common as NF2, but that familial occurrence is inexplicably rare.

- NF2 loss in schwannomatosis is not germline:
 - Detectable in tumors
 - Differs among various lesions in any one patient and in tumors from other affected family members
 - Lineage studies of schwannomatosis kindreds place the schwannomatosis locus centromeric to *NF2* on chromosome 22q.
 - Mutation analysis of normal and tumor tissues in familial schwannomatosis found germline mutations of *SMARCB1/INI1* gene; mutations of *SMARCB1/INI1* not typically found in schwannomatosis; tumorigenesis is thought to occur through a four-hit, three-step model, beginning with a germline mutation in *SMARCB1* (hit 1), followed by loss of a portion of chromosome 22 that contains the second *SMARCB1* allele and one *NF2* allele (hits 2 and 3), followed by mutation of the remaining wild-type *NF2* allele (hit 4); expression of *SMARCB1* protein in a proportion of cells from schwannomatosis-related schwannomas suggests that these tumors develop through a mechanism that is distinct from that of rhabdoid tumors in which *SMARCB1* protein is completely absent in tumor cells.
- More common in men than women
- Schwannomas tend to be painful, involve skin and subcutaneous tissues, and may be segmental in distribution
- Schwannomas are of peripheral nerves, cranial nerves, or spinal nerves, but there is no development of the central nervous system neoplasms seen in association with NF2.
- Molecular genetic analysis shows the presence of somatic (in the tumor) but not germline (in all tissues) mutations.
- Pain remains the primary clinical problem and indication for surgery.
- Diagnostic criteria are detailed in Boxes 13-6 and 13-7.
- Meningeal tumors/lesions in NF2 include:
 - Meningiomas and meningioangiomas
 - Multiple meningiomas represent the second hallmark of NF2.
 - Occur earlier in life than sporadic meningioma
 - Meningioangiomas:
 - Cortical lesion characterized by a single, intracortical lesion
 - May be multifocal as well as noncortical
 - May be predominantly vascular or predominantly meningothelial
 - May be associated with a meningioma

BOX 13-6 Schwannomatosis: Diagnostic Criteria**Definite**

- Age >30 years
AND
- 2 or more nondermal schwannomas (at least one with histologic confirmation)
AND
- No MRI evidence of vestibular schwannoma
AND
- No known *NF2* germline mutation
OR
- One histologically proven peripheral (nonvestibular) schwannoma plus first-degree relative meeting above criteria

Possible

- Age <30 years
AND
- 2 or more nondermal schwannomas (at least one with histologic confirmation)
AND
- No MRI evidence of vestibular schwannoma
AND
- No known *NF2* germline mutation
OR
- Age <45 years
AND
- 2 or more nondermal schwannomas (at least one with histologic confirmation)
AND
- No symptoms of eighth nerve dysfunction
AND
- No known *NF2* germline mutation

Data from MacCollin M et al: *Neurology* 64:1838-1845, 2005;
Plotkin SR et al: *Am J Med Genet A* 161A:405-416, 2013.

- In association with NF2 may be multifocal and often asymptomatic; diagnosed at autopsy
- Sporadically occurring, usually single lesion in children or young adults presenting with seizures of persistent headaches
- Glial tumors/lesions in NF2 include:
 - Gliomas and glial microhamartomas
 - Approximately 80% are spinal intramedullary or cauda equina tumors, and 10% occur in the medulla.
 - Ependymomas account for approximately 65% to 75% of all gliomas in NF2 and for almost all spinal gliomas, in which they tend to be multiple intramedullary masses.
 - Diffuse and pilocytic astrocytomas occur in NF2 but are less common.
 - Glial microhamartomas:
 - Cerebral cortical lesions
 - Common in and pathognomonic of NF2
 - Not associated with mental retardation or astrocytomas
- Other findings include cerebral calcifications and peripheral neuropathy:

BOX 13-7 Schwannomatosis: New Proposed Diagnostic Criteria

Diagnostic criteria proposed by MacCollin et al predated the ability to perform molecular testing for schwannomatosis and did not take account of the possibility of multiple meningiomas as a presenting feature. Based on these findings, Plotkin et al propose the following new criteria for diagnosis of schwannomatosis:

Molecular Diagnostic Criteria

- Two or more pathologically proved schwannomas or meningiomas
AND
- Genetic studies of at least two tumors with loss of heterozygosity (LOH) for chromosome 22 and two different *NF2* mutations; if there is a common *SMARCB1* mutation, this defines *SMARCB1*-associated schwannomatosis
- One pathologically proved schwannoma or meningioma

Clinical Diagnosis

- Two or more nonintradermal schwannomas, one with pathologic confirmation, including no bilateral vestibular schwannoma by high-quality MRI (detailed study of internal auditory canal with slices no more than 3 mm thick). Recognize that some mosaic NF2 patients will be included in this diagnosis at a young age and that some schwannomatosis patients have been reported to have unilateral vestibular schwannomas or multiple meningiomas
- One pathologically confirmed schwannoma or intracranial meningioma AND affected first-degree relative
- Consider as possible diagnosis if there are two or more nonintradermal tumors but none has been pathologically proven to be a schwannoma; the occurrence of chronic pain in association with the tumor(s) increases the likelihood of schwannomatosis

Patients with the following characteristics do not fulfill the diagnosis for schwannomatosis:

- Germline pathogenic *NF2* mutation
- Diagnostic criteria for NF2
- First-degree relative with NF2
- Schwannomas in previous field of radiation therapy only

Data from MacCollin M et al: *Neurology* 64:1838-1845, 2005;
Plotkin SR et al: *Am J Med Genet A* 161A:405-416, 2013.

- Intracranial calcifications noted on neuroimaging in NF2
 - Preferred localization includes:
 - Cerebral and cerebellar cortices, periventricular areas, and choroid plexus
- Some NF2 patients develop sensorimotor peripheral neuropathy secondary to focal schwannomatous changes or perineurial cell proliferation.
- Extraneural manifestations include:
 - Posterior lens opacities:
 - Common and highly characteristic of NF2
 - Retinal hamartomas
- Café-au-lait spots and neurofibromas are rare in NF2.
- Cytogenetics and molecular biology:

- *NF2* gene is a tumor suppressor gene located on chromosome 22q12.2.
- *NF2* gene is expressed in most normal human tissues including brain.
- *NF2* gene encodes the protein merlin or schwannomin member of the moesin-ezrin-radixin cytoskeleton-associated proteins expressed in:
 - Schwann cells
 - Meningeal cells
 - Lens of the eye
- Most cases of NF2 are associated with absence of the gene product merlin
- A small but significant number of cases of NF2 and sporadic schwannomas either have no NF2 inactivation or have inactivation of only one allele.

Pathology

- Schwannomas:
 - Histologically identical to sporadic-occurring schwannomas
 - Are usually WHO grade I
 - In relation to the vestibular nerve, may entrap facial nerve fibers and have higher proliferative activity
- Meningiomas:
 - All types occur in NF2.
 - Are usually WHO grade I
 - Atypical or malignant meningiomas are not increased in NF2.

Treatment and Prognosis

- Surgery is indicated for many of the tumors associated with NF2 and should be directed at excising the tumor while preserving functional integrity of the affected site.
- Clinical course varies widely between families and within families.

BENIGN MYOGENIC TUMORS

- Benign myogenic tumors of the neck are uncommon and include tumors of smooth muscle differentiation (leiomyomas) and skeletal muscle differentiation (rhabdomyomas).
- Leiomyomas are benign mesenchymal tumors with smooth muscle differentiation.
- For a more complete discussion of smooth muscle neoplasms see Section 1, Chapter 4, Sinonasal Tract.

Rhabdomyoma

Definition: Benign mesenchymal tumor with skeletal muscle differentiation.

- Rhabdomyomas can be classified as cardiac or extra-cardiac and by histology; the histologic classification includes:
 - Adult
 - Fetal
 - Juvenile

NOTE: The separation of adult-type from fetal-type and juvenile-type rhabdomyomas is based on their histologic appearance rather than the age of the patient.

Adult-Type Rhabdomyoma

(Fig. 13-27)

Clinical

- More than 90% occur in the head and neck.
- Considerably less common than their malignant counterparts (rhabdomyosarcoma)
- Much more common in men than in women; may occur over a wide age range but tends to occur in older population than fetal type, usually in adults over 40 years of age
- Predilection for the head and neck:
 - The most commonly affected site is the neck.
 - Other sites of occurrence include the oral cavity (base of tongue and floor of mouth), oropharynx, and larynx.
- Majority are solitary; up to 20% may be multifocal, synchronous, or dyssynchronous.
- Symptoms vary according to site and include painless neck mass, dysphagia, dyspnea, and hoarseness.
- No association with tuberous sclerosis (unlike cardiac rhabdomyomas, which are associated with tuberous sclerosis)

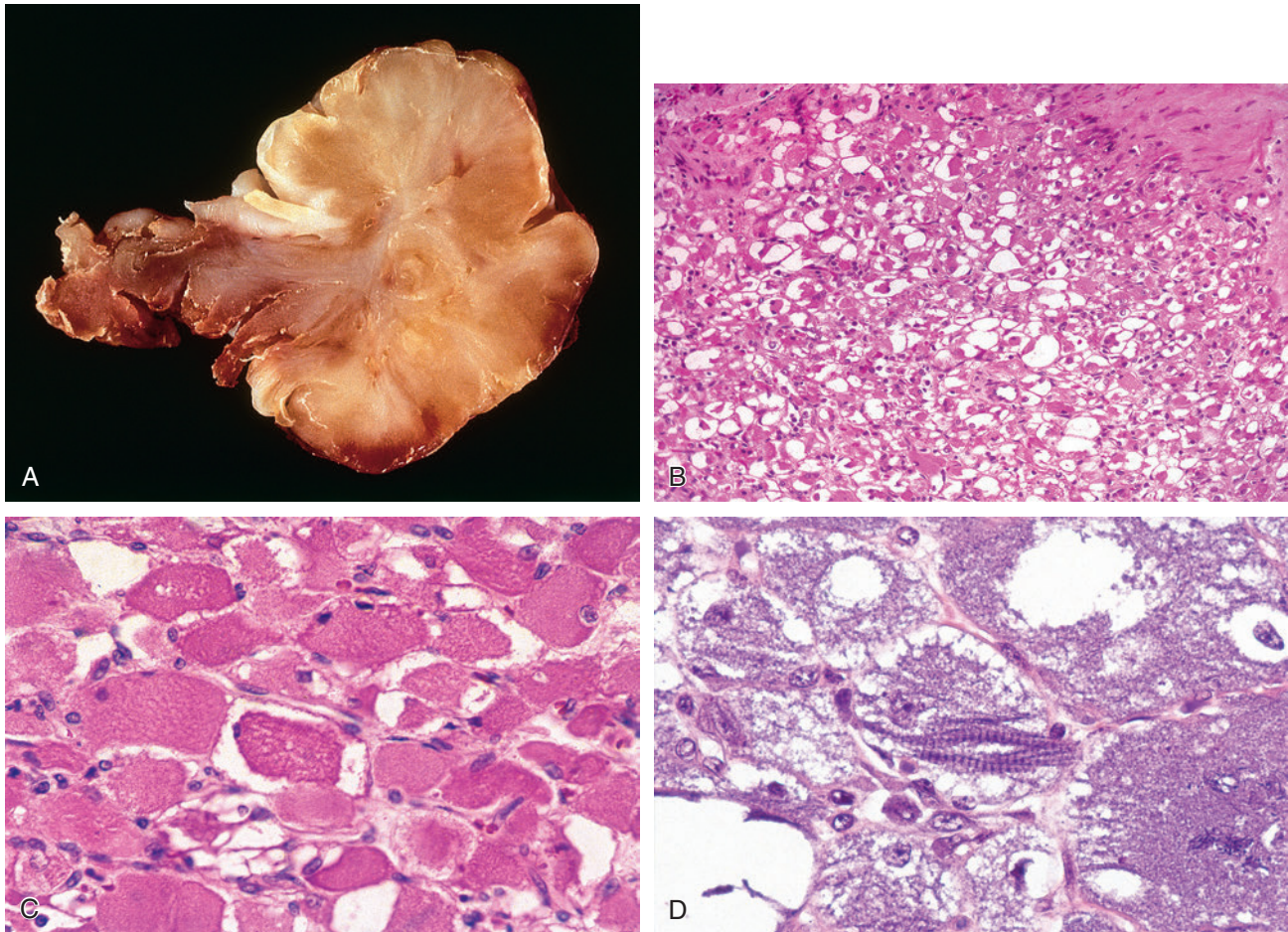


Fig. 13-27. Adult-type rhabdomyoma of the lateral neck.

A, Circumscribed, multinodular, red-brown mass. **B,** Low-power view of adult rhabdomyoma characterized by admixture of deeply eosinophilic polygonal cells with small peripherally placed nuclei and cells with vacuolated cytoplasm. **C,** At higher magnification cells have a finely granular-appearing cytoplasm. **D,** The identification of cross-striations may be aided by staining with phosphotungstic acid-hematoxylin (PTAH).

Pathology

Gross

- Well-delineated or circumscribed, (multi)lobulated, red-brown mass ranging in size from 0.5 to 6.0 cm in greatest dimension; larger tumors may occur

Histology

- Sheet-like proliferation of tightly packed large, polygonal to round cells with abundant deeply eosinophilic, granular cytoplasm and one or two peripherally placed vesicular nuclei; prominent nucleoli occasionally may be prominently identified:
 - Many cells show prominent cytoplasmic vacuolization due to intracytoplasmic glycogen accumulation.
 - Some cells are elongated cells showing similar nuclear and cytoplasmic features may be present.
 - Some cells have a small central acidophilic cytoplasmic mass connected by thin strands of cytoplasm to a condensed rim of cytoplasm at the periphery so-called spider cells, which are more prevalent in cardiac rhabdomyomas than extra-cardiac rhabdomyomas
 - Intracytoplasmic cross-striations may be identifiable.
- Cross-striations are usually readily identifiable; intracytoplasmic rod-like (jackstraw-like) crystalline structures may also be readily identifiable.
- Mitoses and necrosis are absent.
- Histochemistry:
 - Contain abundant cytoplasmic glycogen as seen by the presence of intracytoplasmic diastase-sensitive, PAS-positive material
 - Phosphotungstic acid-hematoxylin (PTAH) stain cross-striations and crystalline structures
- Immunohistochemistry:
 - Immunoreactive for muscle-specific actin, desmin, and myoglobin
 - Variably immunoreactive for vimentin, S100 protein, and smooth muscle actin
 - No immunoreactivity for cytokeratins, EMA, chromogranin, synaptophysin, glial fibrillary acidic protein, or CD68
- Electron microscopy:
 - Haphazard arrangement of intracytoplasmic thin and thick myofilaments with varying degree of differentiation measuring 50 to 70 nm
 - Distinct Z lines are identified within the I band
 - Cells are surrounded by basal lamina with focal infoldings of the plasma membrane.
 - Variable number of mitochondria and glycogen
 - Absence of cell junctions
- Cytogenetics and molecular genetics:
 - Reciprocal translocation of chromosomes 15 and 17

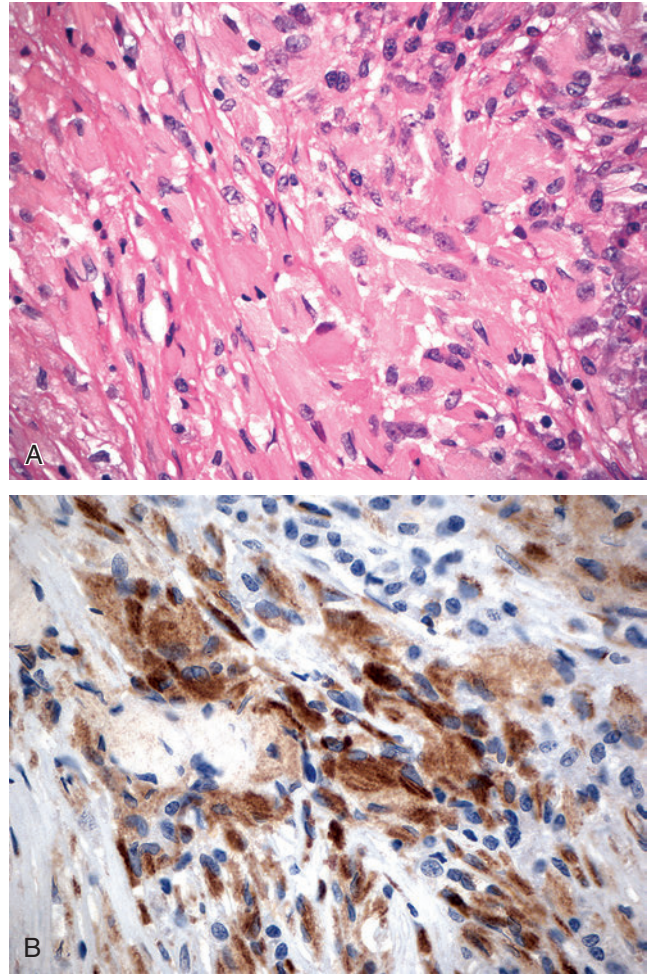


Fig. 13-28. Crystal storing histiocytosis.

A, Cells simulate those seen in rhabdomyoma due to intracellular immunoglobulin crystal deposition. **B**, Cells are immunoreactive for CD68 (KP1).

- Abnormalities in long arm of chromosome 10
 - Above findings lend support to the neoplastic (rather than hamartomatous) nature of rhabdomyomas

Differential Diagnosis

- Granular cell tumor
- Alveolar soft part sarcoma
- Hibernoma
- Paraganglioma
- Crystal storing histiocytosis (Fig. 13-28):
 - Intracellular immunoglobulin crystal deposition in histiocytes is rare and can be seen in association with lymphoplasmacytic or plasma cell neoplasms.
 - Represents a dysproteinemia-associated lymphoproliferative process
 - Occurs in soft tissues particularly in the head and neck region, as well as the lung and other sites

- Light microscopic features simulate the cells seen in rhabdomyoma
- Crystal-containing cells are positive for CD68 (KP-1), but negative for desmin, muscle-specific actin, or myoglobin.
- Ultrastructural findings of the crystalline material show a lattice pattern with periodicity of 45 to 60Å the crystalline material consistent with immunoglobulin

Treatment and Prognosis

- Complete surgical excision is curative.
- May recur if incompletely excised

Rhabdomyoma, Fetal and Juvenile-Intermediate Types

Definition: Tumors showing spectrum of skeletal muscle differentiation ranging from immature, predominantly myxoid tumors (fetal type) to tumors showing a high degree of cellular differentiation with limited to absent myxoid matrix (intermediate type).

Rhabdomyoma, Fetal Type

(Fig. 13-29)

Synonym: Fetal rhabdomyoma, myxoid type

Clinical

- Rare tumor
- Much more common in males than females; most common in patients under 3 years of age; rare in adults
- Most common sites of occurrence include postauricular and preauricular subcutaneous tissues; less common sites of occurrence include the nasopharynx, parotid gland, and neck.
- Symptoms vary according to site:
 - Postauricular region presents as a slow-growing, painless mass.
- Usually solitary but may be multifocal:
 - Multifocal tumors reported in association with nevoid basal cell carcinoma syndrome:
 - Autosomal-dominant disorder
 - Characterized by multiple basal cell carcinomas occurring early during childhood, various skeletal abnormalities, and odontogenic keratocyst
 - Mutations in PTCH tumor suppressor gene implicated in development of this syndrome

Pathology

Gross

- Solitary, well to moderately circumscribed nodule measuring from 1 to 8 cm with a gray to pink, mucoid, glistening appearance

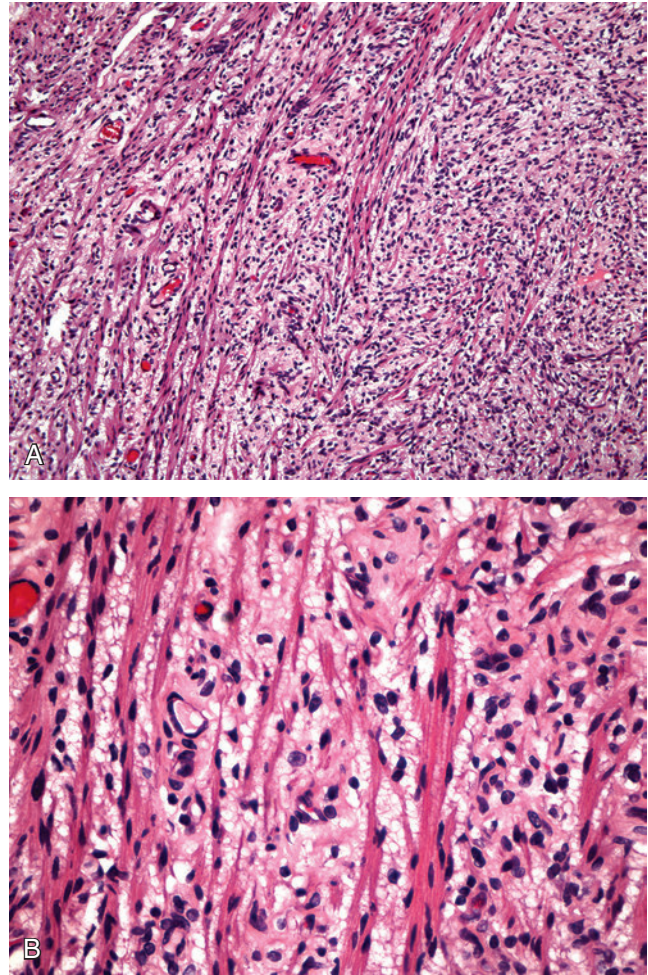


Fig. 13-29. Fetal rhabdomyoma.

A, The tumor comprises an admixture of primitive round and spindle-shaped cells and differentiated myofibrils arranged in short fascicles within a myxoid stroma. **B,** At higher magnification the myofibrils show little variation in size or shape of the muscle cells with absent mitoses, which would contrast to the features seen in association with rhabdomyosarcoma. Tumor cells are immunoreactive for desmin, muscle-specific actin, and myoglobin (not shown).

- Mucosal-based lesions are smooth with a polypoid or pedunculated appearance.

Histology

- Superficially located rather than deeply situated within muscle
- Cellularity varies to include sparse to moderately cellular (myxoid) and cellular types.
- Primarily composed of primitive undifferentiated oval to spindle-shaped cells with indistinct cytoplasm; interspersed immature skeletal muscle fibers within a copious myxoid stroma are identified:

- Immature cells have uniform small, round to oval to spindle-shaped nuclei, inconspicuous to identifiable nucleoli, scanty indistinct cytoplasm and bipolar and multipolar eosinophilic cytoplasmic processes
- Cell arrangement may include short bundles or be isolated in the myxoid stroma
- Strap cells with cross-striations rarely discernible
- Occasionally, large round cells with eosinophilic cytoplasm similar to those seen in adult rhabdomyoma may be identified.
- Nuclear atypia is not present; mitoses and necrosis are typically absent; in limited examples both may be present, but atypical mitoses are not identified.
- Rarely, intimate association with peripheral nerves may be present:
 - Referred to as neural variant of fetal rhabdomyoma
 - Similar to and must be differentiated from neuromuscular choristoma (benign Triton tumor)
- Histochemistry:
 - Masson trichrome and phosphotungstic acid-hematoxylin (PTAH) assist in the possible identification of cross-striations.
- Immunohistochemistry:
 - Desmin, muscle-specific actin, and myoglobin positive
 - Variable (and often limited to absent) reactivity for smooth muscle actin, S100 protein, and vimentin
 - Glial fibrillary acidic protein (GFAP), keratin, EMA, and CD68 negative
- Electron microscopy:
 - Organized bundles of myofilaments (thick myosin and thin actin) with characteristic banding in differentiated muscle cells
 - Rod-like cytoplasmic inclusions and hypertrophied Z-band material may be identified but are less common as compared with adult rhabdomyoma
 - Intracellular glycogen
 - Spindle cells lack cellular differentiation
- Cytogenetics and molecular genetics:
 - Aberrations at PTCH1 locus including PTCH1 frameshift mutation and homozygous deletions of PTCH1 suggest that activated Hedgehog signaling contributes to the biology of fetal rhabdomyomas.

Differential Diagnosis

- Rhabdomyosarcoma, embryonal and spindle cell types:
 - Presence of nuclear atypia and mitotic figures, including atypical mitoses as well as necrosis and

infiltrative growth, assists in differentiating fetal rhabdomyoma from rhabdomyosarcoma.

- Utility of myogenin and MyoD1 in differentiating from rhabdomyoma remains uncertain

Treatment and Prognosis

- Conservative but complete surgical resection is curative.

Rhabdomyoma, Juvenile-Intermediate Type (Fig. 13-30)

Clinical

- Rare tumor
- More common in men than in women; affects older ages as compared with fetal (myxoid)-type rhabdomyoma, affecting adolescents (usually older than 15 years of age) and adults
- Predilects to the head and neck region with common sites of occurrence, including:
 - Orbit, tongue, nasopharynx, and soft palate
- Symptoms vary according to site but usually is that of a slow-growing, painless mass.
- Some consideration has been given to fetal-type and juvenile-type rhabdomyomas representing a hamartoma or congenital anomaly rather than a true neoplasm; however, support of the neoplastic nature of these lesions includes:

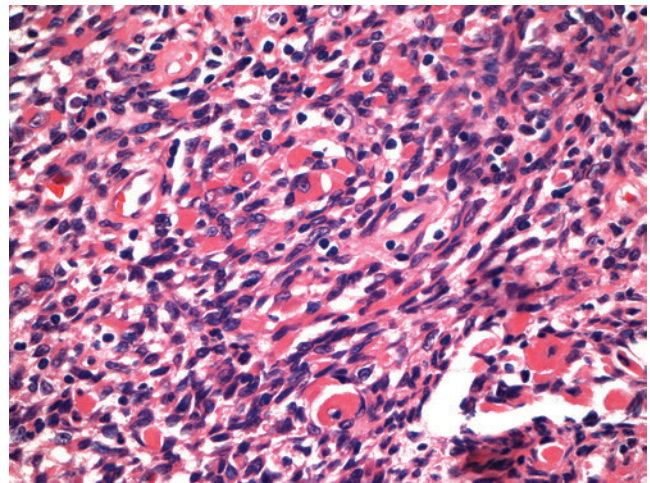


Fig. 13-30. Rhabdomyoma, juvenile-intermediate type.

Cellular tumor characterized by the presence of cells showing skeletal muscle differentiation, including strap-shaped muscle cells and ganglion-like cells with large vesicular nuclei and prominent nucleoli. Tumor cells are immunoreactive for desmin, muscle-specific actin, and myoglobin (not shown).

- Association with nevoid basal cell carcinoma syndrome:
 - Autosomal-dominant disorder
 - Characterized by multiple basal cell carcinomas occurring early during childhood, various skeletal abnormalities, and odontogenic keratocyst
 - Mutations in PTCH tumor suppressor gene implicated in development of this syndrome

Pathology

Gross

- Similar to fetal-type rhabdomyoma

Histology

- Superficially located rather than deeply situated within muscle
- Characterized by the presence of numerous cells showing skeletal muscle differentiation:
 - Predominant cell is strap-shaped muscle cell with abundant eosinophilic cytoplasm and centrally located vesicular nuclei; cells with cross-striations are frequently identified.
 - Cells with rhabdomyoblastic maturation, including prominent ganglion-like cells with large vesicular nuclei and prominent nucleoli, are present.
 - Cells with vacuolated cytoplasm due to increased glycogen can be seen.
 - Typically there is little to absent myxoid stroma.
- Transitional areas showing a coexisting intermediate-type and fetal (myxoid)-type rhabdomyoma are not infrequently identified.
- Nuclear atypia, increased mitotic activity, and necrosis are typically absent; in limited examples both may be present, but atypical mitoses are not identified.
- Rarely, intimate association with peripheral nerves similar to neuromuscular choristoma may be present.
- Histochemistry:
 - Intracytoplasmic diastase-sensitive, PAS-positive material indicative of glycogen is present.
 - Masson trichrome and phosphotungstic acid-hematoxylin (PTAH) assist in the possible identification of cross-striations.
- Immunohistochemistry:
 - Desmin, muscle-specific actin, and myoglobin positive
 - May be positive for SMA, S100 protein, vimentin
 - Cytokeratin, EMA, and CD68 negative
- Electron microscopy:
 - Organized bundles of myofilaments (thick myosin and thin actin) with characteristic banding in differentiated muscle cells
 - Rod-like cytoplasmic inclusions and hypertrophied Z-band material may be identified but

are less common as compared with adult rhabdomyoma

- Intracellular glycogen
- Spindle cells lack cellular differentiation.

Differential Diagnosis

- Rhabdomyosarcoma, embryonal, and spindle cell types:
 - Presence of nuclear atypia and mitotic figures, including atypical mitoses, assists in differentiating fetal rhabdomyoma from rhabdomyosarcoma.
 - Utility of myogenin and MyoD1 in differentiating from rhabdomyoma remains uncertain

Treatment and Prognosis

- Conservative but complete surgical resection is curative.

TERATOMATOUS NEOPLASMS

Teratoma (Fig. 13-31)

Definition: Tumor composed of a variety of mature tissues derived from two or three germ layers and foreign to the site of occurrence.

Clinical

- In the head and neck rare neoplasms accounting for less than 2% of all teratomas.
- No gender predilection; majority occurs in newborns or infants and is rarely seen over the age of 1 year (cervical teratoma) and 2 years (nasopharyngeal teratoma):
 - Most tumors in neonates are benign.
 - May be seen in the adult population
 - More than 50% of tumors in adults are malignant.
- Most common locations in the head and neck include:
 - Neck and nasopharynx
 - Other less commonly involved sites include oral cavity (tonsil, tongue, palate), sinonasal cavity, external and middle ear and temporal bone, mandible and maxilla, and thyroid gland.
- Presenting symptoms include:
 - Cervical teratoma: neck mass that may compress the trachea, resulting in airway obstruction (stridor, apnea)
 - Nasopharyngeal teratoma: mass protruding into the oral cavity or pharynx causing associated dysphagia and/or airway obstruction
- May present prenatally with signs and symptoms, including:
 - Polyhydramnios, fetal hydrops, and identification of mass by fetal ultrasound

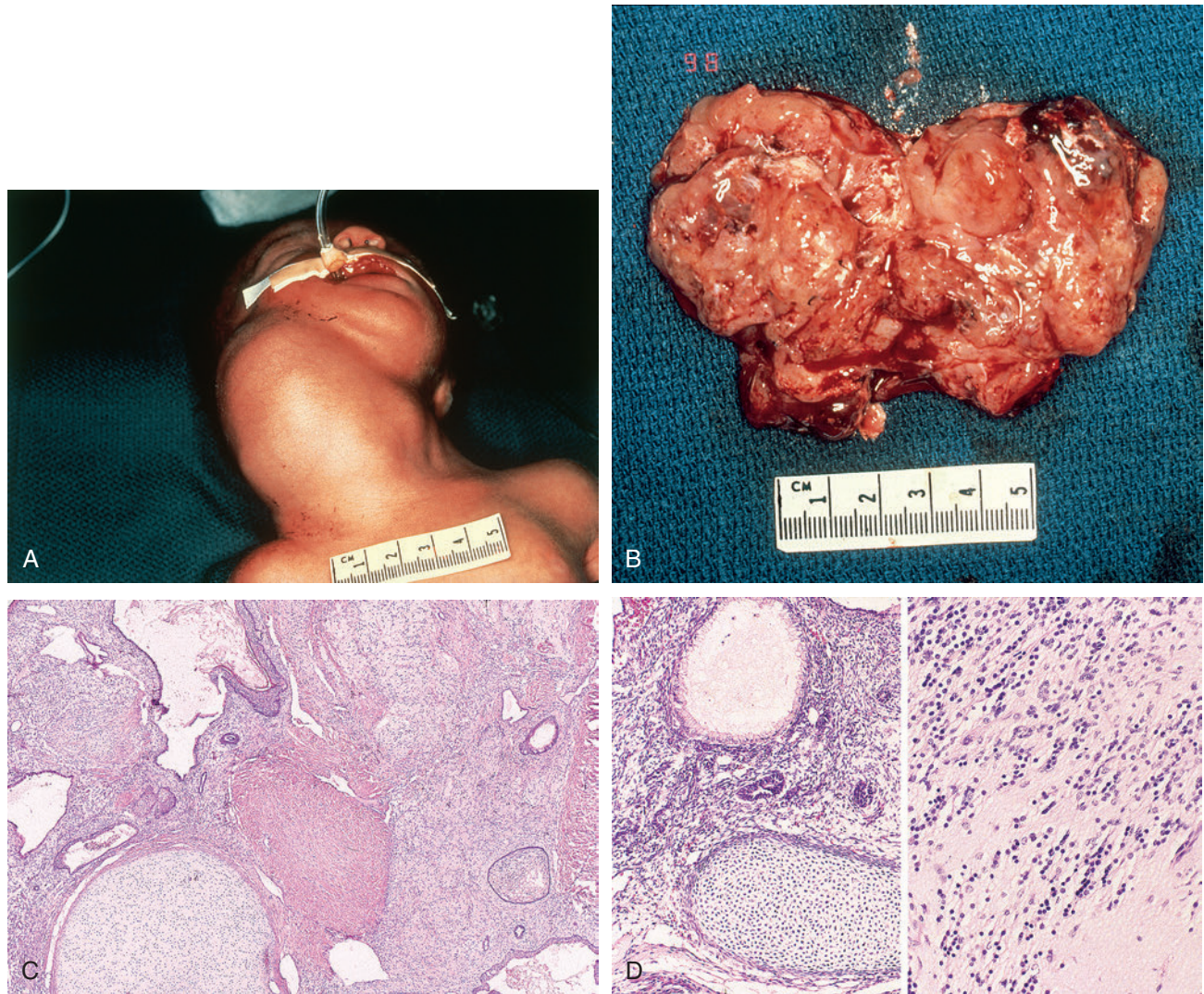


Fig. 13-31. Cervical neck mature teratoma.

A, Large mass that clinically compressed the trachea, resulting in airway obstruction. **B**, Cut section showing predominantly solid tissue with a tan-brown to fleshy appearance. **C**, Histologic composition of teratomas includes elements from all germ cell layers, including epithelial (squamous and columnar), mesenchymal structures (cartilage), and central nervous system tissue. **D**, *Left*, epithelial lined glands and immature cartilage; *right*, central nervous system tissue.

- May be associated with maternal hydramnios and stillbirth
- In contrast to teratomas occurring in the pediatric population, teratomas of the head and neck in adults:
 - Occur much less frequently
 - Tendency for a larger percentage of these tumors to be malignant
- Derivation thought to be from primordial germ cells or primitive somatic cells

Pathology

Gross

- Encapsulated cystic, solid, or multiloculated mass measuring in size from 5 to 17 cm in diameter

Histology

- Composition includes the identification of tissue arising from all three germ layers, including:
 - Epithelial: keratinizing squamous, columnar, ciliated respiratory or gastrointestinal-type epithelium, cutaneous adnexa, minor salivary glands; thyroid parenchyma may be found in a minority of cases
 - Neuroectodermal and central nervous system tissue:
 - Particularly in nasopharyngeal and sinonasal teratomas, neuroectodermal and neural tissue components predominate.

- May include mature glial tissue, neurofibrillary matrix, neural rosettes, and/or choroid plexus
- Mesenchymal: cartilage, bone, fat, and smooth muscle
- Epithelial-lined cystic spaces are prominent.
- Immature or embryonal tissue components can be identified throughout the tumor.
- Necrosis and hemorrhage may be seen.
- Grading:
 - Completely mature tumors: grade 0
 - Predominantly mature: grades 1 and 2
 - Mostly immature: grade 3 or malignant
- Malignant teratoma and germ cell tumors (Fig. 13-32):
 - Rare tumors in the head and neck
 - No gender predilection; occur over a wide age range from the third through the eighth decades of life
- Malignant teratoma:
 - Histologic evaluation demonstrates a prominent neural component associated with poorly differentiated carcinoma and/or sarcoma.
 - In the adult setting, increased cellular immaturity has prognostic significance as demonstrated by a greater malignant potential; additionally, adult teratomas with benign histology may recur or metastasize.
 - Metastases commonly occur via lymphatic and vascular routes.
 - Aggressive therapy is indicated.
- Prognosis is poor.
- Germ cell tumors:
 - Yolk sac tumor (endodermal sinus tumor)
 - Rare in the head and neck
 - May occur in association with immature teratoma or independent of a teratoma as exclusive histopathologic element

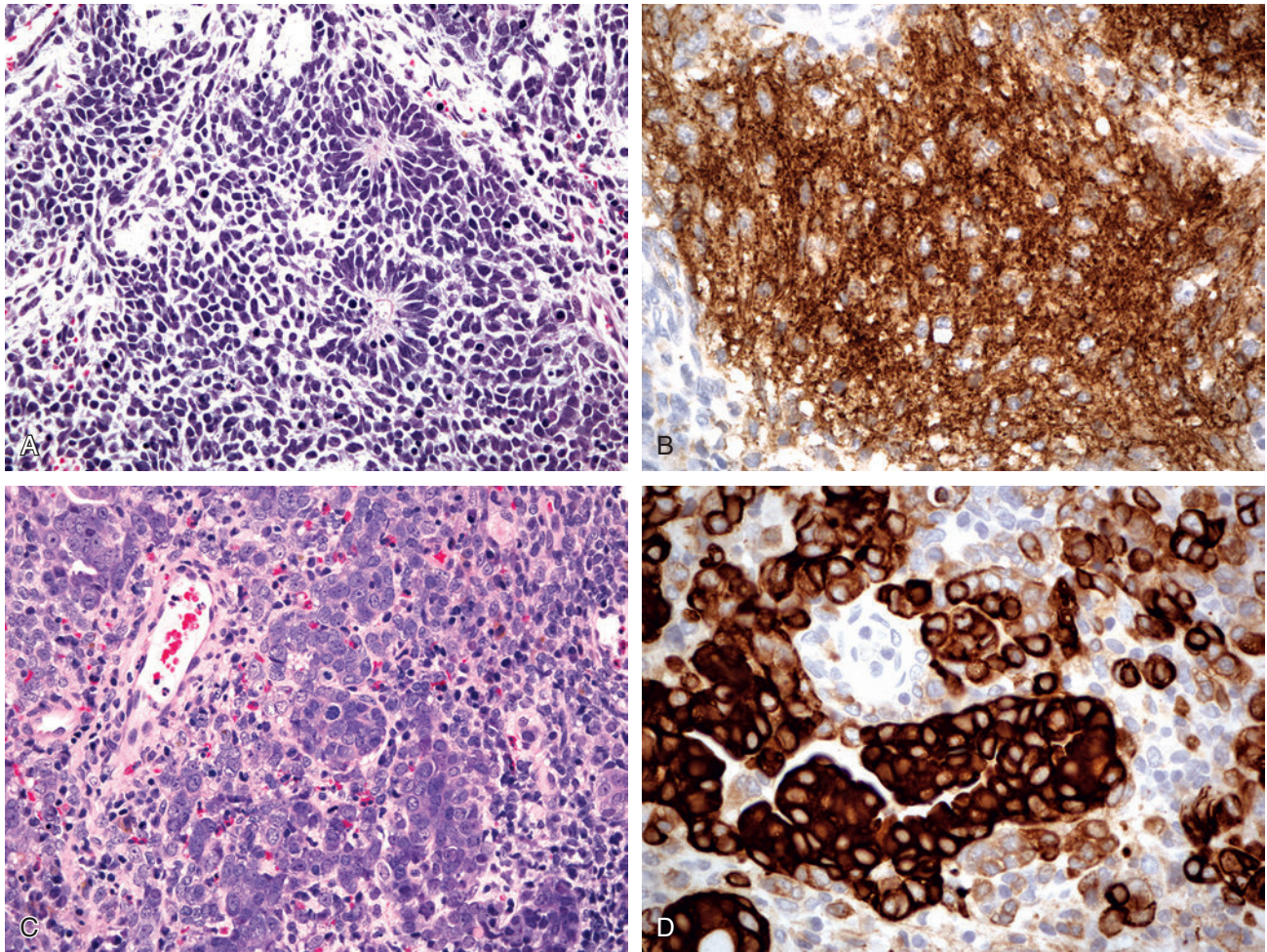


Fig. 13-32. Cervical neck immature (malignant) teratoma.

A, Immature neural-type tissue with neural rosettes. **B**, Synaptophysin reactivity in the immature neural tissue infiltrate. **C**, Cohesive clusters of undifferentiated malignant cells. **D**, Cytokeratin reactivity confirms the epithelial nature (i.e., carcinoma) of the undifferentiated malignant cells.

- Rare reports include occurrence in association with sinonasal nonkeratinizing carcinoma.
- Majority of patients are children under 1 year of age.
- Sites of occurrence may include oral cavity, nasopharynx and/or sinonasal tract, oropharynx, ear, salivary glands.
- Associated with elevated serum alpha-fetoprotein (AFP)
- Histology identical to gonadal yolk sac tumors including:
 - Intermingling of epithelial and mesenchymal elements in organoid manner
 - Growth patterns include reticular (microcystic, vacuolated), macrocystic, papillary, solid, glandular/alveolar, endodermal sinus (perivascular, festoon), myxomatous, hepatoid, sarcomatoid, polyvesicular vitelline
 - Perivascular Schiller-Duval bodies (glomeruloid bodies) represent most distinctive feature, characterized by papillary core of fibrous tissue with central small blood vessel ringed by layer of malignant-appearing cuboidal to columnar cells
 - Hyaline globules (intracytoplasmic) consistently present: not specific for yolk sac tumor; tend to occur in clusters iastase-resistant, PAS positive
 - Immunohistochemical reactivity includes: alpha-fetoprotein (AFP) positive (cytoplasmic staining); pancytokeratin and SALL4 (nuclear) positive; glypican 3 positive (cytoplasmic and membranous); CK7 typically negative; OCT3/4 negative; hyaline globules usually AFP negative but may be positive
 - May rarely occur in association with choriocarcinoma
- Aggressive tumor requiring equally aggressive management including
 - Complete surgical excision is recommended, although this may not be possible.
 - Combination radiation and chemotherapy; use of platinum-based chemotherapy has improved survival
 - Often metastasizes to lymph nodes and viscera (e.g., bone, lungs, liver, others)
 - Serum AFP level can be used to monitor response to treatment as well as in detecting tumor recurrence
- Choriocarcinoma:
 - Rarely occurs outside the genital tract
 - Occurrence in the head and neck is rare and presence in head and neck should prompt exclusion of metastasis from genital tract.
 - To date, identification limited to sinonasal tract
 - Associated with elevated serum beta-human chorionic gonadotropin (HCG) levels
 - Usually hemorrhagic and necrotic tumors
 - Histology includes:
 - Admixture of syncytiotrophoblast cells with large atypical nuclei with mononuclear trophoblast cells (cytotrophoblasts) creating biphasic pattern; syncytiotrophoblast cells show variable morphology but most often include large cells with hyperchromatic irregular nuclei and eosinophilic to amphophilic cytoplasm; distinct cytoplasmic vacuoles or lacunae are present, which may contain erythrocytes; cytotrophoblasts consist of mildly pleomorphic nuclei with prominent nucleoli and pale to clear cytoplasm; discrete cell borders usually present; syncytiotrophoblasts “cap” proliferating cytotrophoblast cells (villus-like pattern); more common to show random admixture of syncytiotrophoblast cells with cytotrophoblast cells; vascular invasion commonly seen
 - Immunohistochemical reactivity includes: presence of hCG in syncytiotrophoblasts and occasionally positive in cytotrophoblasts; syncytiotrophoblasts reactive for inhibin, epidermal growth factor, and glypican 3; cytokeratin reactivity in syncytiotrophoblasts and cytotrophoblasts; EMA positive mainly in syncytiotrophoblasts; p63 (nuclear) reactivity in cytotrophoblasts
 - Treatment includes chemotherapy for germ cell malignancy.
- Too few cases reported in the literature to suggest true outcome but may metastasize and prove lethal or respond to therapy with disease-free survival.

Differential Diagnosis

- Teratoid lesions (dermoid cysts, nasopharyngeal “hairy polyp”)
- Heterotopic central nervous system tissue or encephalocele
- Cystic hygroma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Prenatally diagnosed cases can be delivered preterm by cesarean section with immediate intubation

and ventilation aim for respiratory stabilization followed by elective resection.

- Morbidity may be high due to the size and location of the tumors.
- Mortality rates are low if surgical intervention is initiated early; however, death may ensue if not adequately treated and is usually caused by complications of respiratory obstruction.
- Nasopharyngeal teratomas may extend intracranially.
- Lymph node metastases may be seen but may reflect “benign” metastases rather than an indication of malignancy.

- In the pediatric age group, malignant transformation or behavior of a head and neck teratoma has not been reported.
- Adult teratoid lesions of the head and neck should be considered to be malignant teratomas until proven otherwise.
- Finding of immature or embryonic tissue components is not of any prognostic significance.

MALIGNANT TUMORS OF THE NECK

HEMATOLYMPHOID MALIGNANT NEOPLASMS

General Considerations

- Malignant lymphomas are generally divided into two major categories: non-Hodgkin lymphoma and Hodgkin disease.
- The vast array of clinical and pathologic features of the malignant lymphoproliferative diseases are beyond the scope of this text.
- See sections on the sinonasal tract (Section 1) and pharynx (Section 3) for detailed discussion of site-specific lymphomas.
- Follicular dendritic cell sarcoma can arise in lymph nodes of the cervical neck or extranodal sites, in particular, the tonsils; see Section 3, Pharynx, for a more complete discussion.

SARCOMAS OF THE NECK

- In general, sarcomas of the neck are uncommon.
- Although uncommon, virtually all types of sarcomas may occur in these sites.

Malignant Peripheral Nerve Sheath Tumors (MPNST)

(Figs. 13-33 and 13-34)

Definition: Malignant neoplasm (sarcoma) arising from cells intrinsic to the nerve sheath or having differentiation along the lines of various elements of the nerve sheath.

- Diagnosis is predicated on:
 - Origin from a nerve (exclusive of perineurium) or preexisting benign nerve sheath tumor (usually neurofibroma but may also include schwannoma, ganglioneuroblastoma)

- Ultrastructural evidence of Schwann cell differentiation
- Development of a spindle cell sarcoma in patient with NF1 with histologic features of MPNST
- In the absence of the above findings, a diagnosis can be made based on histologic, immunohistochemical, and ultrastructural features of Schwann cell differentiation.

Synonyms: Malignant schwannoma; neurogenic sarcoma; neurofibrosarcoma

Clinical

- Uncommon tumor accounting for approximately 5% of all soft tissue sarcomas; most commonly occurs in the lower extremity
- Up to 20% may occur in the head and neck:
 - Most common site of involvement is the neck.
 - Less frequently, other sites of involvement include sinonasal tract, nasopharynx, and oral cavity.
- Symptoms include:
 - Neck:
 - Mass with associated pain, paresthesia, and weakness
 - Sinonasal tract, nasopharynx, oral cavity:
 - Mass lesion, pain, epistaxis, and nasal obstruction
- Occur in varying settings with different epidemiologic findings, including:
 - De novo (sporadic) MPNST
 - In the setting of neurofibromatosis 1 (NF1) characterized by loss of function mutations to the tumor suppressor neurofibromin
 - May also occur in areas previously irradiated

Sporadic or De Novo MPNST

- No gender predilection or slightly more common in women; occur over a wide age range but most frequent in the fifth decade
- No known cause

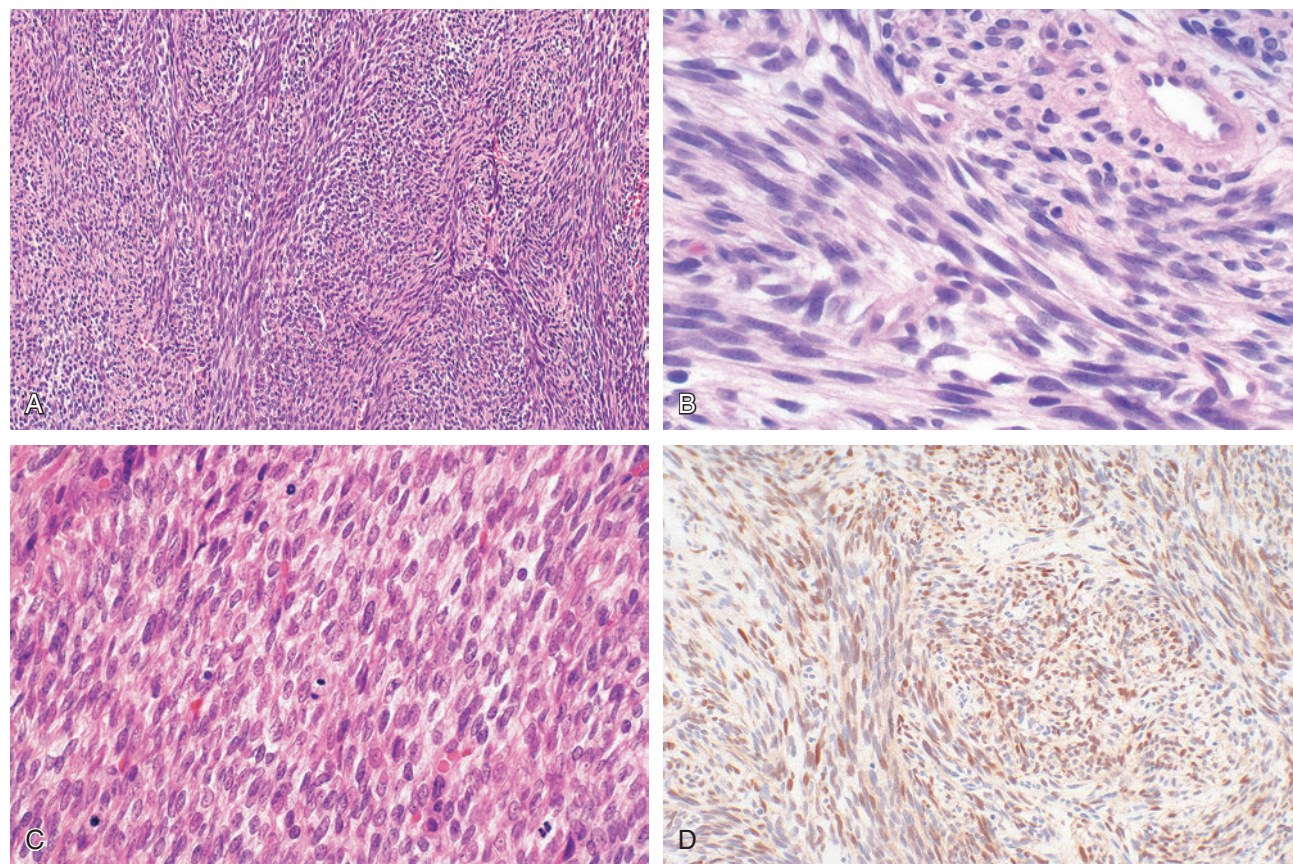


Fig. 13-33. Malignant peripheral nerve sheath tumor, low grade.

A, Infiltrating cellular tumor arranged in a fascicular growth with long sweeping ("herringbone-like") fascicles that swirl or interdigitate with one another. **B**, Neoplastic cells have elongated nuclei with an irregular contour and tapered ends when seen in profile and are asymmetrical oval when seen en face. **C**, Increased mitotic activity. **D**, S100 protein positive. Increased cellularity with nuclear pleomorphism and increased mitotic activity assist in differentiating low-grade malignant peripheral nerve sheath tumor from cellular schwannoma.

MPNST Associated with NF1

- Accounts for approximately 30% to 50% of all MPNSTs:
 - Lifetime risk in patients with NF1 is 5% to 10%
- No gender predilection or slightly more common in women; tends to occur in a younger age group (10 to 15 years younger) as compared with sporadic MPNST and is primarily seen in the third to fourth decades of life; can also occur in children
- Estimated risk of patients with NF1 developing MPNST varies from 4% to 50%
 - Occurrence typically follows a latent period of from 10 to 20 years
- MPNST not associated in patients with NF2 although rare example of MPNST spontaneously developing in patient with NF2 reported:
 - Rarity of development of MPNST in NF2 patients may be attributed to resistance of nonmelanotic schwannomas (which occur in NF2) to malignant transformation.

Radiation-Induced MPNST

- Approximately 10% are radiation-induced with post-treatment latency period usually greater than 10 years

Pathology

Gross

- Fusiform-shaped mass with a fleshy, tan-white appearance usually measuring more than 5 cm in diameter; attachment to a nerve may be identified.
- Cyst formation, hemorrhage, and necrosis are frequently present.

Histology

High-Grade MPNST

- Most MPNSTs are high grade and the following reflects those high-grade lesions; see later for a discussion on low-grade MPNST.
- Unencapsulated hypercellular proliferation composed of spindle-shaped cells:

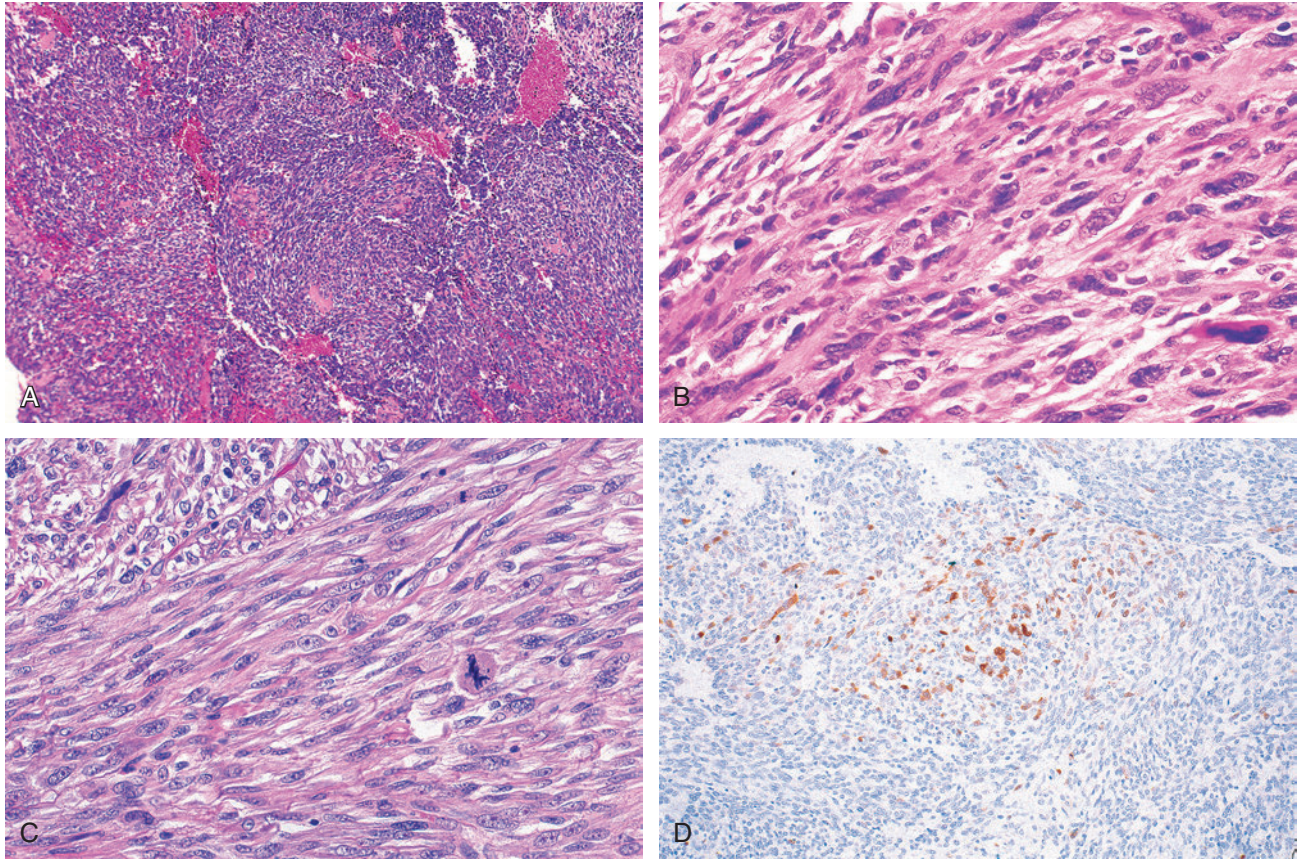


Fig. 13-34. Malignant peripheral nerve sheath tumor, high grade.

A through **C**, Hypercellular neoplasm with less conspicuous fascicular growth as compared with its low-grade counterpart, but with increased cellularity, nuclear pleomorphism, hemorrhage, necrosis, and increased mitotic activity, including atypical forms. **D**, Focal S100 protein immunoreactivity.

- Cells have elongated nuclei with an irregular contour, tapered ends, and appearing wavy or buckled when seen in profile and asymmetrically oval when seen en face; cytoplasm is indistinct
- Cells are arranged in a fascicular growth with long, sweeping (“herringbone-like”) fascicles that swirl or interdigitate with one another.
- Perivascular accentuation or whorling of lesional cells that sometimes may include infiltration of lesional cells into vessel walls
- Abrupt alternation between cellular and hypocellular, myxoid areas
- Less common growth patterns may include nodules or whorled arrangement of neoplastic cells.
- Nuclei tend to be hyperchromatic and pleomorphic with inconspicuous nucleoli.
- Mitoses generally readily identifiable:
 - Most cases show at least four mitotic figures per 10 high-power fields.
 - Mitotic counts of 10 to 20 per 10 high-power fields are common.
- Necrosis can be found, including geographic type; tendency to spare lesional cells surrounding blood vessels (peritheliomatous pattern)
- In approximately 10% of cases abundant myxoid stroma may be present (myxoid MPNST)
 - Hypocellular areas with a myxoid stroma can be seen alternating with areas of greater cellularity.
- Nuclear palisading may be seen but typically is present in a minority of cases (less than 10%) and when present tends to be focally identified within a given tumor:
 - Nuclear palisading more common in other sarcomas (e.g., leiomyosarcoma, synovial sarcoma)
- Other findings seen include:
 - Presence of hyaline bands and nodules resembling giant rosettes when seen in cross-section
 - Perineural and intraneural spread of tumor
 - Proliferation of tumor in subendothelial zones of blood vessels given the appearance of tumor cells herniating into the lumen

- Heterologous elements can be identified in up to 10% to 15% of cases, especially those arising in NF1 patients:
 - Tend to be more commonly seen in association with MPNST than other sarcomas
 - Most commonly includes rhabdomyosarcomatous elements (malignant Triton tumor; see later)
 - Frequently includes osteosarcomatous or chondrosarcomatous differentiation
 - Angiosarcomatous differentiation rare
- Diagnosis of MPNST assisted by finding nerve fascicle(s) overrun by plexiform neurofibroma with or without perineurium involvement or a symmetrically expanded nerve infiltrated by tumor
- Invasion into soft tissue, lymph-vascular invasion, and osseous invasion may be seen.
- Immunohistochemistry:
 - S100 protein reactivity:
 - Represents most widely used marker in the diagnosis of MPNST
 - Low-grade MPNSTs consistent S100 protein positive while high-grade MPNSTs are variably positive
 - Variable reactivity reported, including from 50% to 90% of cases to 30% to 67% of cases:
 - Absence of S100 protein does not exclude diagnosis.
 - Not a unique marker for MPNST and seen in a wide variety of neoplasms (benign and malignant)
 - Sox10, a transcription factor in neural crest development and differentiation of neural crest cells into melanocytic and schwannian lineage, reactive (nuclear staining) in MPNSTs with reports showing better sensitivity and specificity in the diagnosis of MPNST than S100 protein
 - Vimentin positive
 - GFAP reactivity in 20% to 30% of cases
 - Variable reactivity for Leu-7 (CD57)
 - p53 expression (nuclear) present in high proportion of cases
 - Immunohistochemical staining for the newly developed monoclonal antibody binding to the C-terminus of neurofibromin (NFC) revealed loss of neurofibromin in 88% of NF1-associated 43% of sporadic MPNST.
 - Strong association of neurofibromin loss with deletions affecting the *NF1* gene
 - Limited loss of NFC in large series of other soft tissue tumors of different histotypes
 - Loss of neurofibromin not observed in synovial sarcomas, schwannomas, solitary fibrous tumors, low-grade fibromyxoid sarcomas, dedifferentiated liposarcomas, myxoid liposarcomas, angiosarcomas, extraskeletal myxoid chondrosarcomas, and epithelioid sarcomas
- Immunohistochemistry using antibody to NFC may substantially facilitate diagnosis and differential diagnosis of MPNST.
- Epithelial, neuroendocrine, melanocytic, and hematolymphoid markers typically negative:
 - EMA reactivity is rare and if present suggests perineurial differentiation.
- TLE1 negative
- p16 negative
- Cases with rhabdomyosarcomatous or angiosarcomatous differentiation stain for appropriate markers including desmin and myogenin for skeletal muscle differentiation and CD31, Factor 8, Fli-1, and ERG1 for endothelial differentiation.
- Electron microscopy:
 - Given relative lack of differentiation in high-grade MPNSTs, no more than approximately 50% show schwannian differentiation.
- Cytogenetics and molecular genetics:
 - No consistent karyotypic pattern
 - Complex and nonspecific karyotype abnormalities including chromosomal gains and losses
 - Often show *NF1* gene deletion or mutation:
 - Patients with NF1 carry germline alterations in *NF1* gene.
 - Biallelic mutations of *NF1*, whether occurring sporadically or in association with NF1
 - *TP53* gene mutations and alterations of protein expression are rare.
 - PTEN downregulation implicated in genesis of MPNSTs in NF1 (and in plexiform neurofibromas)
 - Homozygous deletions of *CDKN2A* gene:
 - Encodes two nonhomologous isoforms, *p14ARF* and *p16INK4a*
 - Both have important impact on cell-cycle progression;
 - Occurs in progression of neurofibromas to MPNST
 - Found in 50% of MPNST
 - Not present in neurofibromas
- Low-grade MPNST:
 - A minority of cases are low-grade and distinction from benign nerve sheath tumor with atypical features can be problematic
 - As compared with benign nerve sheath tumors, low-grade MPNSTs have:
 - Increased cellularity and increased mitotic activity; mitoses may be few in number but atypical mitoses are not typically present; necrosis is usually not present
 - May demonstrate infiltrative growth

- Histologic variants of MPNST include (all usually uncommon in the head and neck):
 - MPNST with rhabdomyosarcoma (malignant Triton tumor):
 - Approximately 60% associated with NF1
 - Rhabdomyoblasts are identified scattered throughout the tumor and their numbers vary from case to case:
 - Typically are mature in appearance with abundant eosinophilic cytoplasm
 - Cross-striations can be identified, especially in cells with elongated cytoplasm
 - Immunoreactive for desmin, myoglobin, and myf-4 (nuclear staining); actin reactivity may be present.
 - Glandular MPNST:
 - Rare variant
 - Almost all arise in patients with NF1
 - Contains gland formation:
 - Intestinal appearance most often are benign appearing, composed of well-differentiated, nonciliated cuboidal or columnar cells and clear cytoplasm; goblet cells may be present
 - Intracellular and intercellular mucin may be present.
 - Rarely, squamous differentiation may be present.
 - Immunoreactivity for cytokeratin, carcino-embryonic antigen, epithelial membrane antigen, and neuroendocrine markers
 - Rarely, glands are histologically malignant.
 - Epithelioid MPNST
 - Rare variant representing approximately 5% (or less) of cases
 - Not associated with NF1
 - Most common type to arise in association with a pre-existing benign schwannoma
 - Most are deep seated:
 - Lesions classified as superficial epithelioid MPNST likely represent benign epithelioid schwannoma or, less often, melanoma
 - Typically show lobulated growth
 - Predominantly or exclusively composed of cells with polygonal epithelioid appearance:
 - Large round nuclei with abundant eosinophilic cytoplasm
 - May include tumors with clear cells or rhabdoid cells
 - May be associated with abundant extracellular myxoid matrix with lobular growth
 - Immunohistochemistry:
 - Diffuse and intense S100 protein staining is present in a majority of cases.
 - Approximately 50% lack *SMARCB1* (INI1) immunostaining.

- Negative for melanocytic markers
- Approximately 50% of cases negative for INI1
- May be cytokeratin positive
- MPNST with perineurial differentiation (perineurial cell MPNST):
 - Seen in a very small percentage of cases
 - Perineurial component characterized by spindle cells with whorled or storiform growth pattern
 - EMA reactivity present rather than S100 protein

Differential Diagnosis

- Fibrosarcoma
- Leiomyosarcoma
- Synovial sarcoma, monophasic variant
- Malignant melanoma
- Benign tumors including:
 - Schwannoma, neurofibroma, soft tissue perineurioma

Treatment and Prognosis

- Complete surgical excision (gross total resection) is the preferred treatment:
 - Most are high-grade malignancies necessitating wide en bloc resection and postoperative radiotherapy
 - Chemotherapy is used for inoperable tumors and disseminated tumors.
- Local recurrence is common, reported in up to 50% of patients.
- Regional nodal metastases are uncommon (10% or less of patients) and as a result nodal neck dissection is generally not warranted.
- Distant metastases occur in approximately 33% of cases and most commonly spread to the lungs; less common metastatic sites include bone, pleura, and liver.
- Owing to the prevalence of higher-grade lesions, overall 5-year survival rate approximately 30% to 60%
- Survival of patients with NF1-associated MPNST previously believed to be lower than in patients with sporadic MPNST, but this is a controversial issue and likely not valid.
- Additional adverse prognostic findings include:
 - Larger tumor size (greater than 5 cm)
 - Location:
 - Truncal location slightly worse than extremity and head and neck
 - Resection with positive margin and (local) recurrence
 - Distant metastasis:
 - Increased risk of distant metastasis in large tumor, AJCC stage III, lack of S100

protein staining, and in patients requiring chemotherapy

- Radiation-induced sarcoma
- Malignant Triton tumors are particularly aggressive.

Additional Facts

- In the sinonasal cavity, MPNST can occur in the clinical setting of a sinonasal polyp:
 - Often low-grade and appears as a nondescript spindle cell proliferation in and around a benign glandular proliferation
 - S100 protein is invaluable in confirming the diagnosis
 - May in fact represent the low-grade sinonasal sarcoma with neural and myogenic features or biphenotypic sinonasal sarcoma (see Section 1, Sinonasal Tract)
- Pediatric MPNST:
 - MPNSTs are rare in childhood.
 - Associated with an unfavorable prognosis
 - Complete resection appears to be the most effective treatment.
 - Role of chemotherapy and/or radiotherapy remains uncertain.
 - Overexpressed survivin RNA reported to correlate with a higher tumor grade (grade 1 and 2 vs. grade 3) and with a lower survival probability, supporting the concept that survivin can be regarded as a useful prognostic marker for pediatric MPNST and a promising target for therapeutic interventions

Myoepithelial Tumors of Soft Tissues (Figs. 13-35 and 13-36)

Definition: Group of primary soft tissue tumors with morphologic and immunohistochemical similarities to their salivary gland counterparts but arising within soft tissue sites unrelated to salivary glands, and associated with *EWSR1* gene rearrangement.

Synonyms: Parachordoma; ectomesenchymal chondromyxoid tumor of the tongue likely represents a myoepithelial neoplasm of soft tissues (see Section 2, Oral Cavity)

- Primary myoepithelial tumors of soft tissues are uncommon and include benign and malignant neoplasms.
- Classification includes:
 - Soft tissue myoepithelioma:
 - Composed exclusively or predominantly of (benign) myoepithelial cells
 - Soft tissue mixed tumor:
 - Composed of tumors with ductular/glandular differentiation in addition to myoepithelial cells

- Presence of ductular/glandular component separates soft tissue mixed tumor from myoepithelioma
- Ductular/glandular component may be seen in up to 20% of soft tissue myoepithelial tumors.
- Myxoid to chondromyxoid stroma can be seen in myoepithelioma and mixed tumor:
 - Chondro-osseous and adipocytic differentiation can be present.
- Soft tissue myoepithelial carcinoma:
 - Soft tissue neoplasm with myoepithelial differentiation, malignant cytomorphologic features, and invasive growth
 - **Synonym:** Soft tissue malignant myoepithelioma

NOTE: As compared with their salivary gland counterpart, a higher proportion of myoepithelial tumors of soft tissues are malignant.

Soft Tissue Myoepithelial Carcinoma

Clinical Features

- No gender predilection; occur over a wide age range with many cases affecting pediatric ages but develop in adult populations as well
- Majority occurs in soft tissues outside the head and neck, most commonly arising in limbs (upper and lower) and girdle with involvement of the subcutis and deep soft tissues
- Uncommon head and neck tumor:
 - Among more common sites of occurrence include the neck and craniofacial region.
- Symptoms usually include a (neck) mass with or without associated pain.
- Unlike salivary gland myoepithelial carcinoma, the majority of which arise in association with a pleomorphic adenoma (i.e., myoepithelial carcinoma ex pleomorphic adenoma), such an occurrence is rare relative to soft tissue myoepithelial carcinoma, the majority of which occur as a *de novo* malignancy.

Pathology

Gross

- Most are circumscribed but cases may have infiltrative margins

Histology

- At low magnification multinodular or lobular architecture is evident:
 - At the periphery of the lobules the lesion is hypercellular arranged in reticular, trabecular, nests, or solid patterns.

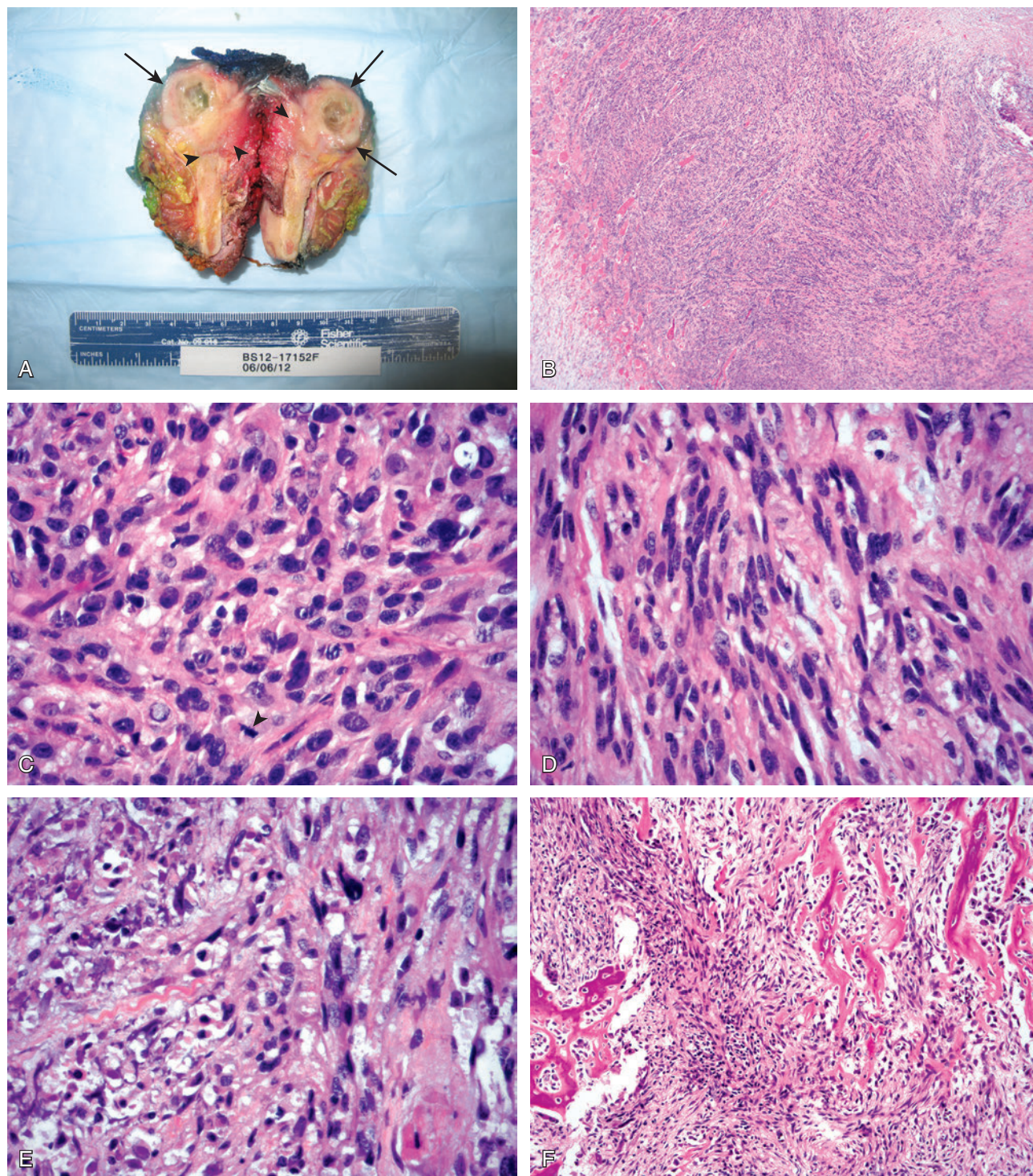


Fig. 13-35. Myoepithelial carcinoma of soft tissue.

A, Resection specimen (partial mandibulectomy) in 23-year-old patient with 4.0-cm mass in the left temporomandibular region. On cut section the mass in part was circumscribed (*arrows*) but had infiltrative margins including into bone (*arrowheads*). Necrotic change appearing as a cystic area is present. **B**, At low magnification the neoplastic proliferation shows fascicular to storiform growth with ill-defined edges and infiltration into skeletal muscle (*left*); lesional cells are characterized by nuclear pleomorphism, hyperchromasia, and increased mitotic activity with varying features including (**C**) epithelioid cells; (**D**) spindle-shaped cells; and (**E**) cells with clear cytoplasm. **F**, Histologic confirmation of osseous invasion was present.

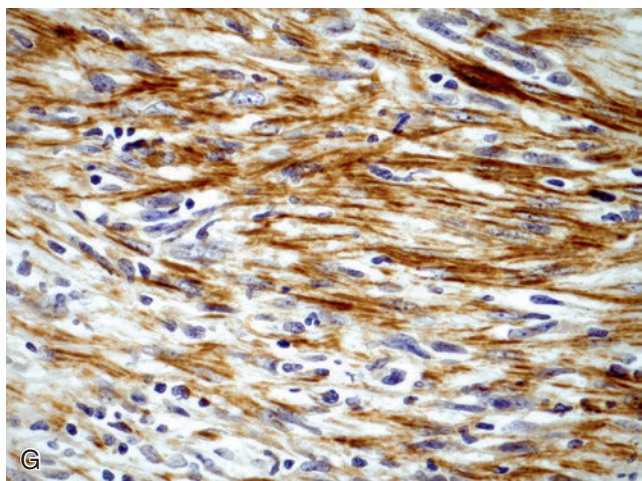
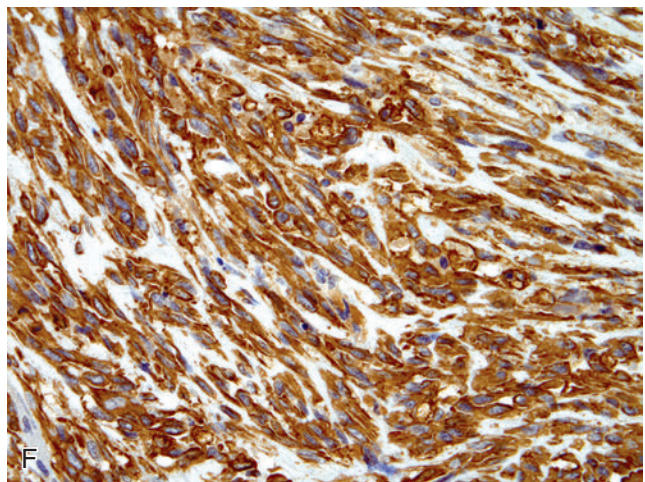
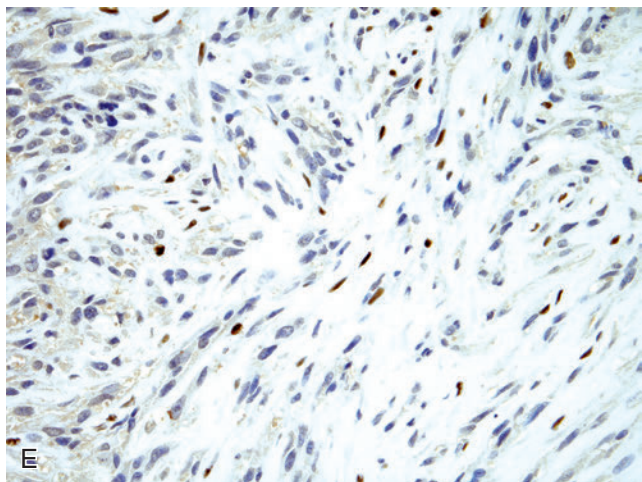
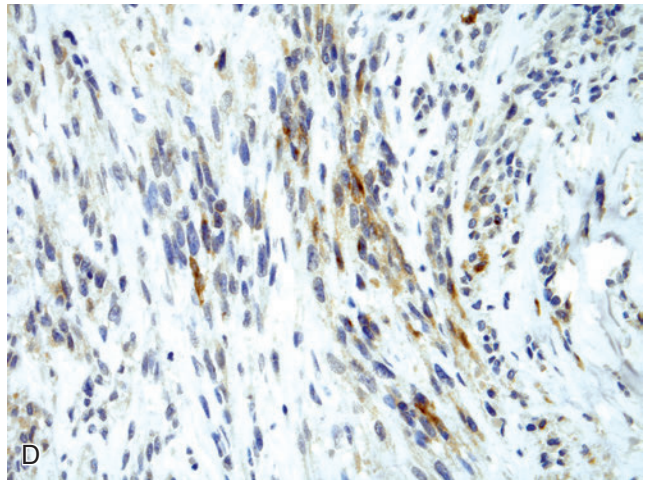
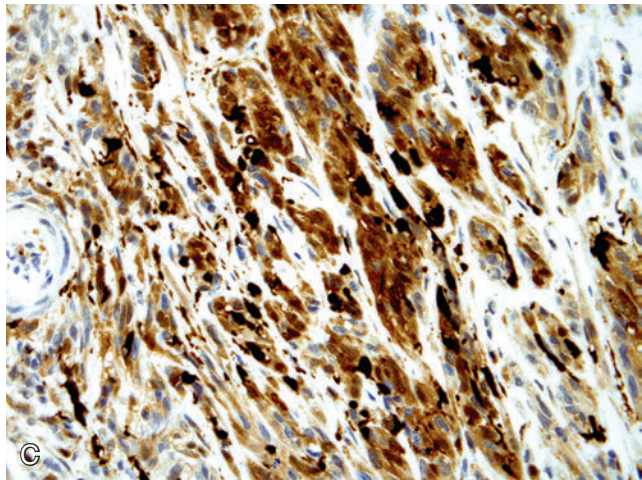
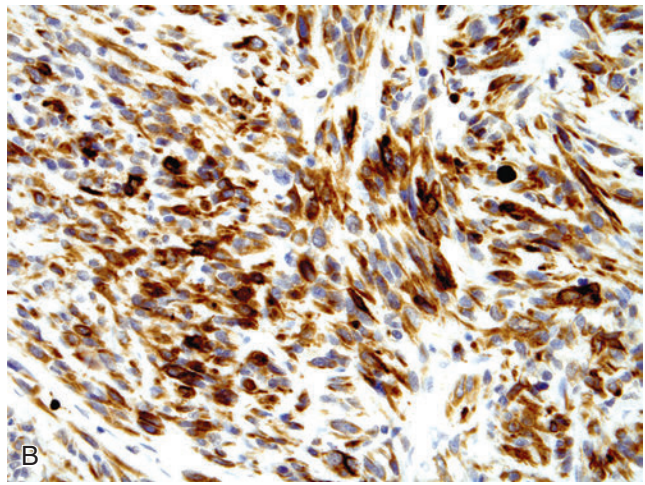
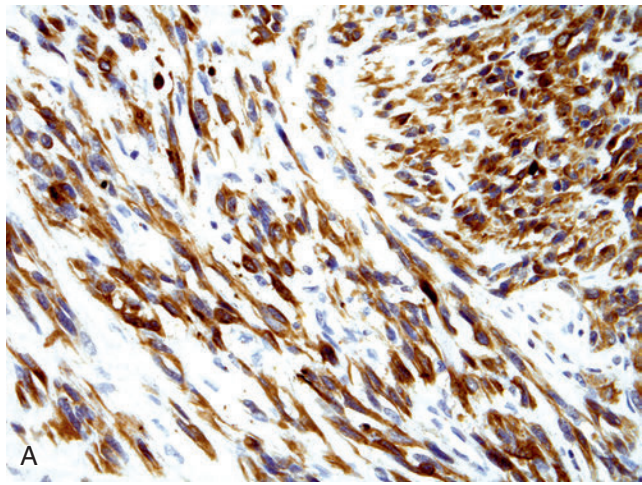


Fig. 13-36. Myoepithelial carcinoma: IHC staining.

Myoepithelial carcinoma of soft tissue, immunohistochemical staining. Most cases show consistent reactivity for (A) cytokeratin (AE1/AE3); (B) CK 8/18 (CAM5.2); and (C) S100 protein. In addition, variable immunoreactivity can be seen for (D) EMA; (E) p63; (F) vimentin; and (G) muscle-specific actin.

- Lesional cells may be epithelioid, clear, spindle-shaped, or plasmacytoid:
 - Characterized by cytomorphologic heterogeneity:
 - Epithelioid type predominates
 - Majority of cases are composed of more than one myoepithelial cell type
 - Cytologic atypia of at least moderate degree is present, including nuclear enlargement, vesicular to coarse-appearing nuclei, and variably prominent nucleoli.
- Increased mitotic activity, tumor necrosis, and lymph-vascular invasion may be present.
- Stromal component includes myxoid change and/or hyalinization.
- Cartilaginous differentiation and metaplastic ossification may be present.

Immunohistochemistry:

- Lesional cells consistently reactive for cytokeratins (AE1/AE3, CAM5.2, PAN-K) and S100 protein
- EMA positive in majority of cases
- Variable calponin, p63, and GFAP staining
- Less consistent reactivity for SMA, MSA, CD10, and vimentin positive
- Loss of expression of *SMARCB1* (INI1) in subset of cases lacking *EWSR1* gene rearrangements and with rhabdoid morphology (sole pattern or in part)
- Immunoreactivity may be present for CD99.
- Desmin, CD34, TLE1, and brachyury are typically negative.
- *PLAG1* (nuclear) staining present in benign myoepithelial soft tissue tumors with ductal differentiation
- Cytogenetics and molecular genetics:
 - Myoepithelial carcinomas:
 - Demonstrate *EWSR1* gene rearrangement with a variety of different fusion partners, most notably *POU5F1* and *PBX1*:
 - Such rearrangements more common in malignant tumors
 - *EWSR1-POU5F1* tumors occur in younger patients
 - *EWSR1-PBX1* tumors have sclerotic appearance and clear cell morphology
 - ◻ Too few cases analyzed to make definitive correlations between rearrangement(s) to pathology and/or biologic behavior
 - Rare cases with t(19;22)(q13;q12) result in *FUS* gene rearrangement.
 - Lack *PLAG1* gene rearrangement
 - Presence of *EWSR1* and absence of *PLAG1* rearrangements support that such tumors are unrelated to their salivary gland counterparts.

- Benign myoepithelial tumors:
 - *PLAG1* gene rearrangement found in cases with ductal differentiation:
 - Supporting concept that such soft tissue tumors are genetically related to their salivary gland counterparts

Differential Diagnosis

- In cervical neck, must exclude origin from primary salivary gland (e.g., parotid) myoepithelial tumor/carcinoma:
 - See Section 6, Salivary Glands
 - Salivary gland myoepithelial carcinoma not associated with *EWSR1* gene rearrangement
- Extraskelatal myxoid chondrosarcoma:
 - *NR4A3* rearrangement, which is absent in myoepithelial carcinoma of soft tissues
- Chordoma
- Epithelioid malignant peripheral nerve sheath tumor
- Synovial sarcoma (poorly differentiated)
- Undifferentiated carcinoma
- Ewing family of tumors

Treatment and Prognosis

- Wide surgical resection for localized tumors and adjuvant radiotherapy with or without nodal dissection
 - Use of chemotherapy is unproven and appears in limited studies to offer no added benefit.
- May recur locally
- Metastasizes in 40% to 50% of cases:
 - Lymph nodes, lungs, bone including clivus
- Appears more aggressive behavior occurs in pediatric ages than in adult population, including death from disease

Rhabdomyosarcoma (RMS)

Definition: Malignant neoplasm showing skeletal muscle differentiation.

- RMS is covered in greater detail in Section 3, Pharynx.

Leiomyosarcoma (LMS)

Definition: Malignant neoplasm with smooth muscle differentiation.

- LMS is covered in greater detail in Section 1, Sino-nasal Tract.

Liposarcoma

Definition: Malignant neoplasm with adipocyte cell differentiation.

- For more complete discussion see Section 5, Larynx and Trachea.

Angiosarcoma

Definition: Malignant neoplasm with endothelial cell differentiation.

- For more complete discussion see Section 1, Sinonasal Tract.

Synovial Sarcoma

Definition: Mesenchymal tumor with variable degree of epithelial differentiation characterized by specific chromosomal translocation $t(x;18)(p11;q11)$, leading to formation of an SS18-SSx fusion.

- For more complete discussion see Section 3, Pharynx.

METASTATIC CERVICAL CARCINOMA WITH AN UNKNOWN PRIMARY TUMOR (MCCUP)

(Figs. 13-37 through 13-46)

Definition: Overt neck mass harboring a cytologically or histologically proven metastatic carcinoma in the absence of signs and symptoms of a primary neoplasm or of a clinically detectable mass and includes:

- No history of previous malignancy or cancer ablation of any indeterminate lesion
- No history of definite symptoms related to a specific organ system

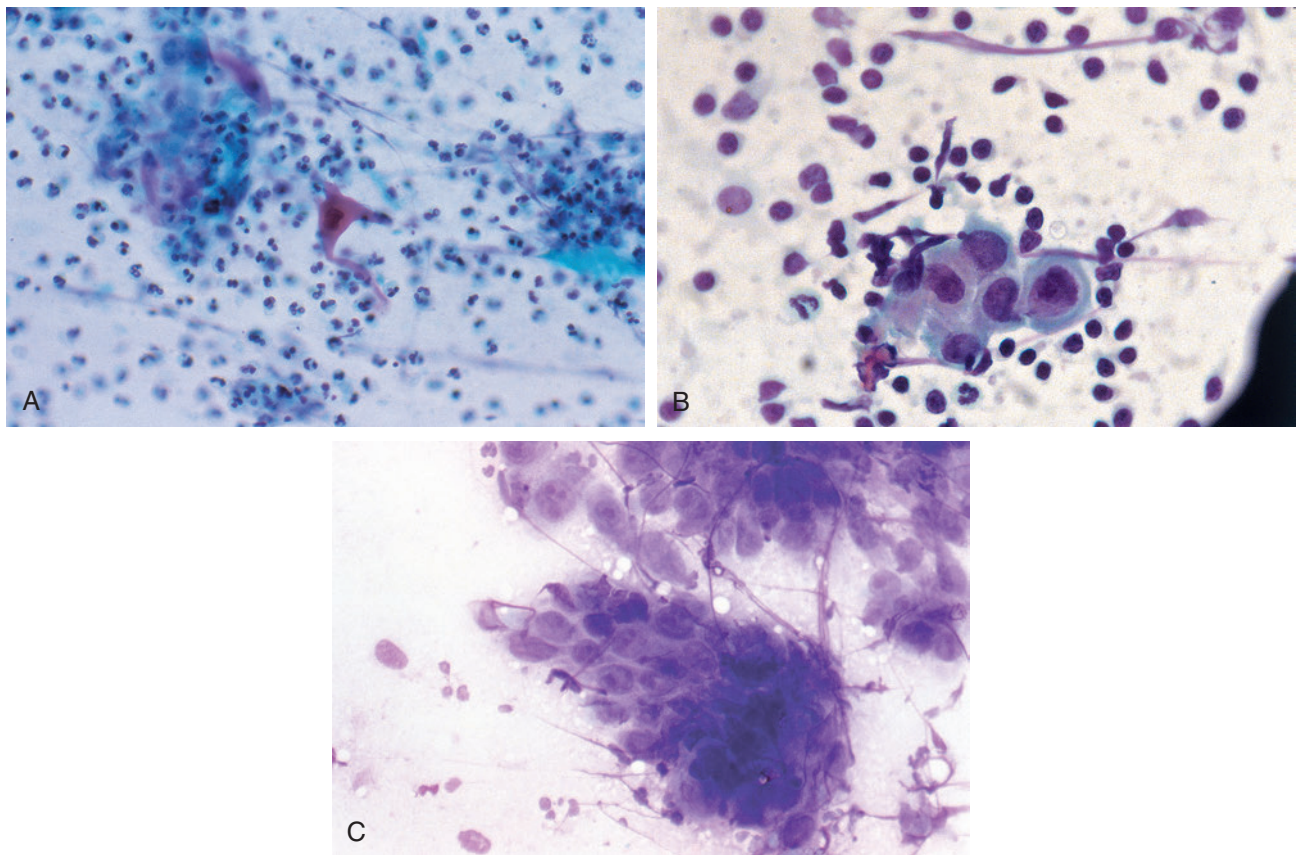


Fig. 13-37. Fine needle aspiration, metastatic squamous cell carcinoma.

Fine-needle aspiration material of metastatic keratinizing squamous cell carcinoma from lateral neck masses include (A) well-differentiated squamous cell carcinoma characterized by cells with individual cell keratinization and hyperchromatic, irregular nuclei; background neutrophilic infiltrate is present; (B) moderately differentiated squamous cell carcinoma characterized by cohesive groupings of malignant squamous cells with atypical nuclei showing increased nuclear-to-cytoplasmic ratio, nuclear membrane irregularities, and marked hyperchromasia. The primary carcinomas for the metastases in A and B originated from laryngeal keratinizing squamous cell carcinomas. C, Poorly differentiated carcinoma characterized by clusters and sheets of malignant squamous cells with tight nuclear overlapping, marked hyperchromasia, increased nuclear-to-cytoplasmic ratio, and prominent nucleoli. All examples were p16 and EBER negative (not shown). The primary carcinoma for the metastasis in C originated from the oral cavity.

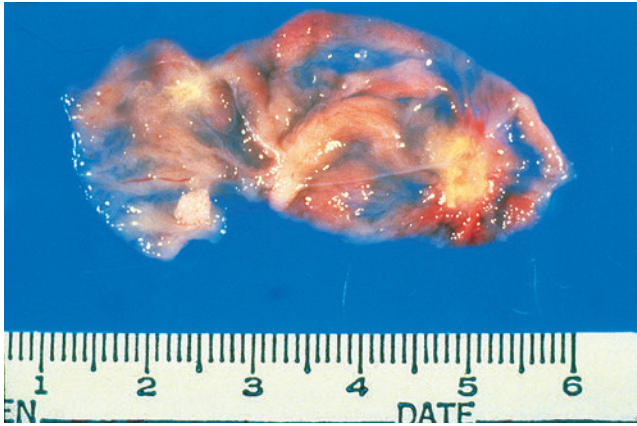


Fig. 13-38. Metastasis to lateral cervical neck.

Resection specimen of a lateral neck mass showing a cystic and solid mass.

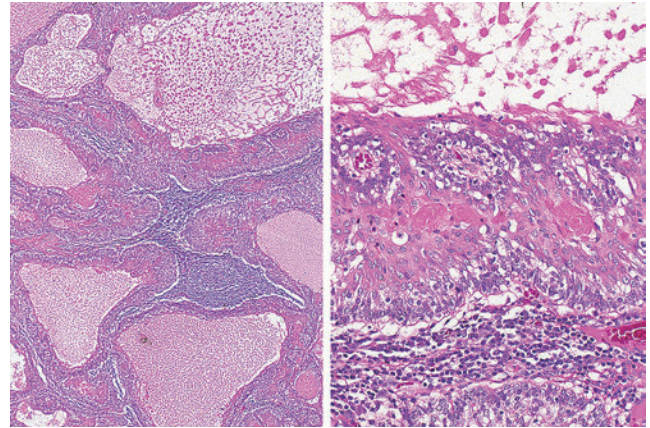


Fig. 13-39. Metastatic cystic keratinizing squamous cell carcinoma.

Multicystic epithelial-lined lesion composed of cells with readily identifiable squamous differentiation. Although p16 staining was negative, the primary carcinoma was found in the ipsilateral tonsil.

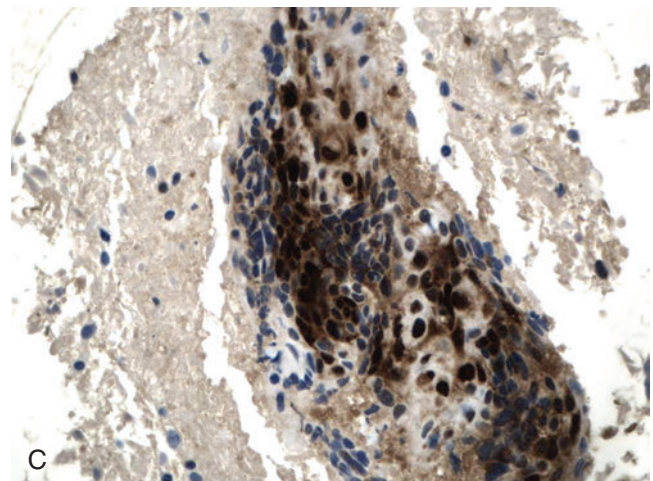
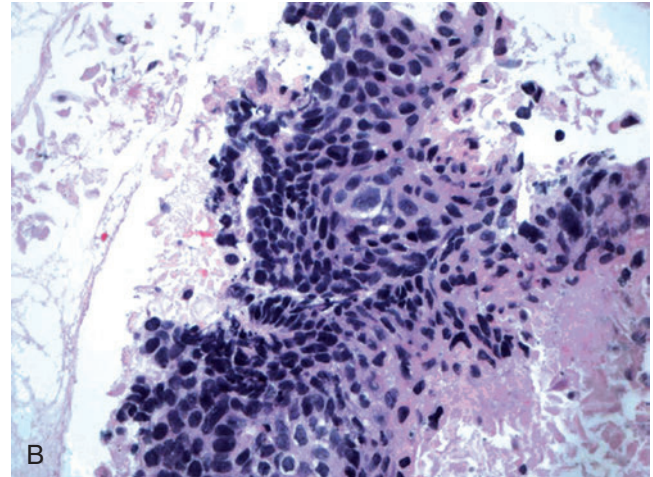
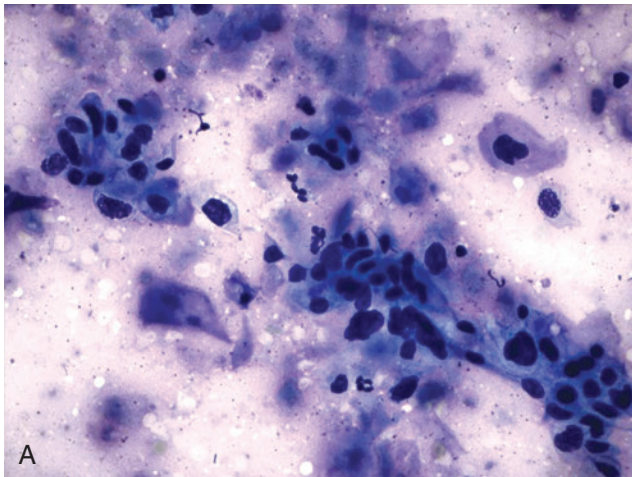


Fig. 13-40. Metastatic nonkeratinizing carcinoma.

A, Fine-needle aspiration of metastatic nonkeratinizing carcinoma characterized by clusters of malignant basaloid cells with pleomorphic, hyperchromatic nuclei lacking evidence of squamous differentiation. **B,** Cell block from this aspirate shows clusters of nonkeratinizing carcinoma. **C,** p16 staining including strong nuclear and cytoplasmic staining represents a surrogate marker for HPV16 and its presence is highly predictive of origin from the oropharynx. A small primary base of tongue carcinoma was subsequently identified.

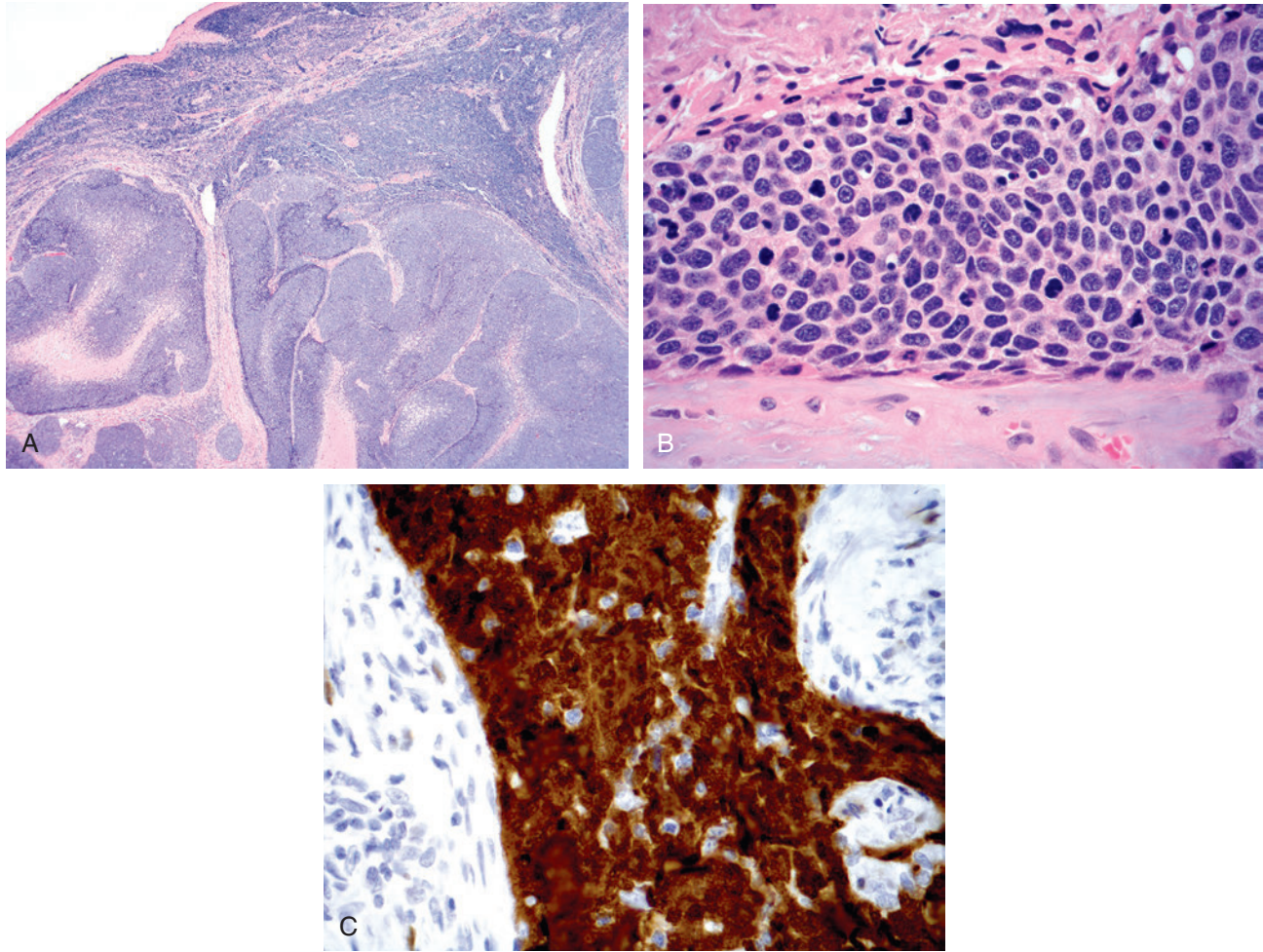


Fig. 13-41. Metastatic cystic nonkeratinizing carcinoma.

A, Resected lymph node replaced by cystic metastatic nonkeratinizing carcinoma with central cystic change and associated necrotic debris. **B**, Malignant epithelium characterized by pleomorphic and hyperchromatic cells with increased cellularity, increased mitoses, and loss of polarity. **C**, Diffuse and strong nuclear and cytoplasmic p16 immunoreactivity. A primary tonsillar carcinoma was detected by radiologic imaging (see next illustration), prompting biopsy with histologic confirmation.

- No clinical or laboratory evidence of a primary neoplasm

Clinical

- Constitutes approximately 3% of all malignant neoplasms
- Represents 2% to 9% of all head and neck cancers
- Demographics are changing due to increasing incidence of HPV-associated head and neck carcinomas with stabilization in the incidence of carcinomas associated with tobacco and alcohol overuse.
- HPV-associated metastatic carcinoma:
 - No gender predilection
 - Younger age groups as compared with squamous cell carcinomas associated with tobacco/alcohol use
 - Caucasian >>>> African American
- Often no known risk factors (usually nonsmokers, nondrinkers)
- Site(s): oropharynx (base of tongue; tonsil)
- Histology: nonkeratinizing carcinoma predominantly composed of basaloid cells
- p16 positive
- Better disease-free and overall survival
- Often present with higher clinical stage disease: more nodal metastasis
- Carcinoma associated with tobacco and alcohol overuse:
 - More common in men than women
 - Most frequently seen in the fifth to seventh decades of life
 - Caucasian = African American
 - Associated with tobacco and/or alcohol use/abuse

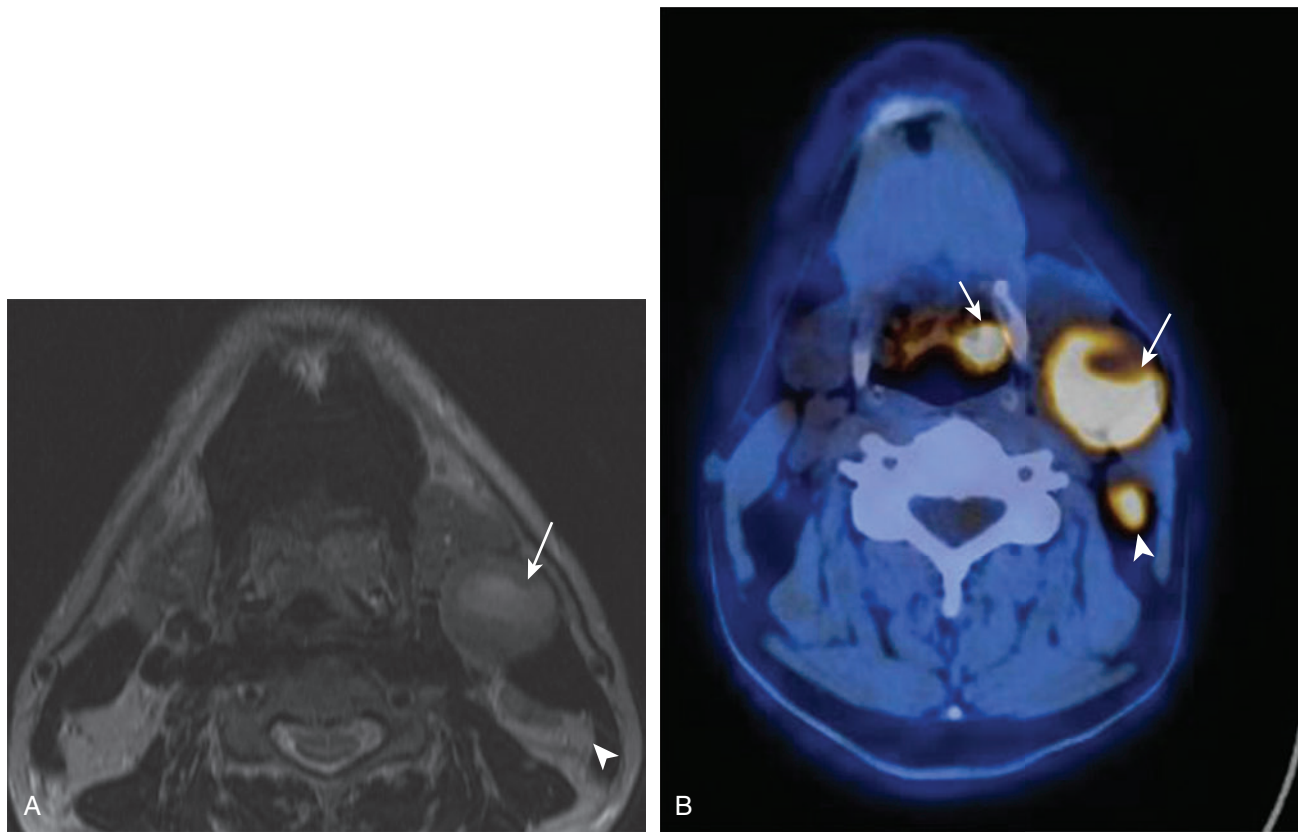


Fig. 13-42. Metastatic HPV-associated carcinoma to the cervical neck.

A, Axial T2-weighted MR image showing a level IIa heterogeneous lymph node (*arrow*) and a level IIb homogeneous lymph node (*arrowhead*). In this imaging the lingual tonsils are symmetric without an identifiable mass. **B**, PET-CT fusion image in the same patient as part A showing the level IIa lymph node to be heterogeneously hypermetabolic, implying nodal necrosis (*long arrow*), the level IIb lymph node to be uniformly hypermetabolic (*arrowhead*), and the presence of asymmetric increased hypermetabolism in the left (ipsilateral) lingual tonsil (*short arrow*). A subsequent biopsy of the lingual tonsil confirmed a primary HPV-associated carcinoma.

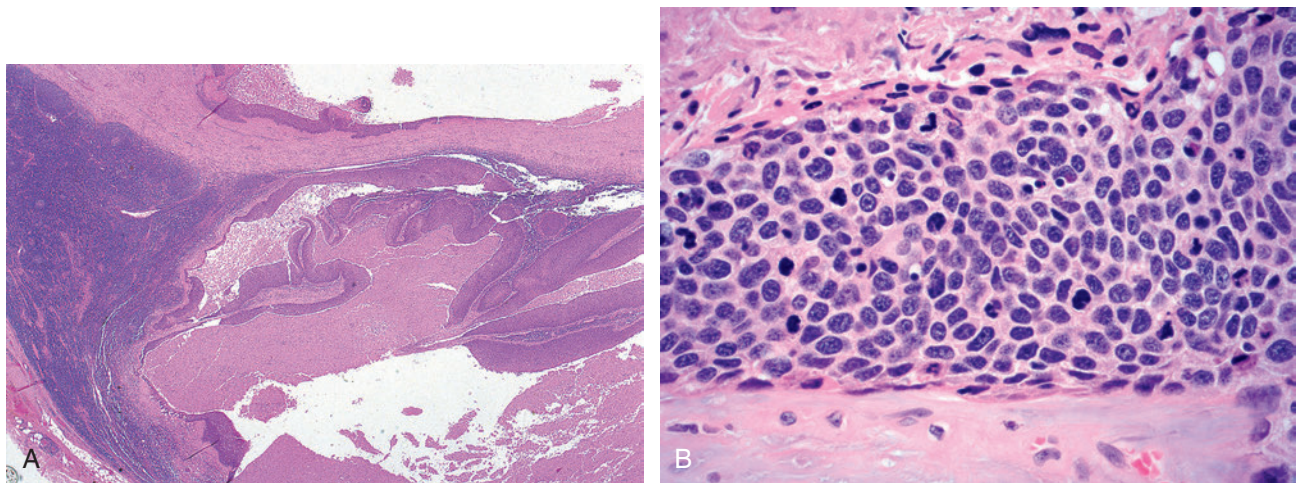


Fig. 13-43. Metastatic nasopharyngeal (EBV-associated) carcinoma, nonkeratinizing differentiated type.

A, Metastatic cystic nonkeratinizing carcinoma of nasopharyngeal origin replacing the involved lymph node and showing central cystic change with associated necrotic debris. **B**, At higher magnification the malignant epithelial cells are nonkeratinizing and histologically similar to carcinomas of oropharyngeal origin.

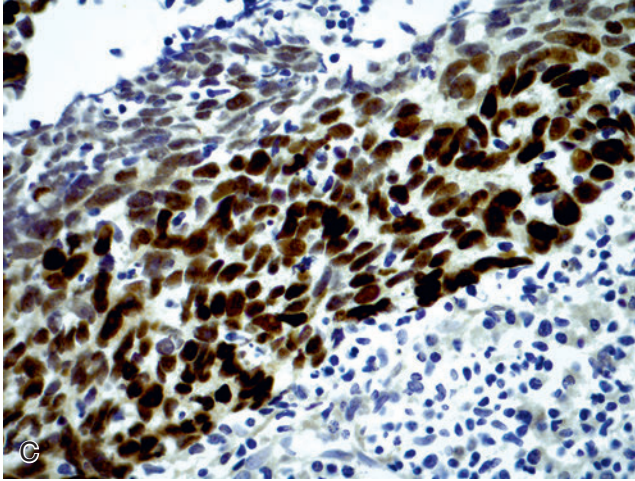


Fig. 13-43, cont'd

C, Lesional cells are positive for EBER (and p16 negative, not shown), supporting origin from the nasopharynx.

- Site(s): all mucosal sites of the upper aerodigestive tract
 - Histology: keratinizing squamous cell carcinoma
 - p16 negative
 - Worse disease-free and overall survival
 - Often present with lower clinical stage disease; less nodal metastasis
- Most common clinical manifestation of a MCCUP is that of a unilateral, fixed, painless neck mass enlarging over several months:
 - Unilateral nodal involvement is most common, occurring in up to 52% of cases.
 - Bilateral nodal involvement seen in approximately 10% of cases
- Location of metastasis in patients with MCCUP:
 - Level II represents the most frequent cervical metastatic site occurring in more than 50% of patients
 - After level II, levels I and III are the next most common metastatic sites.
 - Lower neck and/or supraclavicular lymph node metastases also common but more frequently associated with a primary malignancy below the clavicle (i.e., thorax, abdomen)
- Lymphatic drainage to the cervical lymph nodes is predictable, and the anatomic location of the metastatic focus assists in the search for the primary focus (Table 13-5).
- AJCC staging for MCCUP is detailed in Table 13-6.
- Majority of metastatic carcinomas to the cervical lymph nodes take origin from a head and neck primary tumor and therefore the most common histologic appearance is that of a squamous cell carcinoma, including keratinizing and nonkeratinizing.
- By far, the oropharynx (tonsil and base of tongue) and nasopharynx, collectively referred to as Waldeyer tonsillar ring, are areas harboring the occult primary tumor in the majority of squamous carcinomas metastatic to the neck; other common but less frequent sites of the occult tumor include thyroid, hypopharynx, and larynx (supraglottic region):
 - There is no correlation between the size of the primary carcinoma and the size of the metastasis such that the primary carcinoma may be only a few millimeters in size, whereas the metastasis may be several centimeters in size:
 - Given the potential of the primary carcinoma to be extremely small, it may not be possible to detect the primary by clinical, radiologic, and pathologic examination.
 - Even in the absence of identifying the primary carcinoma, a diagnosis of primary carcinoma arising in a branchial cleft cyst should not be invoked (see later under differential diagnosis).
- Carcinomas arising in the oropharynx and nasopharynx often are viral associated, including:
 - HPV-associated carcinoma arising from the oropharynx
 - EBV-associated carcinoma arising from the nasopharynx
- Laboratory findings:
 - Generally of limited utility as laboratory findings in the setting of MCCUP are not sensitive or specific
 - Serologic studies for EBV are abnormal in nasopharyngeal carcinomas (nonkeratinizing types)
 - Elevated *serum* calcitonin typically present in association with medullary thyroid carcinoma; however:
 - Serum calcitonin is not elevated in nonthyroid neuroendocrine carcinomas (of mucosal sites of the head and neck) although *tissue* calcitonin may be present by immunohistochemical evaluation in nonthyroid neuroendocrine neoplasms.
- Diagnostic work-up for a patient with a unilateral fixed neck mass includes:
 - Fine-needle aspiration biopsy (FNAB) or open biopsy:
 - See later under [Pathology](#).
 - Preferable to obtain basic imaging of the head and neck prior to FNAB or open biopsy
 - Radiographic imaging:
 - Should precede panendoscopy as information generated may assist in directing biopsies
 - Includes contrast-enhanced computed tomography (CECT) and positron emission tomography (PET) with or without computed

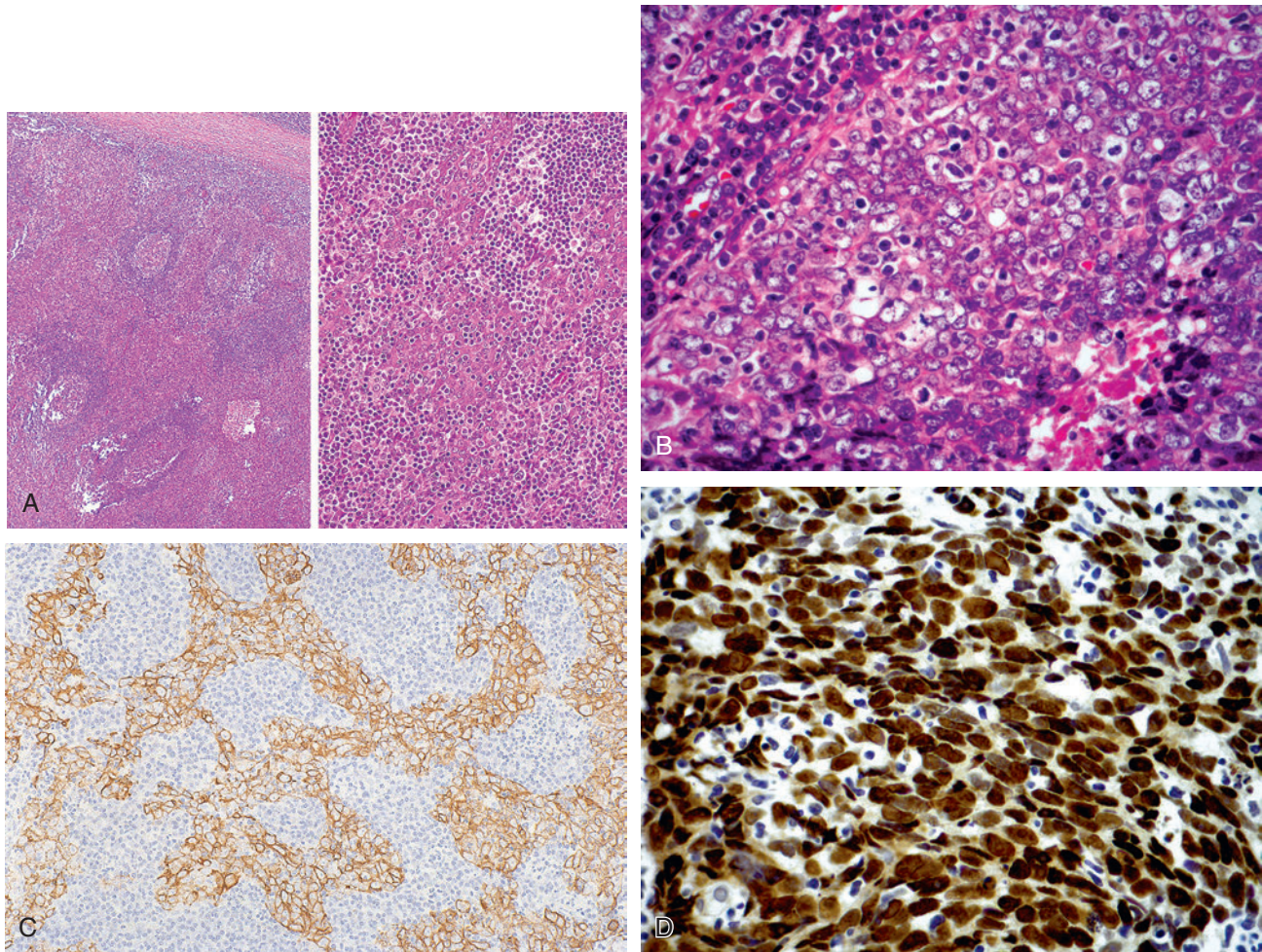


Fig. 13-44. Metastatic nasopharyngeal (EBV-associated) carcinoma, nonkeratinizing undifferentiated type.

A, Left panel, Resected enlarged cervical neck lymph node harboring metastatic carcinoma that at low magnification shows no readily apparent neoplasm due to an absence of a desmoplastic response. **Right panel,** Even at higher magnification the identification of the neoplastic cells can be difficult given the absence of a desmoplastic response.

B, At higher magnification the malignant cells are composed of enlarged vesicular nuclei with prominent nucleoli. **C,** The malignant epithelial cell component is cytokeratin (AE1/AE3) reactive and **(D)** EBER positive. A primary nasopharyngeal carcinoma was detected by radiologic imaging (see next illustration). The absence of a desmoplastic response may occur in primary Waldeyer ring viral-associated carcinomas, including those originating in the oropharynx (HPV positive) as well as from the nasopharynx (EBV positive) and in the metastatic foci.

tomography (CT) and magnetic resonance imaging (MRI):

- Enhances the assessment of neck disease
- Assists in detecting the primary lesion
- CT provides anatomic information
- PET provides metabolic information
- Up to 30% of neck nodes pathologically diagnosed are clinically not palpable (i.e., N0) and necks are upstaged by CT in 20% to 30% of patients
- Sensitivity and specificity of PET scans in detection of primary cancer in patients with MCCUP reported to be 88% and 75%, respectively

- PET scans have higher false positive than false negative rate:
 - Tend to overread tonsillar cancers with a false positive rate of 39%
 - False positive rate also higher in base of tongue with sensitivity of 82% compared with 91% in other head and neck sites
 - Lack of sensitivity in base of tongue thought to occur from the high baseline levels of fluorodeoxyglucose uptake in that area
 - Highest accuracy of PET scans in tumors of the larynx and hypopharynx with sensitivity and specificity of 100%

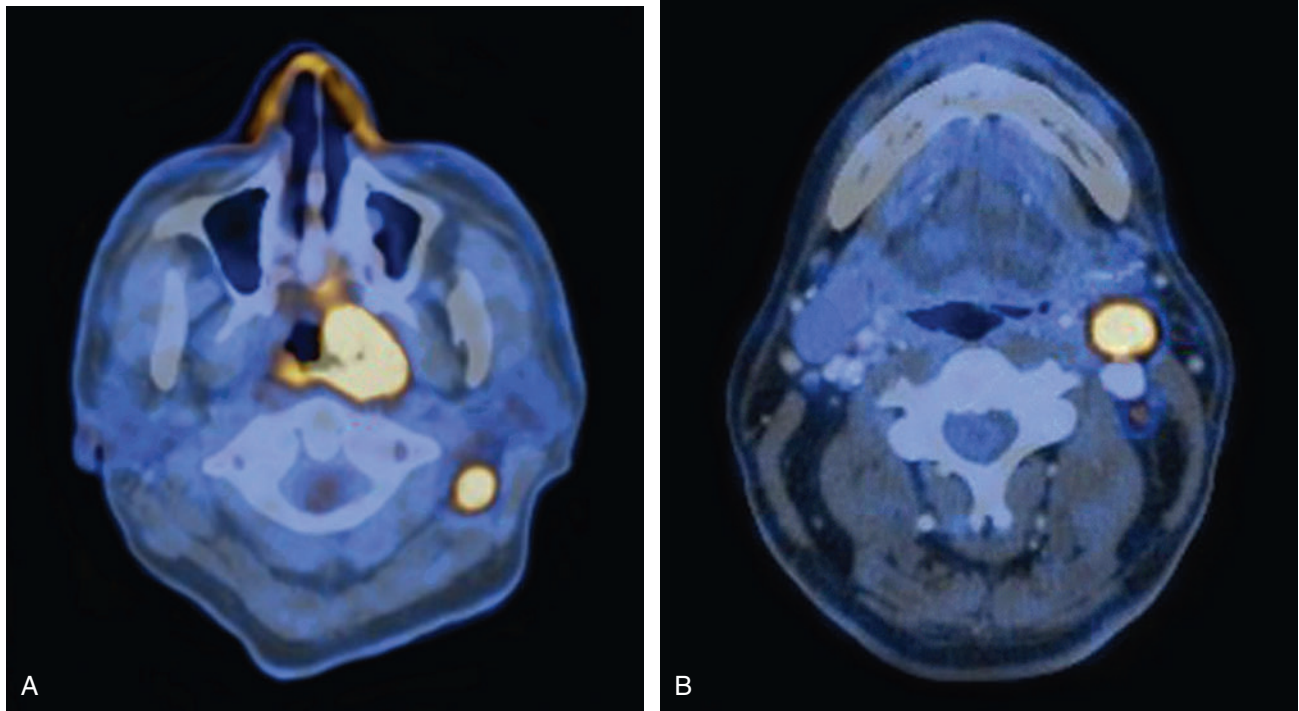


Fig. 13-45. Primary and metastatic nasopharyngeal carcinoma.

Axial fused PET/CT images show a large nasopharyngeal cancer with high PET activity with a left level IIB node (**A**) and a left IIA node (**B**). The level IIA node was a metastatic carcinoma node. The level IIB node, with similar activity, was a reactive node. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 2377, Fig. 38-107.)

- PET/CT:
 - Combination of the two modalities have highest yield in discovering the primary head and neck cancer
 - PET/CT superior to either PET or CT
 - Widely available and represents the preferred imaging modality in MCCUP
 - In addition, benefits include ability to detect unexpected contralateral nodal disease, synchronous malignancies, and distant nodal involvement.
- Metabolic imaging:
 - Neoplasms have increased metabolic activity with respect to surrounding normal mucosa.
 - Isotope ^{18}F -fluorodeoxyglucose (FDG), a glucose analogue, enters cells using normal transport mechanisms
 - The application of FDG uses the fact that glucose metabolism (i.e., FDG uptake) is increased in malignant cells but cannot be further metabolized, remaining in the tumor tissues.
 - Imaging modalities using FDG include positron emission tomography (PET) (FDG-PET):
 - ◻ Increases the detection of primary cancer site by up to 54%
- Chest radiograph:
 - Screening method for primary, metastatic, and secondary primary lung lesions
- Panendoscopy:
 - Includes assessment of the nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, esophagus, and tracheobronchial tree
 - Any mucosal abnormality should be biopsied.
 - If no abnormalities are grossly seen, random biopsies (also referred to as random-guided, directed, or blind biopsies) are indicated.
- Open biopsy:
 - May be required in the face of a neck suspicious for metastatic carcinoma with nondiagnostic fine-needle aspiration biopsy, negative panendoscopic evaluation (clinically and histologically negative)
 - Should be performed in intraoperative consultation (i.e., frozen section) with preparations in place to treat the neck definitively in the presence of a malignant diagnosis by frozen section
- Etiologic factors relate to the development of squamous carcinoma of the head and neck and, as such, are linked to:

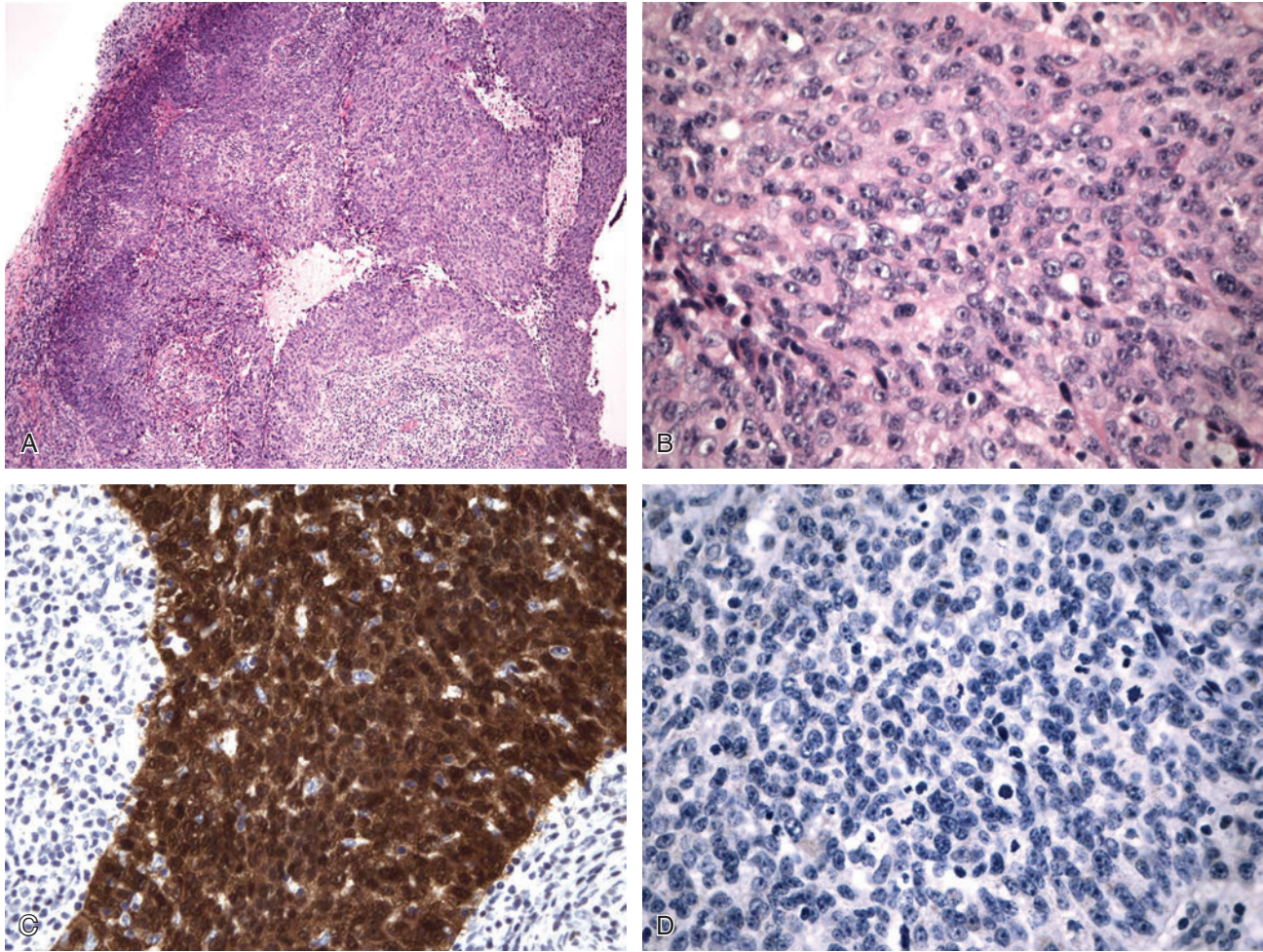


Fig. 13-46. Metastatic oropharyngeal “lymphoepithelial-like” carcinoma.

A, Metastatic cystic carcinoma to a cervical neck lymph node. **B,** At higher magnification the histology of the carcinoma is similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type, but is **(C)** p16 positive and **(D)** EBER negative. The primary carcinoma originated from the oropharynx. This example illustrates the overlapping histologic findings shared by oropharyngeal HPV-associated nonkeratinizing and undifferentiated carcinomas and nasopharyngeal EBV-associated nonkeratinizing and undifferentiated carcinomas. In the presence of an unknown primary carcinoma, cervical lymph node metastases with such histomorphologic should prompt evaluation for p16 and EBER.

- Tobacco and alcohol use
- Viruses, including HPV linked to oropharyngeal cancers and EBV lined to nasopharyngeal cancers

Pathology

Fine-Needle Aspiration Biopsy (FNAB)

- In most cases there is increased cellularity with the cytologic features varying depending on the degree of differentiation:
 - Keratinizing squamous cell carcinoma:
 - Cohesive groupings of cells
 - Cells showing individual cell keratinization characterized by the presence of atypical nuclei with increased nuclear-to-cytoplasmic ratio, nuclear membrane irregularities, and marked hyperchromasia

- Dyskeratotic cells, best appreciated by Papanicolaou stain, have a bright orange color
- Presence of rare, immature atypical nonkeratinized cells with increased nuclear-to-cytoplasmic ratio may be identified.
- Nonkeratinizing squamous cell carcinoma:
 - Sheets or loose groupings of cells
 - Nuclear crowding
 - Cells are more irregular than those of well-differentiated carcinomas with higher nuclear-to-cytoplasmic ratio and large, pleomorphic nuclei with granular-appearing chromatin and large nucleoli.
 - Given these overall findings many of these cancers are considered poorly differentiated; however, in fact, these nonkeratinizing

TABLE 13-5 Lymph Node Levels and Possible Primary Sites for Metastasis

Lymph Node Level	Drainage
I (submental; submandibular)	Anterior oral cavity Anterior nasal cavity
II (upper jugular)	Oral cavity Oropharynx Nasopharynx Larynx Hypopharynx Parotid gland
III (midjugular)	Oropharynx Nasopharynx Larynx Hypopharynx
IV (lower jugular)	Larynx Hypopharynx Thyroid Esophagus
V (posterior triangle)	Nasopharynx Posterior scalp
VI (anterior compartment)	Thyroid Larynx (subglottis) Hypopharynx Esophagus
Preauricular (not assigned a level)	Skin of upper face and temple
Retropharyngeal (not assigned a level)	Nasopharynx Hypopharynx Larynx
Supraclavicular (not assigned a level)	Infraclavicular and subdiaphragmatic
Viral-associated carcinomas:	
HPV-associated	Oropharynx
EBV-associated	Nasopharynx

Modified from Chang SS, Califano J: Metastatic cancer of the neck from an unknown primary site. In Harrison LB, Sessions RB, Kies MS, editors: Head and neck cancer: a multidisciplinary approach, ed 4, Philadelphia, 2014, Lippincott Williams & Wilkins, pp 319-327.

carcinomas recapitulate the tonsillar crypt epithelium and while lacking keratinization are considered as differentiated carcinomas and not poorly differentiated carcinomas.

- Additional findings may include the presence of necrotic debris and numerous neutrophils.

Gross

- Variable including solid gray-white mass to cystic lesion with associated necrosis and hemorrhage.

Histology

- In the setting of MCCUP, metastatic squamous cell carcinoma is the most common:

TABLE 13-6 AJCC Staging for Metastatic Cervical Carcinoma with an Unknown Primary Tumor (MCCUP)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1*	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2*	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a*	Metastasis in a single ipsilateral lymph node more than 3 cm, but not more than 6 cm in greatest dimension
N2b*	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c*	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3*	Metastasis in lymph node more than 6 cm in greatest dimension
M0	No distant metastasis
M1	Distant metastasis

*Note: A designation of "U" or "L" may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical/radiologic ECS should be recorded as E- or E+, and histopathologic ECS should be designated as En, Em, or Eg. Used with permission from Edge et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer-Verlag, p 25.

- 45% to 70% of all metastases in MCCUP are squamous cell carcinomas and morphologically include:
 - Nonkeratinizing squamous cell carcinoma
 - Keratinizing squamous cell carcinoma
 - Undifferentiated carcinoma
- Less common morphologic types include:
 - Adenocarcinoma
 - Thyroid carcinoma
 - Melanoma
- Metastatic (cystic) squamous cell carcinoma, nonkeratinizing and keratinizing:
 - There is partial or complete replacement of the lymph node by an epithelial-lined structure often with central cystic change and associated necrotic debris.
 - Epithelium varies from areas that are bland composed of uniform cells lacking pleomorphism, crowding, or loss of polarity to overtly malignant-appearing epithelium composed of pleomorphic cells with increased cellularity, mitoses, and a loss of polarity

- Keratinization in the form of individual cell varies from completely absent to focally present to more overtly present.
- Histologic appearance strongly suggests origin from oropharynx (tonsil and base of tongue):
 - p16 immunoreactivity including strong and diffuse nuclear and cytoplasmic staining is a surrogate marker for HPV16 and highly predictive of origin from the oropharynx.
 - p16 staining often allows for differentiating a metastatic nonkeratinizing carcinoma (p16 positive) from branchial cleft cyst (p16 negative); however, p16 may be overexpressed in almost 50% of benign branchial cleft cysts potentially limiting the diagnostic utility of p16 in this setting; in such an occurrence molecular testing (in situ hybridization, PCR) would be necessary to confirm presence of HPV and the malignant nature of the cyst
 - Proliferation markers (i.e., Ki67) show increased proliferation rates throughout the epithelium.
- Carcinomas with similar histologic findings may originate from other head and neck sites, including the nasopharynx:
 - Nasopharyngeal carcinoma, keratinizing type:
 - Usually does not present as a MCCUP
 - Not associated with Epstein-Barr virus (EBV) and typically negative for in situ hybridization for Epstein-Barr encoded RNA (EBER)
 - Nasopharyngeal carcinoma, nonkeratinizing differentiated type:
 - May present as MCCUP
 - Associated with EBV and positive for EBER (nuclear staining)
- Metastatic undifferentiated carcinoma:
 - There is partial or complete replacement of the lymph node by cystic and/or solid epithelial proliferation characterized by cells with enlarged nuclei, vesicular chromatin, and prominent eosinophilic nucleoli.
 - Keratinization typically absent
 - Histologic appearance strongly suggests origin from nasopharynx (i.e., nasopharyngeal carcinoma, nonkeratinizing undifferentiated type); however, similar histology may occur in carcinoma originating from the oropharynx and should include staining for carcinomas originating from the nasopharynx and oropharynx:
 - In situ hybridization for Epstein-Barr encoded RNA (EBER) including diffuse and strong nuclear staining confirms origin from the nasopharynx.
 - p16 immunoreactivity including strong and diffuse nuclear and cytoplasmic staining confirms origin from the oropharynx.

Differential Diagnosis

- Branchial cleft cysts:
 - Presence of morphologically malignant epithelium would exclude a diagnosis of branchial cleft cyst
 - p16 reactivity:
 - p16 reactivity in the branchial cleft cysts is usually negative, showing patchy positivity, or is characterized by focal, strong staining limited to involvement of the superficial squamous epithelium; in comparison, diffuse and strong p16 staining characterizes metastatic oropharyngeal carcinoma.
 - p16 may be overexpressed in almost 50% of benign branchial cleft cysts potentially limiting the diagnostic utility of p16 in this setting; in such an occurrence molecular testing (in situ hybridization, PCR) would be necessary to confirm presence of HPV and the malignant nature of the cyst.
 - Ki67 (MIB1) reactivity:
 - Branchial cleft cysts typically show a low proliferation rate (less than 5%) even if inflamed.
- Carcinoma arising in a branchial cleft cyst (branchiogenic carcinoma; malignant branchioma):
 - Criteria used for the diagnosis of a branchiogenic carcinoma include:
 - The metastatic tumor occurs along the line extending from a point anterior to the tragus along the anterior border of the sternocleidomastoid muscle to the clavicle.
 - Histology supports origin from a branchial cleft–derived structure.
 - Histology supports carcinoma arising in the wall of an epithelial-lined cyst.
 - A minimum of 5-year follow-up demonstrates no evidence of a primary source for this neoplasm.
 - Despite the fulfillment of these criteria it is highly unlikely that carcinoma arises in a branchial cleft cyst: rather, all these cystic squamous cell carcinomas take origin from a primary tumor in Waldeyer tonsillar ring with the primary neoplasm being so small as to defy clinical detection but nevertheless is capable of metastasizing.
 - Factors weighing against the existence of a branchiogenic carcinoma include:
 - Branchial cleft anomalies are rare.
 - As almost all patients with MCCUP present with neck masses of recent onset, a large number of subclinical branchial cleft cysts would have to be present to account for the number of cases of MCCUP.

- Presence of p16 reactivity:
 - Metastatic oropharyngeal nonkeratinizing SCC shows diffuse, strong p16 and HPV16 DNA positivity while p16 reactivity in the branchial cleft cysts is negative, shows patchy positivity, or is characterized by focal, strong staining limited to involving the superficial squamous epithelium although as previously noted p16 may be overexpressed in almost 50% of benign branchial cleft cysts; molecular testing (in situ hybridization, PCR) would be necessary to confirm presence of HPV and the malignant nature of the cyst.
- Benign intranodal inclusions:
 - See Section 6, Salivary Glands, for a discussion on the presence of benign nonneoplastic salivary gland parenchyma in periparotid lymph nodes.
 - See Section 8, Thyroid Gland, for a discussion relative to intranodal thyroid epithelium.
 - Intranodal nevi
 - Intranodal benign spindle cell neoplasms such as intranodal myofibroblastoma
- Cervical thymic cyst

Detection of the Primary Neoplasm

- Success rate of finding the primary neoplasm varies from approximately 10% to 82%.
- Nearly 60% of detected primary neoplasms originate from Waldeyer tonsillar ring (i.e., oropharynx, nasopharynx).
- Prior irradiation significantly lowers the incidence of detecting primary cancer.
- Most common primary malignancy below the clavicle is the lungs followed by the gastrointestinal tract.
- Tonsillectomy:
 - Appropriate use of tonsillectomy remains controversial.
 - Detection rate of carcinoma in tonsillectomy specimens when radiographic imaging is negative varies from different institutes, with some reports showing a high prevalence rates (up to 39%) for tonsillary primary tumors in the face of unknown metastatic squamous cell carcinoma to others reporting low prevalence rates (10%).
 - If a tonsillectomy is performed, the entire resected specimen should be submitted for histologic evaluation:
 - Will increase detection of primary carcinoma, especially very small ones
- Micrometastasis:
 - The definition of what constitutes micrometastasis is not completely defined but deposits measuring 3 mm or smaller are considered as qualifying as micrometastatic tumor.

- Micrometastatic deposits are not clinically detectable but are identified by the pathologist following neck dissection with tissue examination.
- Micrometastatic deposits may be visualized by light microscopy or may require immunohistochemical stains for cytokeratin.
- The clinical import of micrometastatic deposits remains unknown.
- Unless identified by light microscopy, at present there is no justification for immunohistochemical evaluation of neck dissections for the identification of micrometastatic deposits.

Treatment and Prognosis

- Management is a discussion on advanced stage squamous cell carcinoma as patients are either Stage III or IV since by definition nodal metastasis precludes Stages I and II.
- Similar to advanced stage squamous cell carcinomas of other head and neck sites, patients are treated by combined modality therapy, including surgery and radiation:
 - Stage III:
 - Surgery includes a comprehensive neck dissection (levels I to V) that in most cases can include preservation of the spinal accessory nerve without compromise of local control.
 - A majority of patients are treated by combined surgery and radiation because of:
 - Inaccuracy of clinical staging to predict microscopic disease
 - Frequent occurrence of extracapsular nodal spread
 - Concern for the development of a late primary tumor in the head and neck
 - A minority of patients can be eligible for single modality therapy.
 - Stage IV disease, including N2 (N2b or N2c) to N3 warrants comprehensive neck dissection with radiation given either before or after surgery.
- Intensity-modulated radiotherapy (IMRT) used primarily in patients with ipsilateral positive nodes:
 - Patients usually receive weekly concomitant cisplatin during course of IMRT.
- Clinical staging and pathologic staging can differ considerably:
 - In unknown primary neck disease that is clinically N1, 45% of patients are found to have multiple nodes by pathologic evaluation after surgery (N2b).
 - In comparing single-node disease (N1 or N2a) 57% of patients have multiple nodes on neck dissection.
- Survival rates vary widely and dependent on many factors, not the least of which is presence or absence of HPV-positive cancers:

- 60% to 90% 5-year survival rates
- 60% to 90% 5-year locoregional control
- Prognostic factors include:
 - Stage of disease:
 - Single most reliable prognostic factor
 - Decrease in 3-year survival rates from 79% to 38% with progression from NX neck to N+ neck
 - HPV positive:
 - Generally have better survival rates
 - Location of the lymph node:
 - Supraclavicular nodal or low cervical nodal involvement associated with worse prognosis rarely cured by any therapeutic intervention
 - Patients with disease in the lower neck have 27% rate of distant metastasis compared with a 13% risk of distant metastasis in patients with disease in the upper neck.
 - Histologic appearance:
 - Metastatic adenocarcinomas (except papillary thyroid carcinoma) have worse survival rates.
 - Metastatic oropharyngeal (HPV-associated) carcinoma and metastatic nasopharyngeal (EBV-associated) carcinoma tend to have better survival than non-viral-associated metastatic carcinomas.
 - Extranodal extension:
 - Spread of metastasis to extranodal soft tissues associated with increased neck failure (i.e., recurrent neck disease), distant metastases, and decreased disease-free survival
 - Presence of distant metastasis:
 - Significantly decreases survival rate
 - Desmoplastic stromal response:
 - Presence of nodal desmoplasia in response to metastatic disease is associated with increased risk of recurrent neck disease.
- Recurrence:
 - Recurrence in patients with MCCUP is an ominous prognostic factor
 - Can be in the ipsilateral or contralateral neck
 - Patients can also develop second primary lesion.
- Typically, metastatic carcinoma to a supraclavicular lymph node originates from a primary source below the clavicle (e.g., thorax, GI tract, others).
- Virtually every other organ may be the primary focus of a metastasis to the head and neck but among the more common primary malignancies to metastasize to the head and neck from a primary malignancy not of the head or neck include:
 - Kidney
 - Prostate
 - Melanoma (often cutaneous but also noncutaneous types)
- As a general rule, when confronted with a malignancy in a head and neck site posing difficulties in histologically classifying it to that specific site, pathologists should give consideration to the possibility of its representing metastasis from a distant (not a head or neck) site:
 - In such a situation morphologic features and immunohistochemical staining may allow for determination of the primary (non-head and neck) site of origin.
 - At the time of metastasis to the head and neck, the primary (non-head and neck) malignancy may be occult or may have occurred years previously.
- Other tumor types that can metastasize to lymph nodes in the presence of an occult primary neoplasm include:
 - Metastatic melanoma:
 - Primary tumor may be of cutaneous or mucosal origin.
 - Primary melanoma may precede the metastasis (including years to decades previously) or synchronously with the metastasis.
 - Immunohistochemistry assists in the diagnosis (e.g., S100 protein, HMB45, melan-A, tyrosinase, MITF1, and vimentin).
 - Metastatic thyroid carcinomas, including papillary carcinoma and medullary carcinoma:
 - Immunohistochemistry assists in the diagnosis:
 - Papillary thyroid carcinoma: thyroglobulin positive (as well as cytokeratins and thyroid transcription factor 1)
 - Medullary thyroid carcinoma: calcitonin, synaptophysin, and chromogranin positive (as well as cytokeratins and thyroid transcription factor 1)
 - **NOTE:** Rarely, neuroendocrine carcinomas from a primary head and neck site (e.g., larynx) may metastasize to cervical neck lymph nodes in the absence of a known primary malignancy; moderately

SECONDARY TUMORS TO THE NECK (OTHER THAN CARCINOMA FROM HEAD AND NECK SITES)

- Metastatic tumors to the neck are not limited to origin from a head and neck neoplasm but may represent primary occult neoplasms from organ systems in the thorax, abdomen, and pelvis:
 - Most common primary site for a metastatic tumor originating from below the clavicle is the lungs

- differentiated NEC (atypical carcinoid) often originates in the supraglottis, where it may be clinically quiescent and give rise to metastatic nodal disease; such NECs may share overlapping light microscopic features and immunohistochemical staining including calcitonin with medullary thyroid carcinoma.
- Differentiation is predicated on identifying the primary malignancy and determining if serum calcitonin is elevated, a finding associated with medullary thyroid carcinoma but not laryngeal (and other non-thyroid-based) neuroendocrine carcinomas.
 - Metastatic adenocarcinoma from above and below the diaphragm:
 - It is extremely uncommon for a primary salivary gland neoplasm to manifest as a metastatic tumor in a cervical neck lymph node without a clinically apparent mass at the site of origin.
 - In the head and neck, difficulty in histologically classifying a given tumor or the presence of an unusual histologic appearance should alert the pathologist to the possibility that the neoplasm represents a metastasis from a distant site.
 - Primary carcinoma for a metastatic tumor in supraclavicular lymph nodes is usually from below the clavicle (e.g., intrathoracic or intra-abdominal).
 - Most common primary site for a metastatic tumor originating from below the clavicle is the lungs followed by the gastrointestinal tract, but virtually every other organ may be the primary focus of a metastasis to the head and neck, including those in which the primary neoplasm may be clinically occult, such as renal cell carcinoma and prostatic adenocarcinoma, although these malignancies are more likely to metastasize to a mucosal or osseous site in the head and neck rather than to a lymph node:
 - Immunohistochemistry may be necessary in the identification of a metastasis from a remote primary site:
 - For lung adenocarcinoma: TTF1 and Napsin A
 - For gastrointestinal carcinoma: CK20, CDX2, villin
 - For renal cell carcinoma: CD10, renal cell marker, PAX8, and racemase
 - For prostatic adenocarcinoma: prostate specific antigen, prostatic alkaline phosphatase, and prostein

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References may be accessed online at ExpertConsult.com.

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Embryology, Anatomy, and Histology of the Larynx and Trachea

LARYNX

Embryology

- Epithelium and glands of the larynx arise from the endoderm lining the laryngotracheal groove.
- Supraglottic larynx arises from the third and fourth branchial arches.
- Glottis and subglottic larynx arise from the sixth branchial arch.
- Cartilage, muscle, and other connective tissue elements develop from the mesenchyme around the foregut:
 - Thyroid, cricoid, arytenoid, corniculate, and cuneiform cartilages derived from the fourth and sixth branchial arch
 - Greater cornu and inferior part of the body of the hyoid bone derived from the third branchial arch cartilage; lesser cornu and superior part of the body of the hyoid bone derived from the second branchial arch cartilage
 - Intrinsic muscles of the larynx muscles derived from the fourth and sixth branchial arch
 - Superior laryngeal and recurrent laryngeal nerves (both branches of the vagus nerve) are derived from the fourth and sixth branchial arch.

Anatomy (Figs. 14-1 through 14-5)

Anatomic Borders

- Superior border:
 - Tip of epiglottis
- Inferior border:
 - Inferior rim of the cricoid cartilage
- Anterior border:
 - Lingual surface of epiglottis (vallecula), thyrohyoid membrane, anterior commissure, thyroid cartilage, cricothyroid membrane, and the anterior arch of the cricoid
- Posterior border:
 - Posterior commissure, arytenoid and interarytenoid space, and the mucoperichondrium overlying the cricoid cartilage
- Lateral border:
 - Aryepiglottic folds

Anatomic Compartments

- Supraglottis:
 - Extends from the tip of the epiglottis to a horizontal line passing through the apex of the ventricle
 - Structures in this compartment include:
 - Epiglottis (lingual and laryngeal aspects), aryepiglottic folds, arytenoids, false vocal cords, and ventricle
 - Supraglottic larynx arises from the third and fourth branchial arches.
- Glottis:
 - Extends from the ventricle to approximately 0.5 to 1.0 cm below the free level of the true vocal cord and includes the anterior and posterior commissures and the true vocal cord:
 - Glottic portion of the larynx arises from the sixth branchial arch.
- Subglottis:
 - Extends from approximately 0.5 to 1.0 cm below the level of the true vocal cord to the inferior rim of the cricoid cartilage:
 - Subglottic larynx arises from the sixth branchial arch.
- Paralumenal spaces
 - Represent potential spaces that lie between the laryngeal cartilages and ligaments and membranes that support them
 - Three main paralumenal spaces include:
 - Pre-epiglottic space
 - Paraglottic space
 - Subglottic space
- Pre-epiglottic space:
 - Not a space but represents a roughly triangular area lying anterior to the epiglottic cartilage that is filled with adipose tissue and loose connective tissue bounded:
 - Anteriorly by hyoid bone, thyroid cartilage, and thyrohyoid membrane
 - Posteriorly by epiglottic cartilage and thyrohyoid ligament
 - Superiorly by hypoepiglottic ligament forming the base
 - Contains lymphatics and blood vessels but no lymph nodes

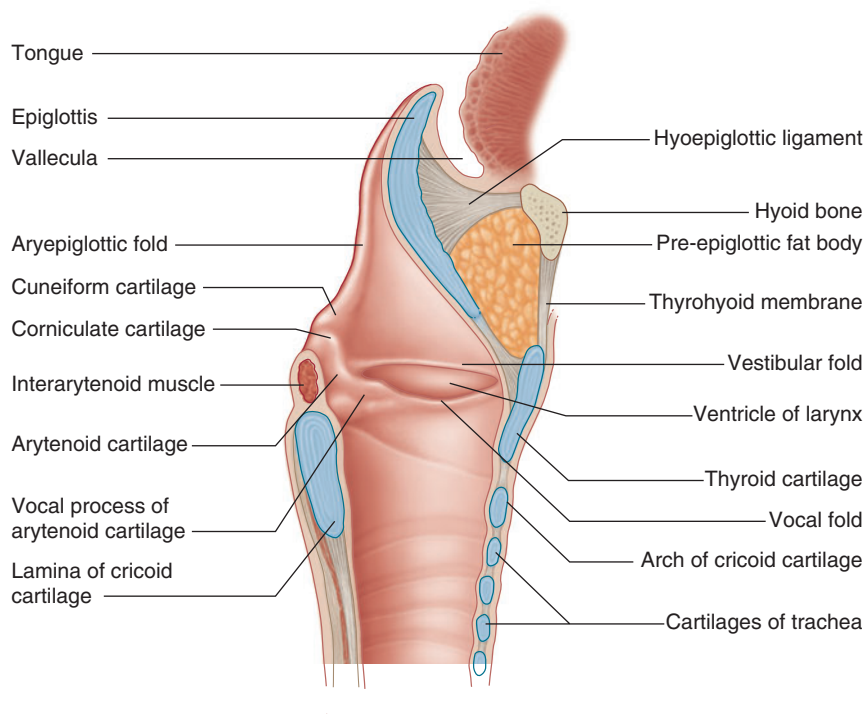


Fig. 14-1. Anatomic borders of the larynx.

(From Standing S: *Gray's anatomy*, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, p 581, Fig. 34.5B.)

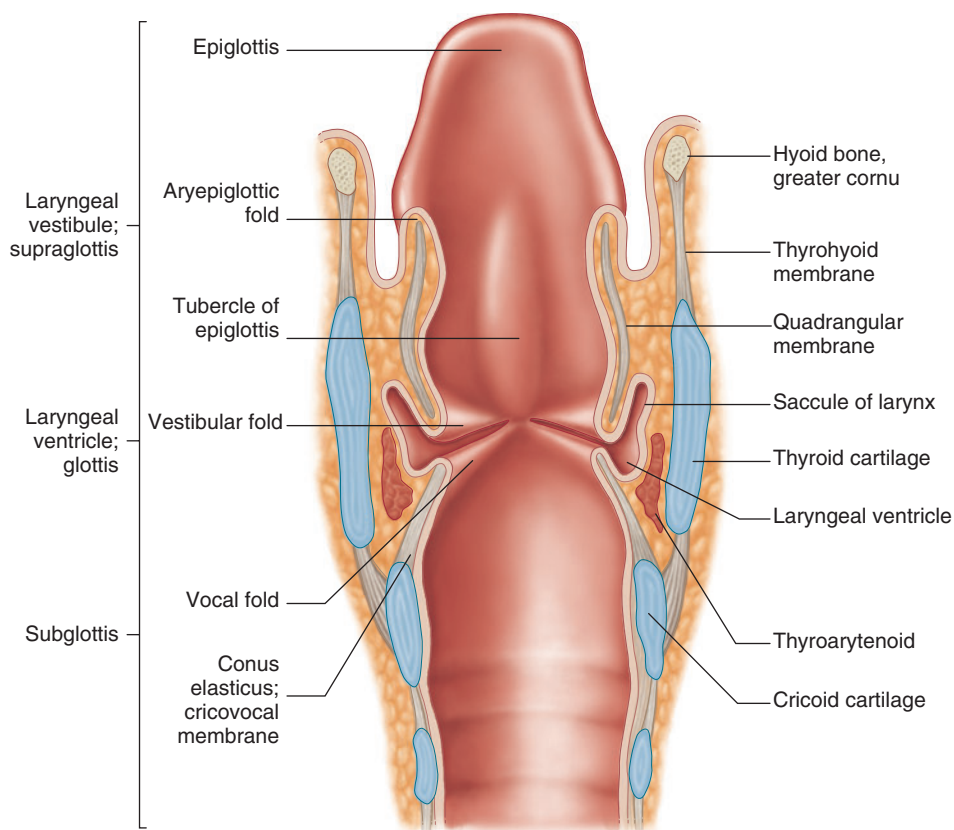


Fig. 14-2. Anatomic compartments of the larynx.

(From Standing S: *Gray's anatomy*, ed 40, Edinburgh, 2009, Elsevier Churchill Livingstone, p 582, Fig. 34.6.)

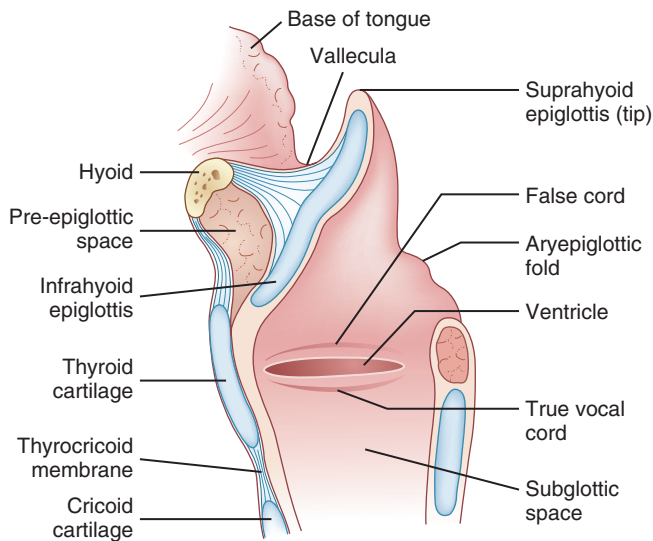


Fig. 14-3. Sagittal section of larynx.

(Redrawn from Sobotta J: *Atlas der anatomie des menschen in 2 volumes*, ed 20, Munich, Germany, 1975, Urban & Fischer Verlag, Fig. 769.)

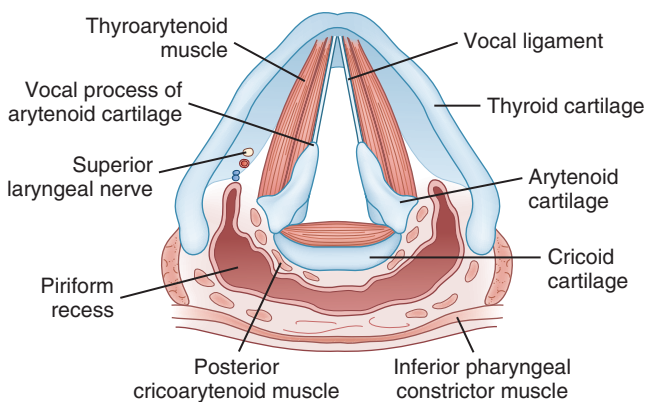


Fig. 14-4. Cross-section of larynx at level of vocal folds.

(Redrawn from Sobotta J: *Atlas der anatomie des menschen in 2 volumes*, ed 20, Munich, Germany, 1975, Urban & Fischer Verlag, Figs. 770, 771.)

- Malignancies of laryngeal surface of the epiglottis may invade fat and areolar tissue of pre-epiglottic space.
- Paraglottic space:
 - Not a space but represents an area deep to the true and false vocal cords that contains adipose tissue and loose connective tissue bounded:
 - Inferiorly by conus elasticus (i.e., cricovocal membrane)
 - Laterally by thyroid cartilage
 - Medially by quadrangular membrane
 - Posteriorly by piriform sinus

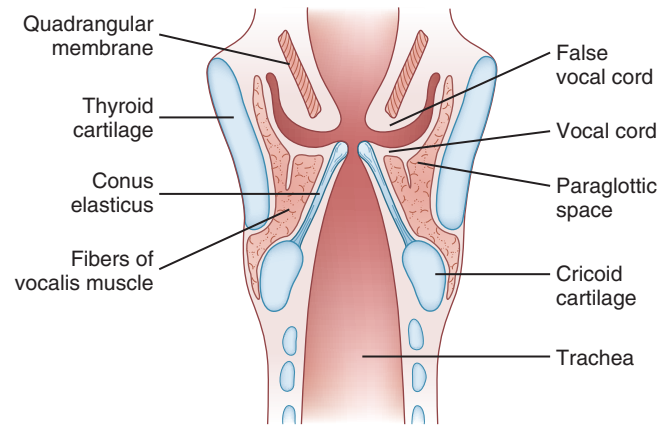


Fig. 14-5. Coronal view of the larynx.

(Redrawn from Sobotta J: *Atlas der anatomie des menschen in 2 volumes*, ed 20, Munich, Germany, 1975, Urban & Fischer Verlag, Fig. 766.)

- Superiorly is in continuity with pre-epiglottic space
- Contains lymphatics and blood vessels but no lymph nodes
- Supraglottic tumors may spread into paraglottic space and reach the subglottis or extend beyond the limits of the larynx.
- Fixation of vocal cord represents good indicator of a tumor in the paraglottic space
- Subglottic space:
 - Bounded:
 - Laterally by conus elasticus (i.e., cricovocal membrane)
 - Medially by mucosa of subglottic region
 - Superiorly by undersurface of Broyle's ligament
 - Continuous with inner surface of cricoid cartilage and its mucosa
 - Broyle's ligament:
 - Site where vocal fold meets anteriorly (known as anterior commissure) and is region where fibers of vocal ligament pass through thyroid cartilage to blend with overlying perichondrium forming Broyle's ligament
 - Broyle's ligament contains blood vessels and lymphatics, representing potential route for escape of malignant tumors of the larynx.
 - Laryngeal cartilage (Fig. 14-6)
- Skeleton of larynx composed of cartilage, fibrous sheets, and bands; attached muscles adjust position of cartilages, changing shape and tension of vocal cords
- Thyroid cartilage:
 - Largest of the laryngeal cartilage
 - Double-winged

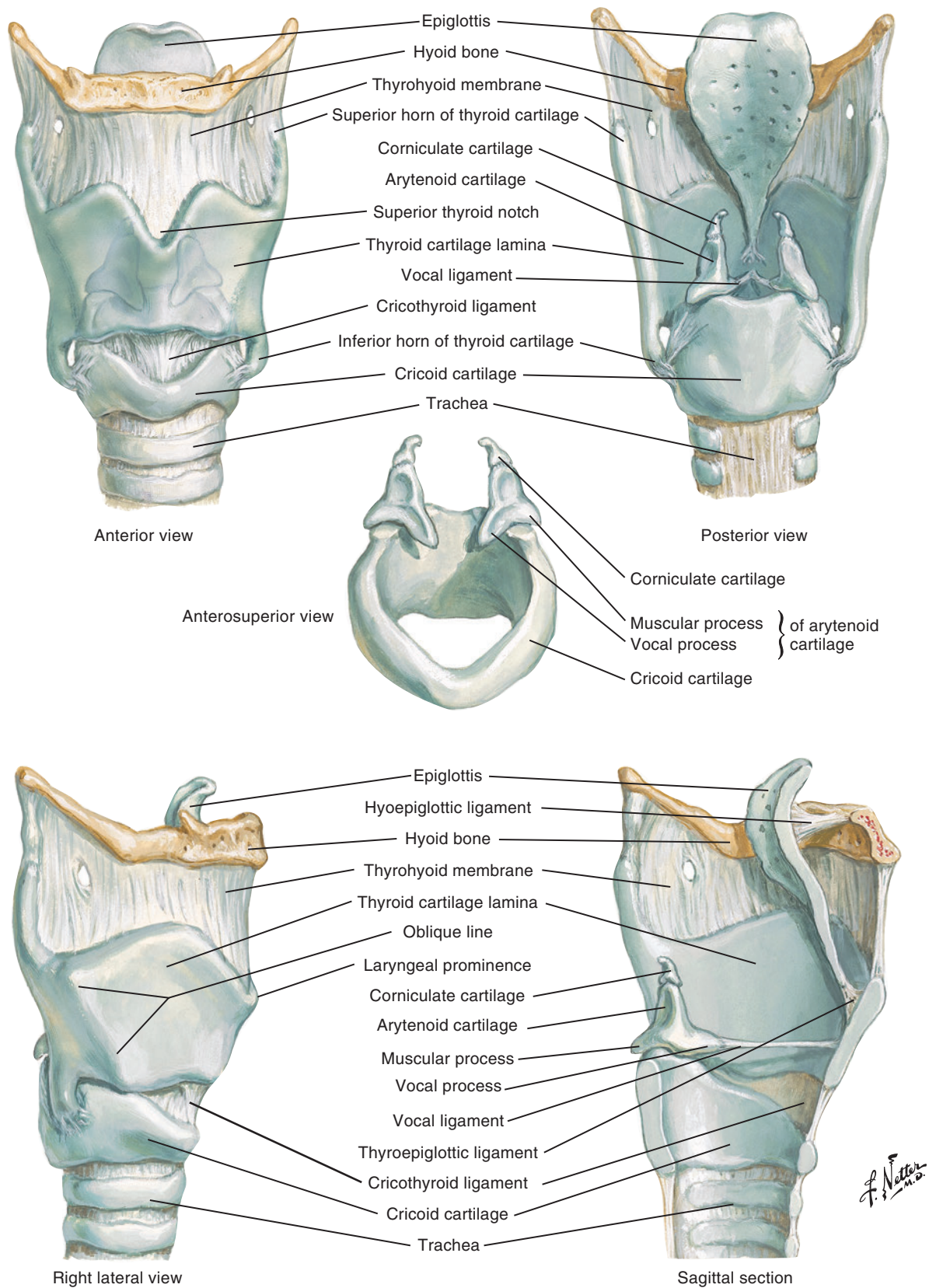


Fig. 14-6. Cartilage framework of the larynx.

(From Som HD, Curtin PM: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 31-7, p 1909. Modified from www.netterimages.com.)

- Cricoid cartilage:
 - Only complete ring in respiratory system
 - Represents foundation of larynx
 - Resembles signet ring with larger part facing posteriorly
- Arytenoid cartilage:
 - Paired cartilage perched on superior edge of cricoid cartilage
 - Each cartilage is pyramidal.
 - At inferior aspect are two projections:
 - Muscular process on posterolateral margin
 - Vocal process located anteriorly
 - Vocal ligament attaches to vocal process of arytenoid cartilage.
 - Superior process represents apex of pyramid:
 - Corniculate cartilage rests on the margin of the superior process of the arytenoid cartilage.
 - Articulations between the various laryngeal joints are synovial and may be involved by an arthritic process.

Innervation

- Innervation of the larynx is by two sets of nerves, both branches of the tenth (vagus) nerve:
 - Superior laryngeal nerve:
 - Largely sensory
 - Inferior laryngeal nerve:
 - Largely motor supplying the intrinsic muscles of the larynx

Vascular Supply and Lymphatic Drainage

- Arteries and veins:
 - Arterial supply to the larynx consists of two pairs: superior and inferior laryngeal arteries derived from the superior and inferior thyroid arteries, which are branches of the carotid artery and the subclavian artery, respectively.
 - Superior and inferior laryngeal veins parallel the arteries.
- Lymphatics:
 - Divided into superior and inferior groups by the vocal fold:
 - Superior group drains to the upper portion of the deep cervical lymph nodes.
 - Inferior group drains to the lower deep cervical lymph nodes.

Histology (Figs. 14-7 through 14-11)

- Epiglottis and true vocal cord:
 - Lined by nonkeratinizing stratified squamous epithelium

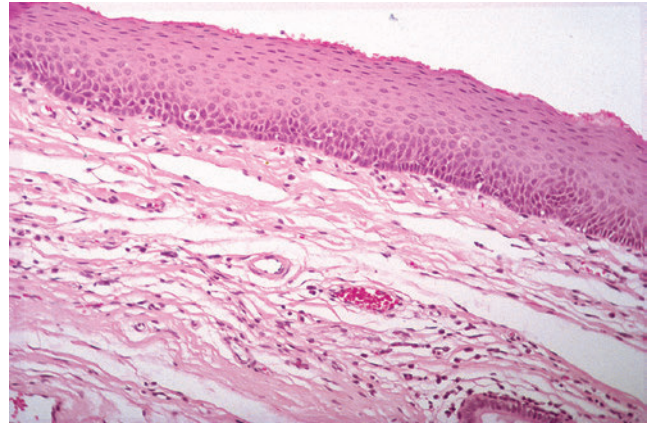


Fig. 14-7. Glottic epithelium.

The “resting” epithelium of the glottic compartment (as well as the epiglottis) is nonkeratinizing squamous epithelium. The epithelium is relatively flat and matures toward the surface. The submucosa of the glottic region is devoid of seromucous glands and as compared with the other compartments of the larynx has fewer lymphovascular spaces.

- False vocal cord, ventricle, and subglottis:
 - Lined by pseudostratified ciliated respiratory epithelium
- Transitional-type epithelium is present between the ciliated respiratory epithelium of the supraglottis or subglottis and the squamous epithelium of the true vocal cord:
 - Squamous epithelial-ciliary respiratory epithelial junction
 - Transitional-type epithelium:
 - Appears abruptly
 - Is composed predominantly of basaloid or immature squamous cells with hypercellularity, disorganization, absence of maturation, and increased nuclear-to-cytoplasmic ratio
 - May be misdiagnosed on biopsy or by frozen section as severe dysplasia or carcinoma in situ (CIS) but in contrast to severe dysplasia/CIS the cells have vesicular nuclei, smooth nuclear contours, absence of significant pleomorphism, and absence of mitoses away from the basement membrane
- Seromucous glands found:
 - Lower two thirds of the epiglottis
 - Ventricular submucosa
 - Most abundant in false vocal cord
 - In subglottis
 - Absent in region of true vocal cord:
 - Glands present immediately above and below squamocolumnar junction

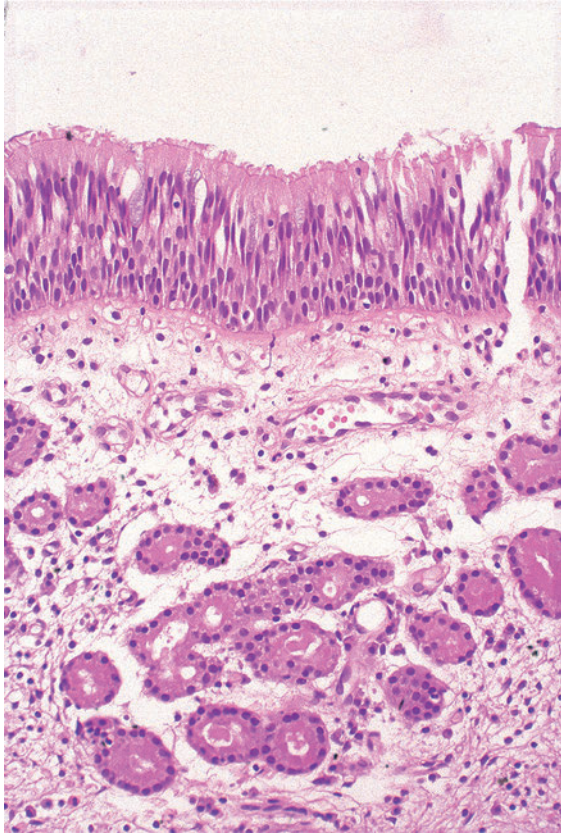


Fig. 14-8. Supra- and subglottic epithelium.

The “resting” epithelium of the supra- and subglottic region is pseudostratified ciliated respiratory epithelium. In contrast to the glottic region, the submucosa in the supra- and subglottic compartments includes submucosal seromucous glands.

- Laryngeal cartilage:
 - Epiglottis, cuneiform, and corniculate cartilages are elastic-type cartilage.
 - Thyroid, cricoid, and arytenoid cartilages are hyaline-type cartilage.
 - Hyaline cartilage components of the larynx may calcify and/or ossify with age:
 - Represents “normal” aging process in the larynx
 - If traumatized may result in a fractured larynx
 - Ossification/calcification of cartilage important to spread of laryngeal carcinoma:
 - Cartilage involved by carcinoma only when ossified
 - Chondrosarcomas frequently occur in cartilage that has ossified/calcified.
- Laryngeal saccule:
 - Pouch that ascends from anterior one third of ventricle between the false vocal cord and the inner surface of the thyroid cartilage in a vertical plane and ends as a blind sac

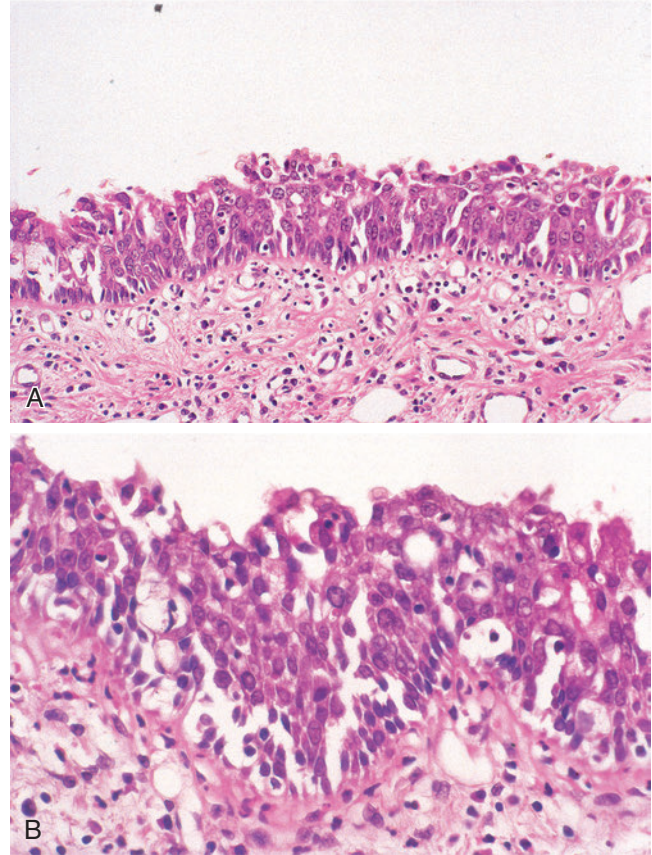


Fig. 14-9. Transitional epithelium.

A and B, Laryngeal transitional-type epithelium is present between the ciliated respiratory epithelium lining of the supraglottic and subglottic larynx, and the squamous epithelium of glottic larynx. The transitional-type epithelium is composed predominantly of basaloid or immature squamous cells with hypercellularity, disorganization, absence of maturation, and increased nuclear-to-cytoplasmic ratio. These overall features may be misdiagnosed as intraepithelial severe dysplasia or carcinoma in situ (CIS), but in contrast to severe dysplasia/CIS the cells have vesicular nuclei, smooth nuclear contours, absence of significant pleomorphism, and absence of mitoses away from the basement membrane.

- Conical and curved slightly backward
- In infants, saccule is lined by a papillary mucous membrane with associated prominent submucosal lymphoid aggregates and is relatively large.
- In adults, saccule is lined by respiratory epithelium and there is an absence of submucosal lymphoid aggregates.
- Orifice of the saccule at the ventricle is only 0.5 to 1.0 mm in diameter and can become obstructed by infections, tumors, trauma, fibrosis:
 - If there is distention of the saccule by air with an open communication with the laryngeal lumen this is termed a laryngocele.

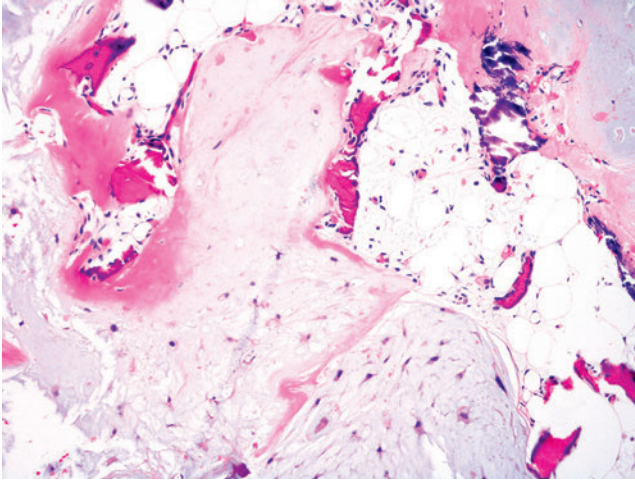


Fig. 14-10. Mineralization of laryngeal cartilage.

With age, the hyaline cartilage of the thyroid, cricoid, and arytenoid cartilages may calcify and/or ossify. This “normal” aging phenomenon may fracture when traumatized and is considered an important pathway for spread of laryngeal carcinoma when involved by carcinoma.

- If there is distention of the saccule with accumulation of secretions, a cyst is formed and this is referred to as a saccular cyst.
- Vocal cord ligament
 - Lies deep to true vocal cord
 - Represents thickened elastic tissue lying under free edge of vocal cord
 - Inserts on thyroid cartilage anteriorly and vocal process of arytenoid cartilage posteriorly
 - Biopsies taken in this anatomic location may include the vocal cord ligament, which, if unrecognized, may be misdiagnosed as a myxoma or peripheral nerve sheath neoplasm.
- Reinke space:
 - Loose connective tissue within the lamina propria of true vocal cord lying between the vocal cord ligament and surface squamous epithelium
 - Contains capillaries but lacks lymphatics
 - Sparse numbers of seromucous glands
 - Common location for vocal cord polyps/nodules:
 - Accumulation of extracellular fluid (Reinke edema)
 - Persists owing to poor lymphatic drainage
 - May be initiated by vocal abuse
 - Carcinomas of this location tend to remain localized owing to limited vascular spaces.

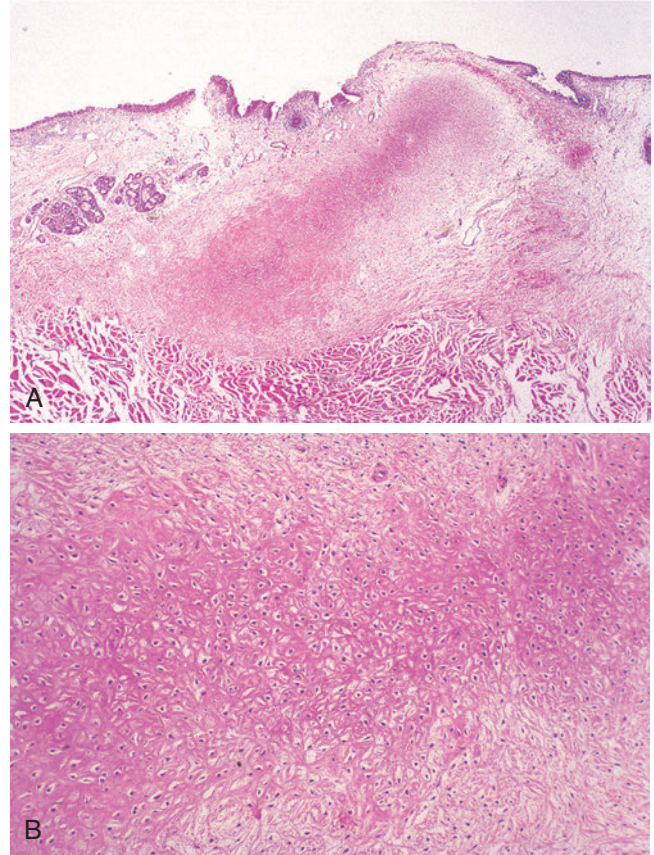


Fig. 14-11. Vocal cord ligament.

The vocal cord ligament, a normal anatomic structure of the larynx representing thickened elastic tissue lying under the free edge of the vocal cord, lies deep to the true vocal cord. Biopsies taken in this anatomic location may include the vocal cord ligament, which, if unrecognized, may be misdiagnosed as a cartilaginous lesion, a myxoma, or a peripheral nerve sheath neoplasm.

HYPOPHARYNX

- As detailed in Section 3, hypopharynx to include the piriform sinus belongs to the pharynx and all details relative to the embryology, anatomy, and histology are provided in that section.

TRACHEA

Embryology

- Endodermal lining of the middle segment of the laryngotracheal tube gives rise to the epithelium and glands of the trachea.
- Cartilage, connective tissue, and muscle derive from surrounding splanchnic mesenchyme.

Anatomic Borders

- Extends from the lower border of the cricoid cartilage to the carina
- In adults, the trachea averages 11 cm in length and 20 to 27 mm transversely.
- There are a total of 18 to 22 tracheal rings with approximately two tracheal rings per centimeter of trachea.
- Superior border:
 - Continuous with the larynx
- Inferior border:
 - Continuous with the bronchi
- Anterior border:
 - Associated with the thyroid gland
- Posterior border:
 - Associated with the esophagus

Innervation

- Cervical portion of the trachea derived from the recurrent laryngeal nerve, which gives off branches to the trachea as it ascends to the larynx

Vascular Supply and Lymphatic Drainage

- Arterial:
 - Main supply by the inferior thyroid arteries

- Thoracic end supplied by the bronchial arteries, which give off branches to anastomose with the inferior thyroid arteries:
 - All of these vessels also supply the esophagus.
- Venous:
 - Veins end in the inferior thyroid venous plexus.
- Lymphatics:
 - Pretracheal and paratracheal lymph nodes
 - Anastomoses with the subcarinal, peribronchial, and esophageal lymph nodes

Histology

- Entire lining is ciliated respiratory epithelium.
- Abundant minor salivary glands (seromucous glands) located in lamina propria
- Cartilaginous rings are incomplete and form about two thirds of a circle:
 - Rings are connected to each other by a fibroelastic annular ligament.
 - Posterior (noncartilaginous) membranous part contains smooth muscle.

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Non-Neoplastic Lesions of the Larynx and Trachea

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE LARYNX AND TRACHEA (Box 15-1)

BOX 15-1 Classification of Laryngeal and Tracheal Non-Neoplastic Lesions

- Vocal cord nodules/polyps
- Laryngocele and laryngeal cysts
- Contact ulcer
- Amyloidosis
- Subglottic stenosis
- Teflon granuloma
- Tracheopathia osteoplastica
- Infectious diseases
- Necrotizing sialometaplasia
- Radiation-induced changes
- Benign epithelial changes
- Others

ACQUIRED AND CONGENITAL LESIONS OF THE LARYNX AND TRACHEA

Vocal Cord Nodules and Polyps (Figs. 15-1 through 15-4)

Definition: Non-neoplastic stromal reactive process related to inflammation and/or trauma.

Synonyms: Screamer's, singer's, or preacher's nodules; corditis nodosa; diffuse polyposis (involvement of the entire vocal cord)

Clinical

- No gender predilection; may be seen in all age groups but most common from the third to sixth decades
- Clinicians distinguishing between nodules and polyps based on whether the lesion(s) is (are) sessile (nodule) or pedunculated (polyp)
- Regardless of terminology, the symptoms related to vocal cord polyps and nodules are similar and include hoarseness or voice changes ("breaking" of the voice).
- May be a single lesion arising from the true vocal cord or bilateral lesions involving the anterior or middle third of the true vocal cord:

- May occur anywhere along the vocal cord but most occur on the free edge at the junction of the anterior and middle thirds
- Point of maximal vibratory impact in the vocal cord is in the middle third of the true vocal cord (membranous cord), representing the most common site for polyps or nodules to occur.
- Follows voice abuse (phonatory trauma), infection (laryngitis), alcohol, smoking, or endocrine dysfunction (hypothyroidism):
 - Phonatory trauma is a central cause of nodule/polyp formation.
 - Infrequently, hypothyroidism may cause vocal cord edema, which may progress to formation of a myxoid polyp.
- *Helicobacter pylori* (HP), a common cause of gastritis and/or gastroesophageal reflux disease, may be associated with vocal fold minimal lesions (VFML) (e.g., polyps, nodules, contact ulcers):
 - HP can be detected by immunohistochemical staining or reverse transcriptase polymerase chain reaction (RT-PCR) in biopsies from patients with VFML.
 - Direct cause and effect between presence of HP and polyps/nodules not established
- Videostroboscopic examination of the glottal cycle is useful in the differential diagnosis of small lesions of the vocal fold cover that cannot be easily visualized:
 - An isolated lesion shows:
 - Irregular, incomplete closure
 - Reduced amplitude of vibration and mucosal wave on the vocal fold on the side of the lesion
 - Bilateral lesions of longer duration show:
 - Greater reduction in vibratory amplitude and mucosal wave due to increased submucosal fibrosis and perhaps presence of surface keratinization

Pathology

Gross

- Fusiform swelling, sessile, or pedunculated lesion(s) with a soft, rubbery, or firm consistency, white, tan, pearly, glistening, or red appearance measuring from a few millimeters up to 1 to 1.5 cm in greatest dimension

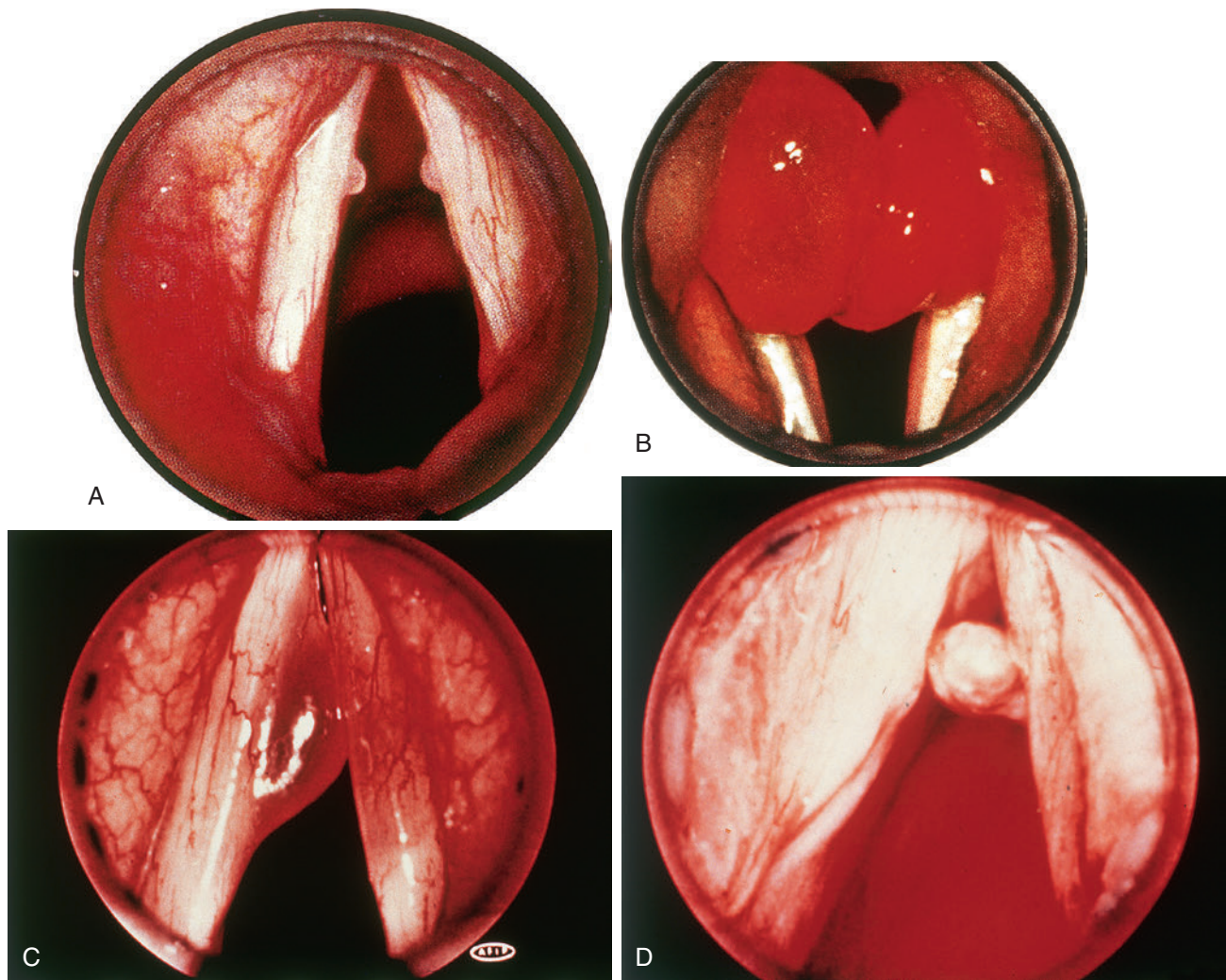


Fig. 15-1. Vocal cord polyps.

Endoscopic appearances of vocal cord polyp and nodules include (A) bilateral identical-appearing polypoid lesions, (B) large beefy-red, bilateral hemorrhagic polyps, (C) unilateral glistening (myxoid-appearing) polyp, (D) unilateral fibrotic polyp.

Histology

- Pathologic process occurs in Reinke's space, the area lying deep to the true vocal cord, which is essentially devoid of blood vessels and in response to injury has a tendency to accumulate fluid.
- Histologic subtypes include:
 - Edematous-myxoid:
 - Submucosal accumulation of pale blue to pink material admixed with a sparsely cellular and variably vascularized stroma
 - Fibrous:
 - Moderately cellular submucosa consisting of uniform oval to spindle-shaped cells associated with a varying amount of fibrous tissue deposition
 - Vascular:
 - Submucosa is marked by prominent dilated vascular spaces with or without associated hemorrhage.
 - Hyaline:
 - Dense eosinophilic submucosal deposition of fibrin material often closely apposed to vascular spaces
 - May suggest the presence of amyloid (Congo red staining is negative)
 - Mixed:
 - Combination of the above subtypes in a single lesion
- For all types the overlying epithelium may be atrophic, hyperplastic, and keratotic; rarely, dysplastic epithelium and/or invasive carcinoma may be identified.
- Histologic changes represent different tissue reactions to the initiating event and do not represent progressive (sequential) changes.
- Rarely, atypical stromal cells (i.e., myofibroblasts) similar to those seen in sinonasal inflammatory polyps may be present, which are:

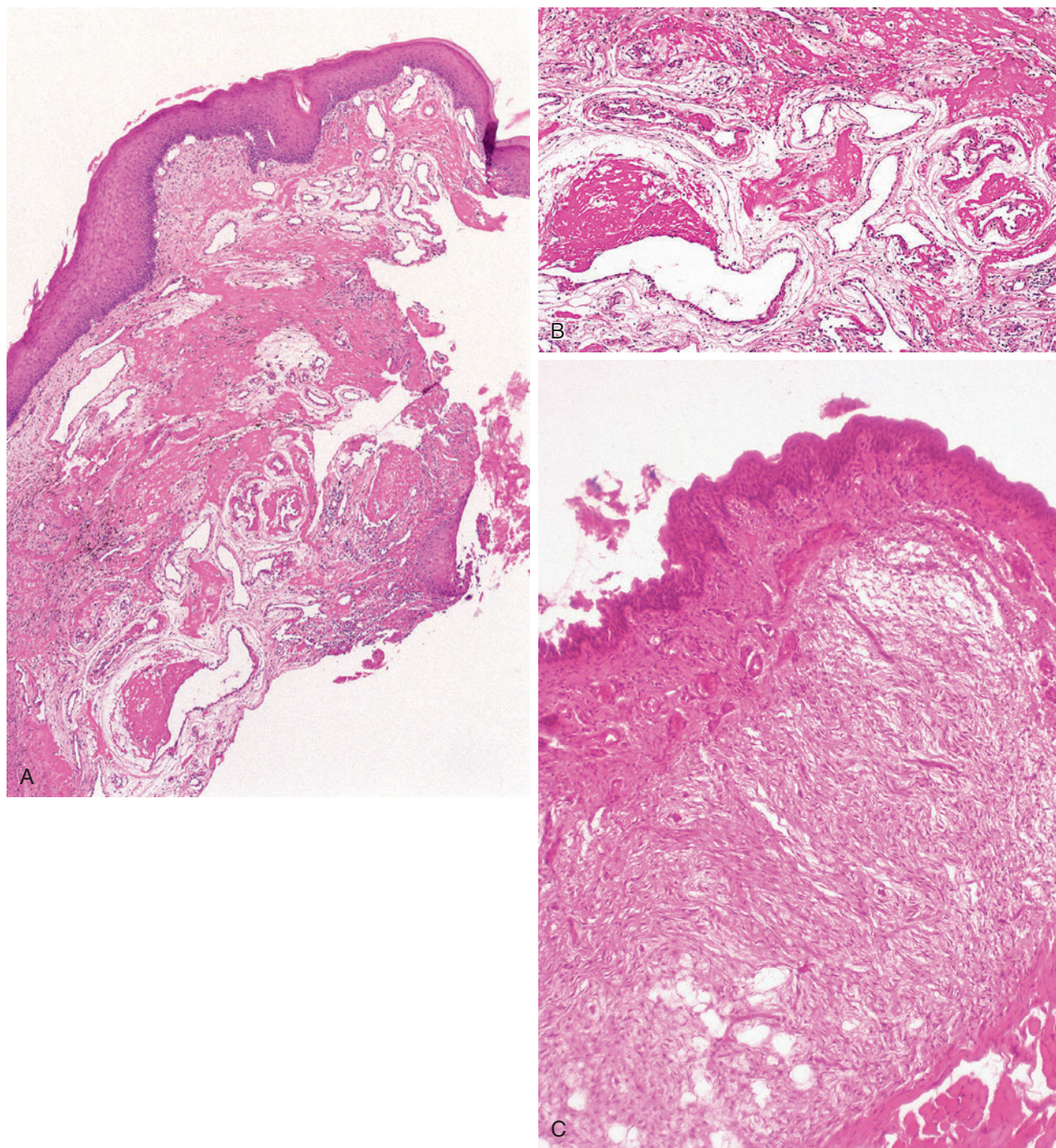


Fig. 15-2. Histology of vocal cord polyps.

Histologic variants of vocal cord polyps/nodules include (**A, B**) vascular-hyaline type characterized by submucosal dilated vascular spaces and deposition of dense eosinophilic fibrin material closely apposed to vascular spaces; the hyaline subtype may be mistaken for amyloid deposition but stains for amyloid (e.g., Congo red) are negative; (**C**) fibrous type characterized by the presence of a moderately cellular submucosa consisting of uniform oval to spindle-shaped cells associated with a varying amount of fibrous tissue deposition;

Continued

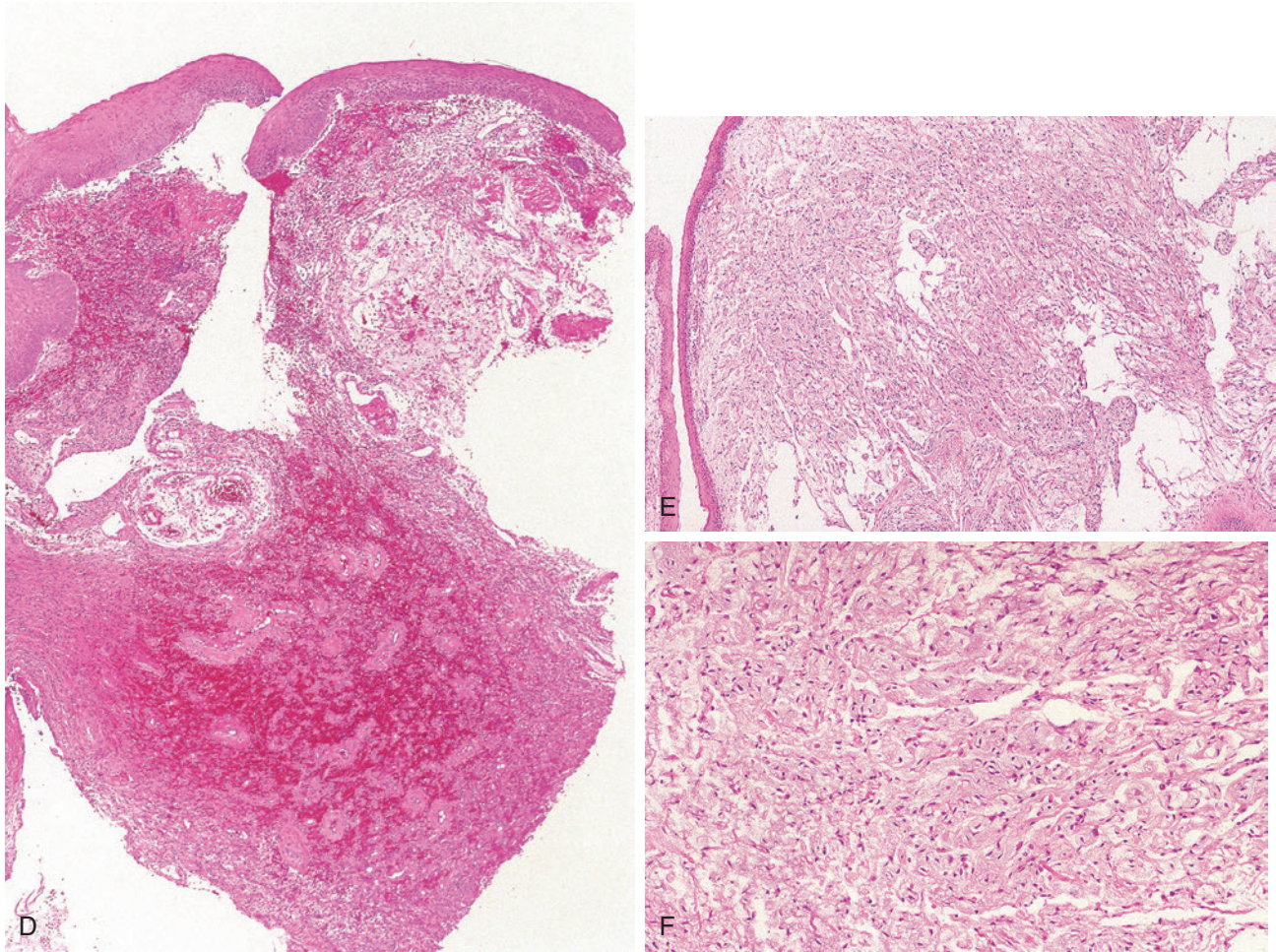


Fig. 15-2, cont'd

(D) hemorrhagic type characterized by submucosal dilated vascular spaces with associated hemorrhage; (E, F) edematous-myxoid type characterized by submucosal accumulation of pale blue to pink material admixed with a sparsely cellular and sparsely vascularized stroma. Rarely, the myxoid type of vocal cord polyp may occur in association with hypothyroidism.

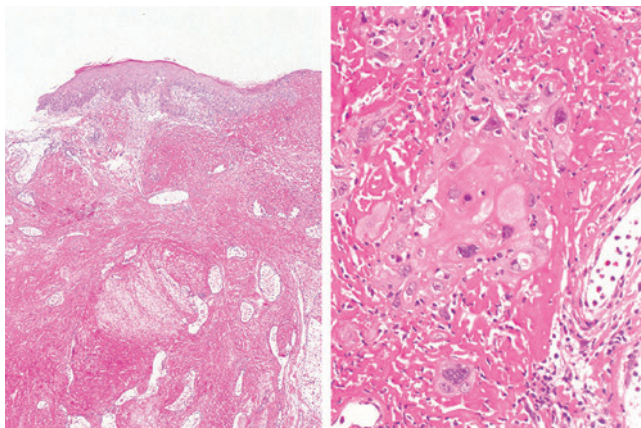


Fig. 15-3. Polyp with carcinoma.

Rare example of a (left) vascular-hyaline vocal cord polyp with associated (right) infiltrating squamous cell carcinoma.

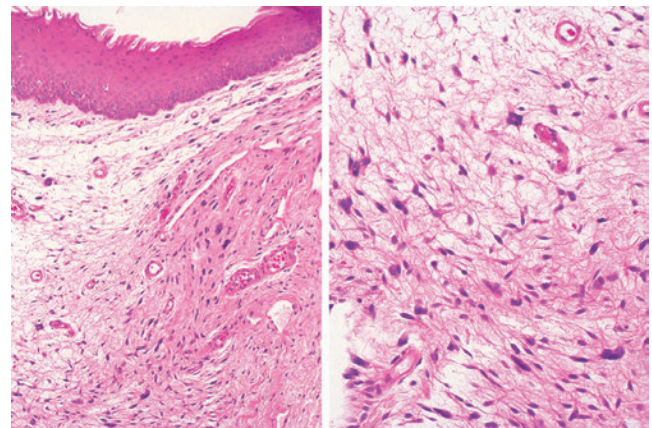


Fig. 15-4. Atypical stromal cells.

Vocal cord polyp with associated atypical stromal cells (i.e., myofibroblasts). Similar to the atypical stromal cells in a sinonasal polyp, these cells in a vocal cord polyp are part of a reactive process (e.g., wound healing) and tend to cluster in proximity to vascular spaces.

- Characterized marked by nuclear enlargement and hyperchromasia
- Not associated with either increased mitotic activity nor a subepithelial condensation of stromal cells (“cambium layer”)
- Typically scattered in distribution over a wide area and do not appear concentrated in location or characterized by hypercellularity
- Histochemistry:
 - Negative staining for amyloid (Congo red, crystal violet, or thioflavin T stains)
- Cytogenetics and molecular genetics:
 - Messenger RNA genotypic profiles for extracellular matrix proteins, including procollagen I, collagenase, elastase, fibronectin, fibromodulin, decorin, hyaluronic acid synthase 2, and hyaluronidase correlated to a videostroboscopic parameter of mucosal wave stiffness showed:
 - Vocal cord polyps, characterized by stiffer mucosal waves, have higher levels of gene expression.
 - Reinke’s edema, characterized by stiffer mucosal wave scores, has lower gene activity levels.
- Generally, there is a good correlation between the clinical findings/diagnosis of vocal cord polyps/nodules and the histopathologic findings; however, except for cysts that are epithelial lined, there may be a lack of correlation between vocal fold lesions that may be clinically distinct (e.g., polyps, nodules, Reinke edema, others) and the histopathologic diagnosis/classification:
 - May be overlapping histologic finding including epithelial hyperplasia, basement membrane thickening, edema, vascular proliferation, and extracellular “amyloid-like” fibrin
 - No histologic feature that reliably distinguished among the lesions
 - In cases in which there may be a lack of correlation between the clinical diagnostic considerations and the histologic diagnosis, treatment should be individualized based on clinical judgment.
- Typically are not covered by surface epithelium as compared with polyps/nodules that typically include overlying surface (squamous) epithelium
- Amyloidosis:
 - Hyaline-type vocal cord nodule may be misinterpreted as amyloid deposition; however, staining for amyloid differentiates between these entities.
- Hemangioma
- Fibroma
- Neurofibroma:
 - Neurofibromas are S100 protein and Sox10 positive.
 - Vocal cord polyps/nodules S100 protein and Sox10 negative
- In rare examples showing atypical stromal cells the differential diagnosis may include a malignant neoplasm, including sarcoma (e.g., rhabdomyosarcoma) and carcinoma (e.g., spindle cell squamous carcinoma):
 - Laryngeal sarcomas are rare; the most common type of sarcoma of the larynx is a chondrosarcoma (see Chapter 16).
 - Atypical stromal cells in a polyp/nodule tend to be localized as compared with diffuse cellularity and nuclear atypia, including increased mitotic activity seen in association with a sarcoma.

Treatment and Prognosis

- Surgery:
 - Laser surgery can be used safely in the larynx to remove benign superficial laryngeal lesions.
- Voice therapy:
 - Postoperative voice therapy decreases the risk of recurrence.
- Vocal cord nodules/polyps can recur up to 5 years after diagnosis/therapy.

Laryngoceles (Figs. 15-5 through 15-9)

Definition: Abnormal dilatation of the saccule (appendix of the ventricle) containing air and maintaining an open communication with the laryngeal lumen.

Clinical

- No gender predilection; most common in the fifth through eighth decades of life:
 - May occur in pediatric ages
- Majority are unilateral but may be bilateral in up to 25% of patients.
- Three types of laryngoceles identified:
 - Internal laryngocoele: dilatation confined to the intrinsic larynx:
 - Reported incidence of 30%
 - External laryngocoele: dilated sac projects upward between the false vocal cord and the thyroid

Differential Diagnosis

- Myxoma:
 - True myxomas are rarely encountered in the larynx.
 - Typically occurs in supraglottic larynx rather than vocal cord (i.e., gottis) where polyps/nodules occur
 - Typically large (≥ 3 cm or larger) rather than small size of polyps/nodules
 - Tend to be avascular as compared with well-vascularized nature of polyps/nodules

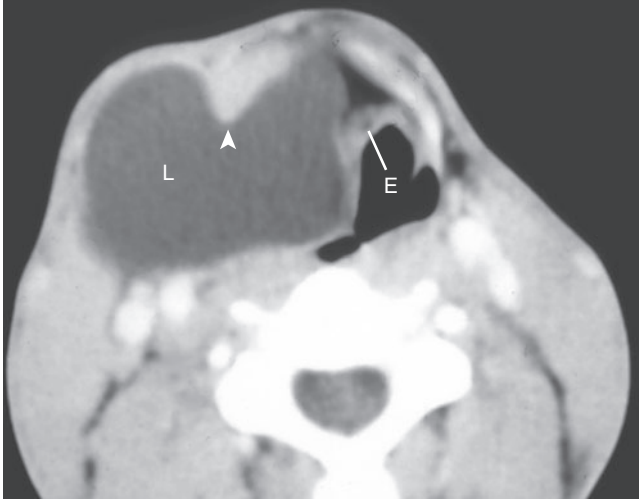


Fig. 15-5. Large laryngocele.

The patient presented with a mass in the right neck. The large fluid-filled saccular cyst (L) fills the supraglottic paraglottic space and extends laterally into the neck. The position of the thyrohyoid membrane is indicated by the arrowhead. E, Epiglottis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 31-111, p 1994.)

cartilage and laterally through the thyrohyoid ligament into the neck:

- Reported incidence of 26%
- Mixed (combined) laryngocele is a combination of internal and external laryngoceles:
 - Reported incidence of 44%
- Symptoms include:
 - Hoarseness, coughing, dyspnea, dysphagia, and sensations of foreign body or mass in the throat
 - External or mixed laryngoceles may present as:
 - Lateral neck mass that fluctuates with changes in intralaryngeal pressure and is compressible
 - Subcutaneous emphysema
 - Infected laryngoceles (laryngopyoceles) associated with pain and tenderness
- Diagnosis of laryngocele is a clinical one:
 - Despite clinical assurance of a diagnosis of a laryngocele, prudent therapy would include additional examination to rule out the presence of a neoplasm.
- Radiology:
 - Thin-walled air-filled cystic lesion communicating with laryngeal ventricle
 - CT (non-contrast-enhanced):
 - Internal laryngocele:
 - Low-density mass in supraglottic space

- Mixed laryngocele:
 - Low-density, thin-walled mass seen in the low submandibular space
 - Can be followed into larynx through thyrohyoid membrane
 - Internal component may be collapsed or dilated.
- Infected laryngoceles by contrast-enhanced CT have a thick, enhancing wall surrounding the laryngocele.
- Cause:
 - Laryngoceles can be congenital or acquired:
 - Acquired laryngoceles are related to occupation and include professions in which there is a tendency to excessively increase intralaryngeal pressures, which may result in the development of a laryngocele (e.g., glassblowers, musicians, and weight lifters).
 - Laryngoceles may have a coexistent (squamous cell) carcinoma:
 - Laryngoceles associated with carcinoma tend to be of the internal type.

Pathology

Gross

- Not as impressive as the clinical presentation; resected specimen is a smooth-surfaced, sac-like structure that may be devoid of fluid or if infected may contain pus.

Histology

- Respiratory epithelial-lined (ciliated, columnar) cyst with a fibrous wall
- Squamous metaplasia may be seen focally or, if infected, may completely replace the respiratory epithelium; in the presence of infection, a chronic inflammatory cell infiltrate may be seen in the wall of the cyst.
- Oncocytic metaplasia of the lining epithelium or minor salivary glands may be seen.

Differential Diagnosis

- Branchial cleft cyst
- Oncocytic papillary cystadenoma
- Laryngeal cysts:
 - Ductal cysts and saccular cysts (see below)

Treatment

- Asymptomatic cases require no treatment.
- Surgery may be necessary in those cases that become large and symptomatic.
 - Microlaryngoscopy involving use of CO₂ laser has become the main therapeutic procedure for the treatment of internal laryngoceles.

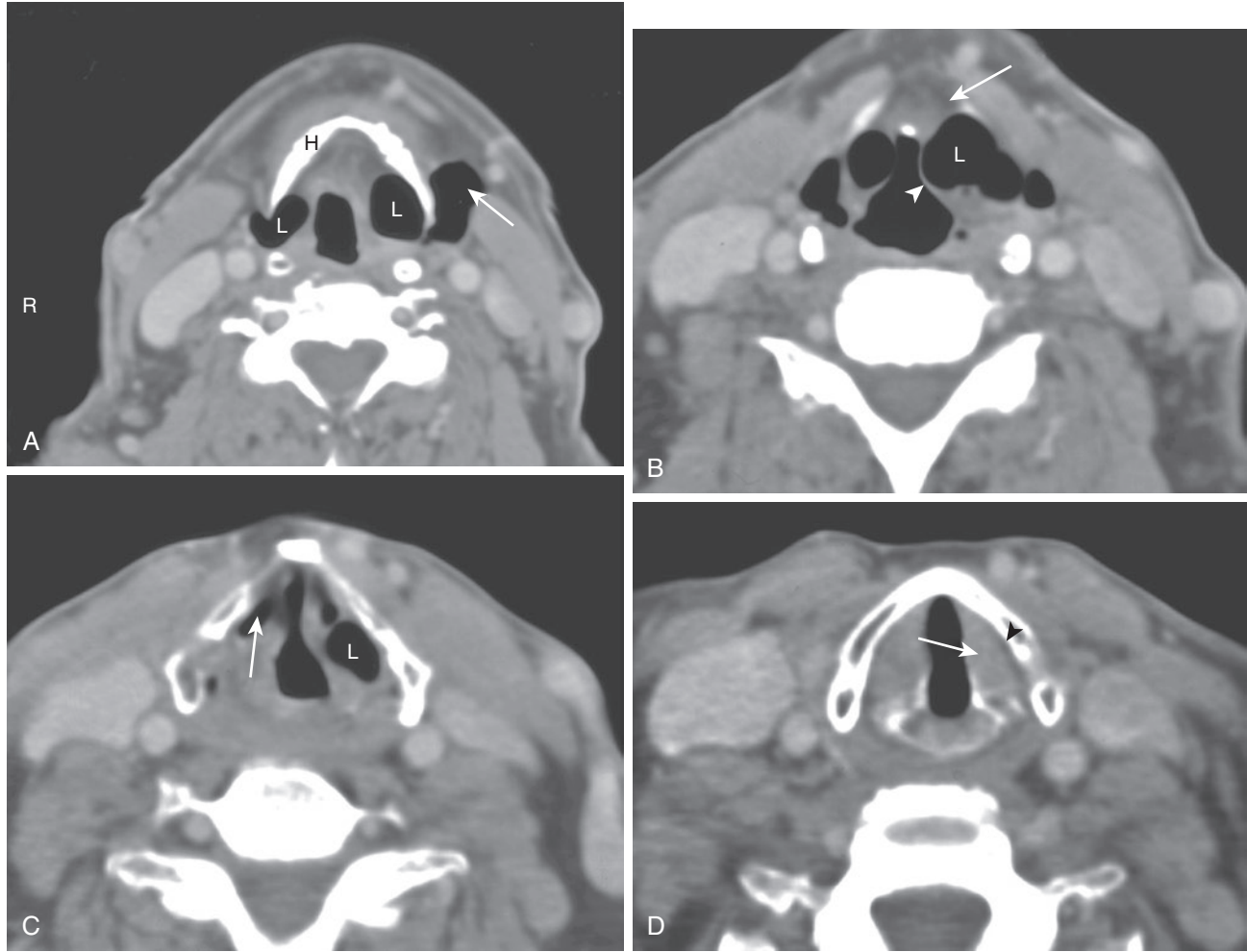


Fig. 15-6. Bilateral air-filled laryngoceles (axial CT).

A, The laryngoceles (*L*) are bilateral. On the left, there is extension between the hyoid bone and the thyroid cartilage into the lateral soft tissues (*arrow*). This is a combined internal/external laryngocele. Hyoid bone (*H*). **B**, Slightly caudad slice shows the bulge of the mucosa (*arrowhead*) at the supraglottic level. Laryngocele (*L*); intact contiguous paraglottic and preepiglottic fat (*arrow*). **C**, Caudad to **B**. The laryngocele (*L*) can be followed anteriorly (*arrow*) as the dilated appendix approaches the ventricle. **D**, The true cord level of the TAM (*arrow*) is identified. Note the crease of fat (*arrowhead*) along the lateral aspect of the muscle, representing the inferior extent of the paraglottic fat. The fat is normal. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 31-110, p 1993.)

- An external approach is main therapeutic approach for the treatment of combined laryngocele.
- Complications associated with laryngoceles include airway obstruction and infection (laryngopyocele):
 - For laryngopyoceles the initial treatment is by incision and drainage followed by antibiotic therapy and then surgical excision after the infection has been controlled.
- Rare complications include vocal cord paralysis and death due to asphyxia.

Laryngeal Cysts (Figs. 15-10 through 15-13)

Definition: Obstruction of the orifice of the laryngeal saccule or obstruction of the mucous gland ducts of the laryngeal saccule with subsequent accumulation of secretions resulting in cyst formation.



Fig. 15-7. Laryngocele.

Clinically, this laryngocele resulted in a large neck mass seen as a subcutaneous bulging mass at surgery.

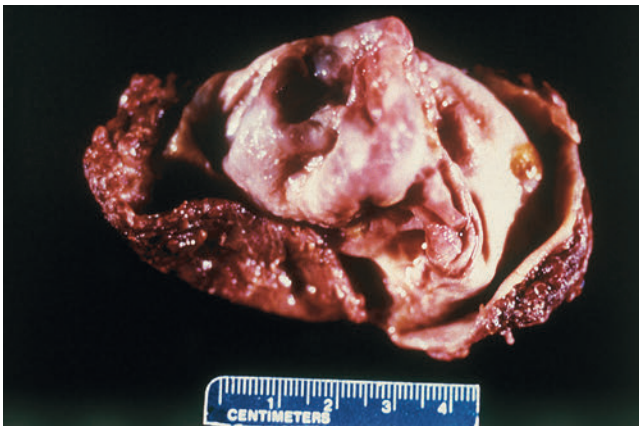


Fig. 15-8. Excised laryngocele.

Resected laryngocele appearing as a smooth-walled cystic structure that contained clear fluid.

Synonyms: Saccular cyst; ductal cyst; oncocytic cyst; epithelial cyst

Classification

- Laryngeal cysts have been divided into two categories:
 - Ductal cysts:
 - Due to obstruction of the mucous gland ducts
 - Represent 75% of all laryngeal cysts
 - Saccular cysts:
 - Due to obstruction of the orifice of the laryngeal sacculi
 - Represent 25% of all laryngeal cysts

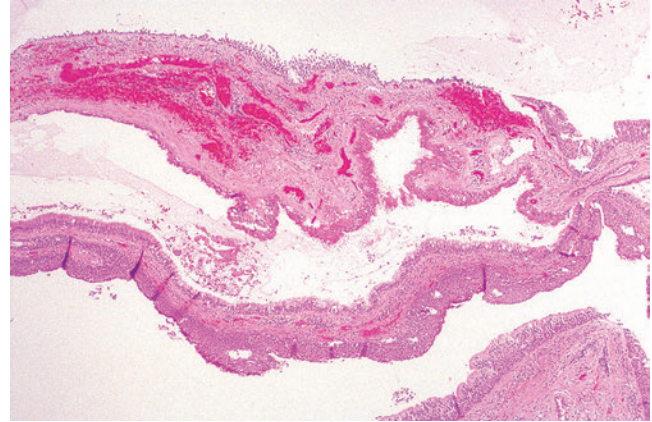


Fig. 15-9. Histology of laryngocele.

The histology of laryngocele is less dramatic than its clinical presentation and is characterized by the presence of a cystic lesion that may be lined by a varying cell types including respiratory (ciliated or columnar), squamous, and oncocytic epithelium. The cyst has focally fibrotic and hemorrhagic wall.

Clinical

- No gender predilection; occur over a wide age range but tend to be most common in individuals older than the sixth decade of life
 - May occur in pediatric ages
- Majority of cysts occur in the supraglottic larynx; less frequently, glottic and subglottic cysts occur.
 - Ductal cysts:
 - Majority occurs in the area of the true vocal cords but not in the region of the free margin, which lacks glands.
 - Next most common site is epiglottis
 - Less frequent sites include false vocal cords, ventricles, aryepiglottic folds, arytenoids, piriform sinus, anterior commissure, and subglottis.
 - Saccular cysts:
 - Occur in the supraglottic larynx:
 - Majority occurs in the region of the ventricles
 - Less often occur in the region of the aryepiglottic folds, lateral larynx
 - Saccular cysts can be further subdivided into anterior and lateral cysts, depending on the location, level of obstruction, and length of the sacculi:
 - Anterior:
 - Develop near the orifice of the ventricle overhanging the anterior glottis
 - Represent the majority of cases

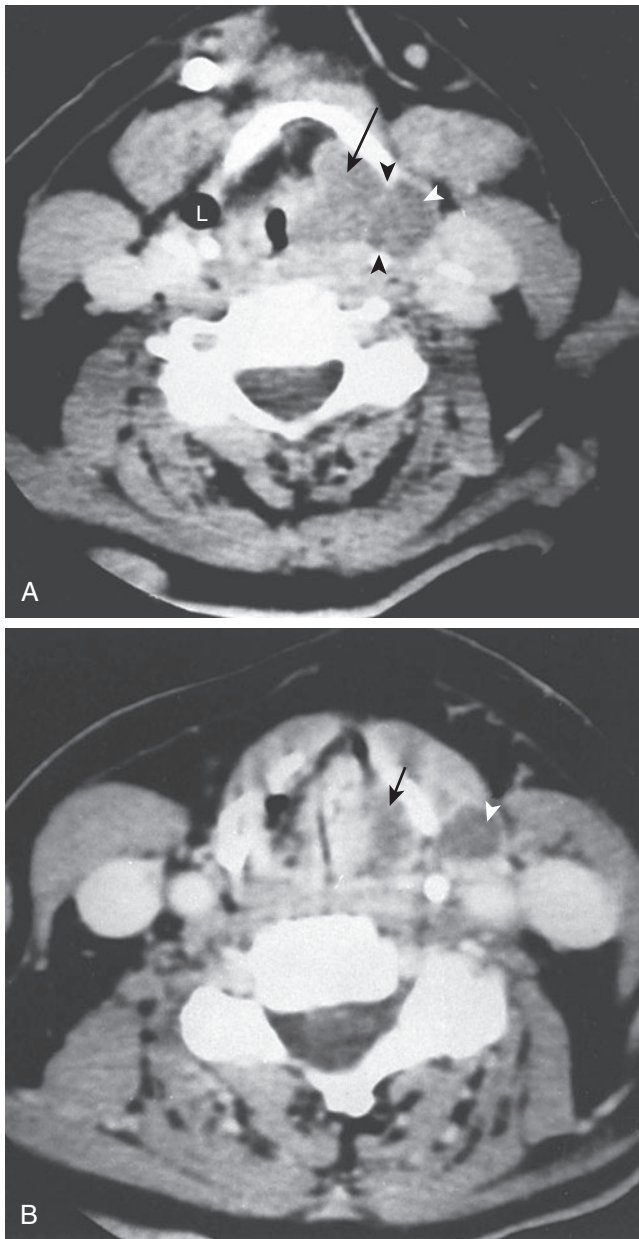


Fig. 15-10. Axial CT of a laryngocele (saccular cyst).

A, There is an internal (*arrow*) and an external (*white arrowhead*) component. The position of the thyrohyoid membrane is signified by black arrowheads. A small air-filled external laryngocele (*L*) is seen on the opposite side. **B**, Lower scan through the supraglottic larynx shows the abnormality in the paraglottic space (*arrow*) and the external component (*arrowhead*). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 1994, Elsevier, Fig. 31-113.)

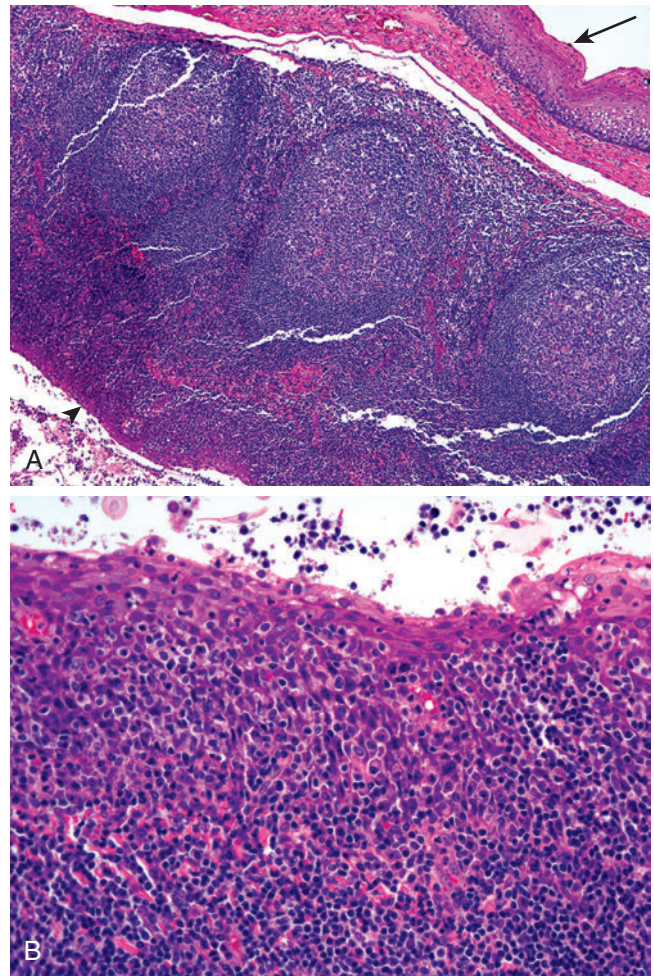


Fig. 15-11. Tonsillar-type cyst.

A, Laryngeal tonsillar-type cyst showing the presence of a submucosal epithelial lined cyst (*arrowhead*) with lymphoid follicles and germinal centers in the cyst wall and an intact surface squamous epithelium (*arrow*). **B**, At higher magnification the cyst is lined by reticulated appearing epithelium infiltrated by type lymphocytes and plasma cells. These overall histologic features resemble palatine tonsillar crypt.

– Lateral:

- Bulge into the aryepiglottic folds, false vocal cords, or epiglottis
- Rarely present as a neck mass with the cyst extending through the thyrohyoid membrane.
- Other cysts types include tonsillar-type, epithelial, and oncocytic (require histologic confirmation—see below):
 - Tonsillar-type cyst:
 - Occurs primarily in the epiglottis, vallecula, or piriform sinus

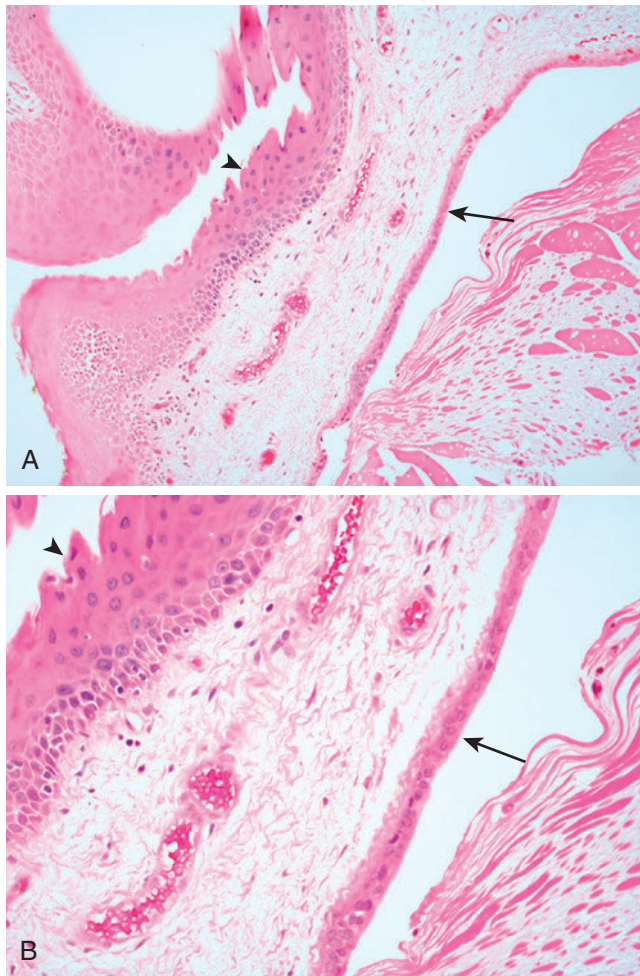


Fig. 15-12. Laryngeal cyst.

A, Laryngeal epithelial-type cyst showing the presence of a submucosal epithelial-lined cyst (*arrow*) and an intact surface squamous epithelium (*arrowhead*). **B**, At higher magnification the cyst is lined by flattened (attenuated) epithelium (*arrow*) located within the submucosa subjacent to surface squamous epithelium (*arrowhead*). The cyst content includes acellular mucinous-appearing debris.

- Epithelial cyst:
 - Occurs primarily in the piriform sinus or vallecula
- Oncocytic cyst:
 - Occurs primarily in the false vocal cords and ventricles
- In general, laryngeal cysts may be solitary or multiple.
- Symptoms include:
 - Asymptomatic and identified incidentally
 - Hoarseness, coughing, dyspnea, dysphagia, sensation of foreign body in the throat, neck mass, pain
 - Infants may present with feeding problems.

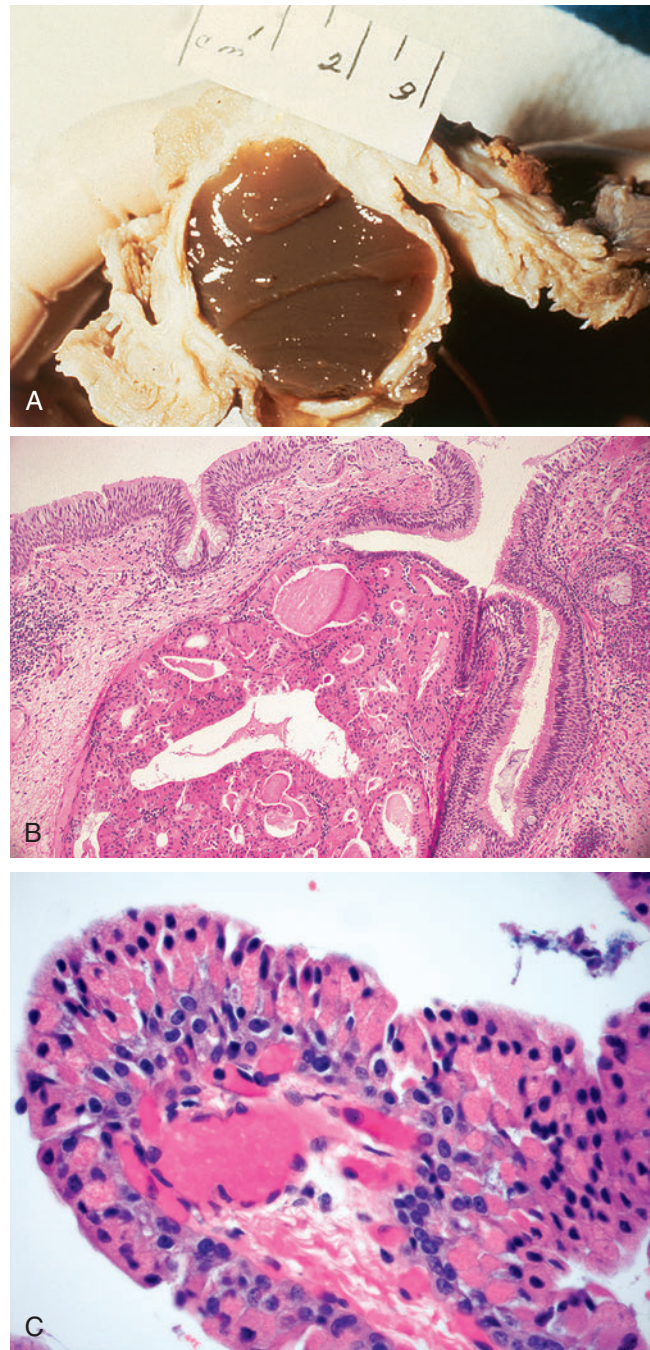


Fig. 15-13. Papillary oncocytic cyst.

A, Resected laryngeal oncocytic cyst characterized by its brown appearance. **B**, Histologically, the cystic proliferation is submucosal and cyst formation with (**C**) papillary architecture and cells with oncocytic cytoplasmic change. Depending on the presence of various structures, these cysts have also been referred to as oncocytic papillary cysts or oncocytic papillary cystadenomas.

- Radiology:
 - Fluid-filled cystic lesion in supraglottic larynx
- Cause:
 - Laryngeal cysts can be congenital or acquired:
 - Supraglottic cysts are due to obstruction of the orifice of the laryngeal saccule or obstruction of the mucous gland ducts of the laryngeal saccule with subsequent accumulation of secretions.
 - Glottic cysts may be due to vocal cord abuse.
 - Subglottic cysts may occur after intubation.
 - Congenital cysts may associated with other congenital or developmental abnormalities, including:
 - Down syndrome, cystic fibrosis, cardiac anomalies, laryngomalacia, conductive hearing loss, hydrocephalus, microcephalus, micrognathia, others

Pathology

Gross

- Ductal cysts:
 - Usually measure less than 1 cm in diameter
 - Tend to be superficial
- Saccular cyst:
 - Submucosal range in size from 1 to more than 7 cm in greatest dimension.

Histology

- Ductal and saccular cysts are lined by respiratory or squamous epithelium:
 - Histologic differentiation of ductal from saccular cysts is not possible, and this differentiation rests on clinical parameters.
 - Cyst may be lined by an oncocytic epithelium.
- Other histologic cyst types include:
 - Tonsillar type cyst:
 - Resembles palatine tonsillar crypt
 - Lined by stratified squamous and/or reticulated epithelium
 - Keratin-filled lumen
 - Lymphoid follicles with germinal centers seen in cyst wall
 - Epithelial cyst:
 - Lined by respiratory and/or squamous epithelium or an flattened (attenuated) epithelium
 - Epithelial lining may be papillary in architecture.
 - May contain keratin or mucin
 - May have lymphoid component in cyst wall
 - Oncocytic cyst:
 - Lined by oncocytic epithelium
 - May have prominent papillary architecture and referred to as oncocytic papillary cyst or oncocytic papillary cystadenoma

- Aside from the above, oncocytic metaplasia and hyperplasia can be seen in association with other laryngeal lesions, and these changes most likely represent an aging (metaplastic) phenomenon.

Differential Diagnosis

- Branchial cleft cyst
- Laryngocele

Treatment

- Conservative management is often advocated to include needle aspiration, deroofing of the cyst, laser marsupialization, or endoscopic removal:
 - Especially for infants and children to avoid stenosis
- Smaller anterior saccular cysts can be managed by endoscopic excision.
- Saccular cysts can be managed endoscopically in many cases, but if persistent after two or three endoscopic procedures, a prolonged course can be anticipated.
- Larger saccular cysts tend to recur repeatedly.
- Complete excision, endoscopically or through an external surgical approach, may shorten the clinical course.
- Tracheotomy may be required, some under emergent conditions.

Contact Ulcers of the Larynx

(Figs. 15-14 and 15-15)

Definition: Benign, tumor-like condition occurring most commonly along the posterior aspect of one or both vocal cords.

NOTE: Although termed as an ulcerative process, not infrequently due to chronicity of disease areas of the lesion may be ulcerated and other areas may show epithelial hyperplasia, the latter a reactive/regenerative process.

Synonyms: Pyogenic granuloma of the larynx; intubation granuloma

Clinical

- More common in men than women; occur over a wide age range:
 - Generally seen in the adult population
 - Uncommon in children but not restricted to any specific age group
- Most common site of occurrence is along the posterior aspect of one or both vocal cords primarily in the area of the vocal cord process of the arytenoid cartilage:
 - Propensity for contact ulcers to occur along the posterior vocal cords includes:

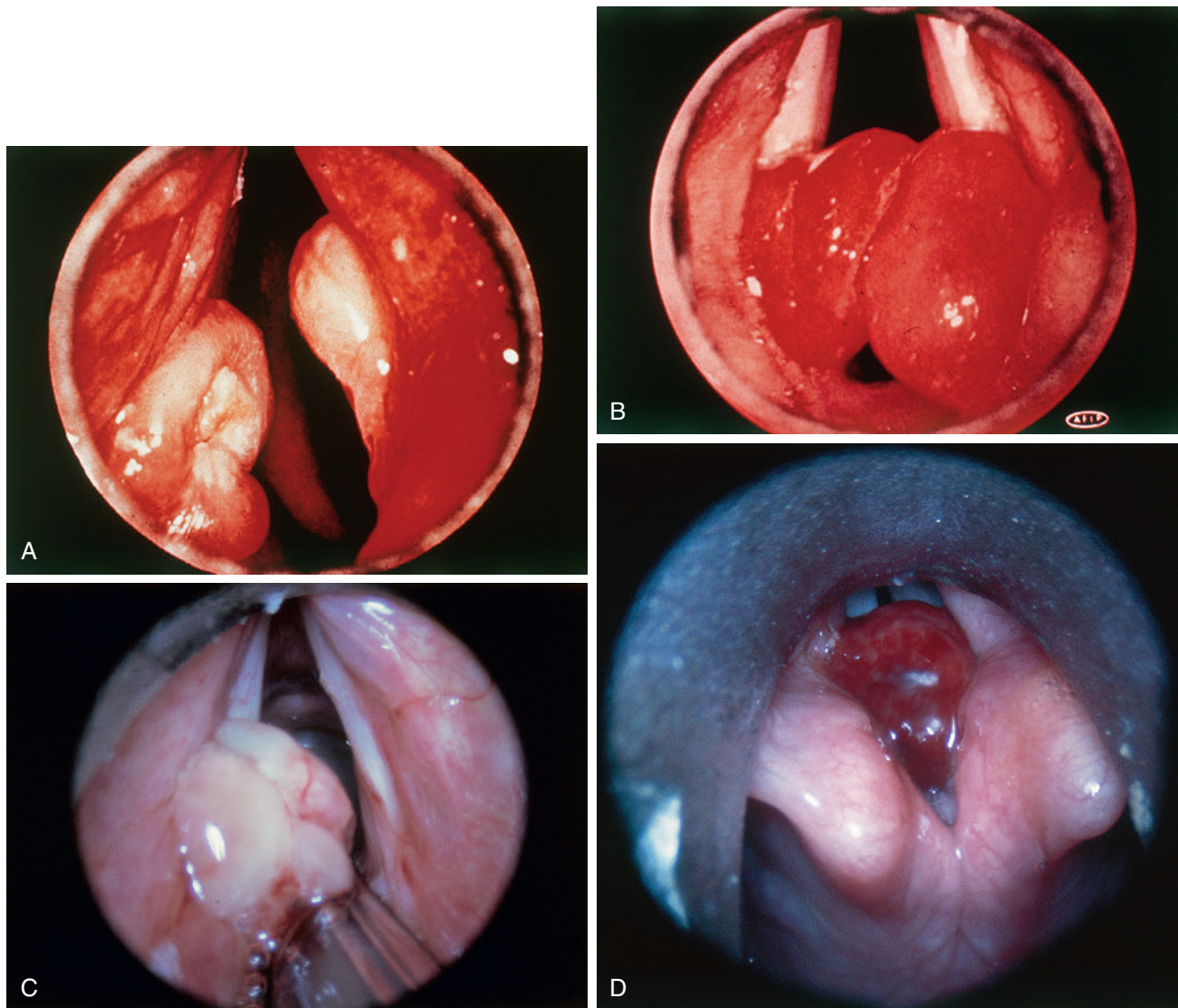


Fig. 15-14. Laryngeal contact ulcers.

Contact ulcers of the larynx (CUL) appearing as **(A)** bilateral polypoid and focally ulcerated, tan-white masses; **(B)** bilateral polypoid beefy red masses; **(C)** unilateral friable polypoid proliferation; and **(D)** large mass filling and obstructing the airway. All of these lesions developed after intubation.

- Posterior vocal cord experiences the greatest excursion during opening and closing of the glottis.
- Mucoperichondrium overlying the posterior vocal cord is extremely thin and more susceptible to injury.
- Additionally, the subepithelial connective tissue in this area is relatively sparse.
- Although the majority occurs along the posterior vocal cords, other vocal cord sites may be affected.
- Symptoms include:
 - Hoarseness most common
 - Less commonly, may include dysphagia, sore throat, dysphonia, difficulty breathing, choking, foreign body sensation in the throat, and pain
 - Duration of symptoms may be from weeks to years.
- Etiologic factors include:
 - Gastroesophageal reflux disease (GERD) with acid regurgitation
 - Not infrequently patients may be unaware of their condition and while supine during sleep the refluxed acid injures the posterior cord resulting in contact ulcer
 - Tends to be more common in men

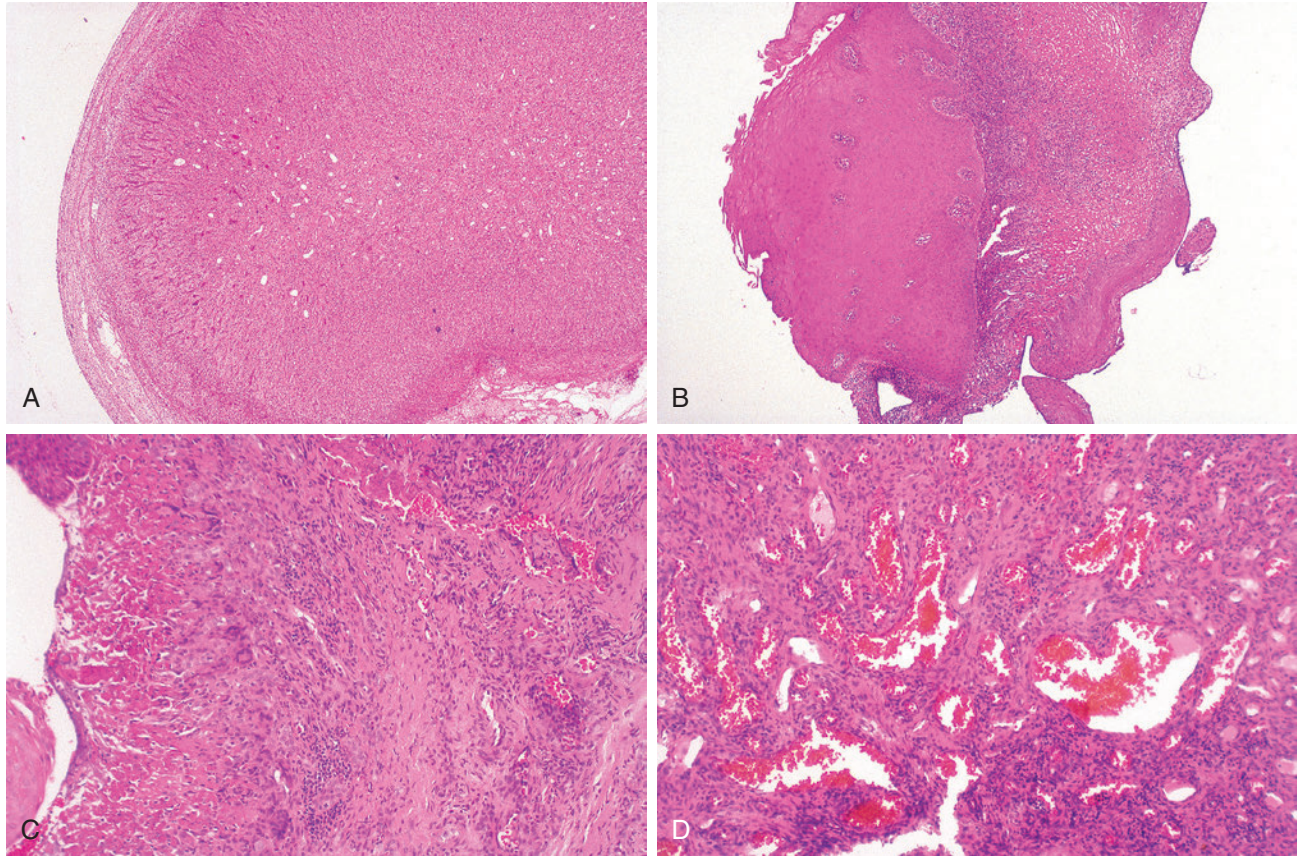


Fig. 15-15. The histology of CUL.

A, Polypoid, ulcerated lesion with associated granulation tissue and inflammation. Note the linear perpendicular orientation of the superficial blood vessels to the surface, a feature often seen in association with reactive processes. **B**, Often CULs are recurrent (chronic) lesions resulting in a combination of concurrent ulceration (active disease) and hyperplastic squamous epithelium (reactive/healing process). **C**, Active lesions show ulceration with associated fibrinoid necrosis and the presence of subjacent scattered multinucleated giant cells and granulation tissue. **D**, Within the granulation tissue component dilated blood-filled vascular spaces may be seen, simulating the appearance of a vascular neoplasm.

- *Helicobacter pylori* (HP) may be detected by immunohistochemical staining or reverse transcriptase polymerase chain reaction (RT-PCR):
 - HP also may be identified in oral cavity, sino-nasal tract, pharynx, and middle ear mucosa.
 - Direct cause and effect between HP and development of contact ulcer and/or other upper aerodigestive tract lesions (non-neoplastic and neoplastic) not established
- Vocal abuse:
 - Shouting, persistent coughing, or throat clearing
 - Tends to be more common in men
- Postintubational trauma:
 - Postintubational contact ulcers tend to occur more frequently in women as a result of the smaller luminal diameter seen in women.
- Lesions may not become manifest until weeks to months after intubation injury.

Pathology

Gross

- Ulcerated, polypoid, nodular, or fungating mass with a beefy red to tan-white appearance ranging in size up to 3 cm in diameter

Histology

- Most often includes presence of an ulcerated lesion with associated fibrinoid necrosis, granulation tissue, and acute and chronic inflammation; additional associated findings may include:
 - Scattered multinucleated giant cells especially lying just below the ulceration:
 - Well-formed granulomas are not a feature.

- Marked vascular proliferation:
 - May be proliferative/exuberant, suggesting a vascular neoplasm (e.g., hemangioma), which are rare in the larynx
 - Papillary endothelial hyperplasia may be present.
- Reactive spindle cells (myofibroblastic) proliferation:
 - May be bizarre appearing with enlarged hyperchromatic nuclei but ample amount of fibrillar-appearing cytoplasm present (low nuclear-to-cytoplasmic ratio)
 - May include increased mitotic activity but atypical mitoses not present
- As a result of recurrent (chronic) disease reactive changes including epithelial hyperplasia may be present:
 - May occur concurrently with surface ulceration
 - May occur in the absence of an ulcerative component
- Histochemistry:
 - Special stains for microorganisms are negative.
- Immunohistochemistry:
 - Generally of limited utility
 - Reactive myofibroblasts variably reactive for actins (muscle-specific, smooth muscle) and desmin but typically negative for cytokeratins and/or p63

Differential Diagnosis

- Infectious disease(s)
- Squamous carcinoma and variants thereof especially spindle cell squamous carcinoma:
 - Squamous cell carcinoma occurring in the posterior vocal cord area is decidedly uncommon.
- Inflammatory myofibroblastic tumor (see Chapter 16)
- Vascular neoplasms:
 - Lobular capillary hemangioma
 - Angiosarcoma
 - Kaposi sarcoma

Treatment

- Identify and direct treatment to the underlying cause:
 - Medical therapy for GERD, including proton-pump inhibitor therapy
 - Voice therapy for voice abuse
- Persistence and recurrences are common:
 - Awareness that this is a specific clinicopathologic entity results in a definitive diagnosis rather than a descriptive histopathologic diagnosis.
 - A descriptive diagnosis, although not technically incorrect, may not suggest that the lesion is usually caused by an extralaryngeal process that requires therapy.

- Failure to suggest a diagnosis of contact ulcer may result in delay in appropriate curative therapy, thereby resulting in persistence and recurrence of disease.

Amyloidosis (Figs. 15-16 and 15-17)

Definition: Protein misfolding disease characterized by extracellular accumulation of fibrillar proteins (amyloid)

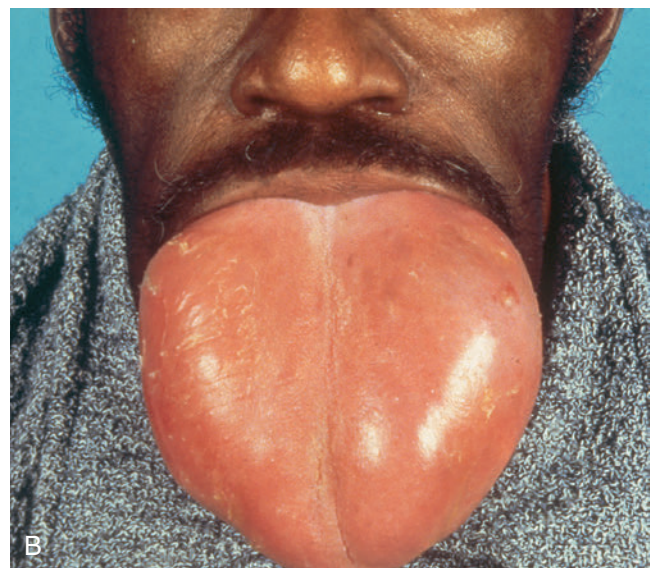
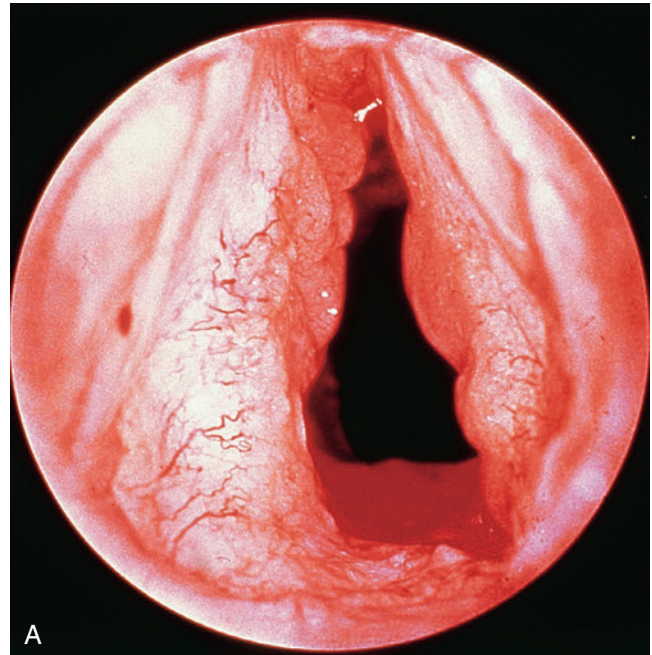


Fig. 15-16. Amyloidosis.

A, Laryngeal amyloidosis as seen by the presence of mucosal covered, diffuse swelling in the glottic and subglottic region. **B**, Lingual amyloidosis resulting in macroglossia.

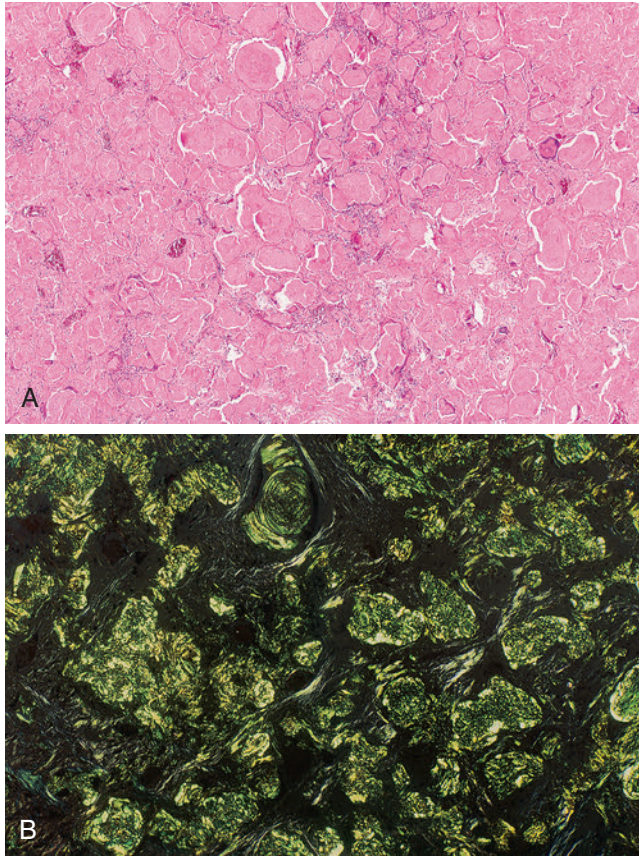


Fig. 15-17. Amyloidosis.

A, The histologic appearance of amyloid includes deposition of eosinophilic, acellular, amorphous, somewhat nodular material throughout the submucosa including around vascular spaces; **B**, Congo red staining for amyloid showing characteristic apple-green birefringence.

identified in association with a variety of clinical settings and occurring in a variety of tissue sites.

- Amyloidosis is the name for 30 protein-folding diseases characterized by extracellular deposition of a specific soluble precursor protein that aggregates in the form of insoluble fibrils:
 - Rigid and unbranching fibrils approximately 10 nm in diameter characterized by a molecular beta-pleated sheet structure that is usually composed of peptides arranged in an antiparallel configuration
 - Structure of the fibrils is responsible for its insolubility, resistance to proteolysis, and binding affinity for Congo red dye that shows a characteristic green birefringence when viewed under polarized light.
 - Extracellular deposition of amyloid fibrils in organs and tissues results in tissue infiltration and swelling, leading to progressive loss of function of the affected organ.

Clinical

- Classification of amyloidosis includes:
 - Primary systemic amyloidosis:
 - Defined as not being associated with an underlying chronic disease
 - Amyloid deposition present in a variety of viscera including heart, gastrointestinal tract, tongue, others
 - Chemical composition: IgG light chain (kappa or lambda) origin (AL)
 - Myeloma-associated amyloidosis:
 - Chemical composition: IgG light chain (kappa or lambda) origin (AL)
 - Localized (solitary) amyloidosis:
 - Chemical composition: IgG light chain (kappa or lambda) origin (AL)
 - Secondary (systemic) amyloidosis:
 - Defined as being associated with an underlying chronic disease and with amyloid deposition in the kidneys, adrenal glands, liver, and spleen
 - Chemical composition: serum amyloid A (SAA)
 - Familial Mediterranean fever:
 - Chemical composition: serum amyloid A (SAA)
 - Familial amyloidosis:
 - Chemical composition: transthyretin (TTR; prealbumin)
 - Senile amyloidosis:
 - Chemical composition: transthyretin (TTR; prealbumin)
 - Dialysis-associated amyloidosis:
 - Chemical composition: β_2 -microglobulin (β_2M)
- In head and neck, amyloid generally is localized or solitary in form.
- Amyloidosis can affect almost every head and neck site but the most common sites of occurrence include the larynx and tongue:
 - Other sites of involvement may include nasopharynx, sinonasal tract, hypopharynx, trachea, external and middle ear, others.

Laryngeal Amyloidosis

- Most often is localized (solitary) and rarely part of systemic disease:
 - Laryngeal amyloidosis is generally a solitary lesion.
 - In up to 15% of patients amyloid deposition may occur in other head and neck sites (trachea, bronchus, tongue).
 - Rarely may be associated with primary or secondary amyloidosis:
 - Diagnosis of laryngeal amyloidosis should prompt clinical evaluation to exclude the

presence of primary or secondary amyloidosis, including:

- Serum and urine electrophoresis
- Immunoelectrophoresis
- Needle aspirate of abdomen to evaluate for the presence of amyloid, which would be positive in up to 95% of patients with primary (systemic) amyloidosis and approximately two thirds of patients with secondary (systemic) amyloidosis
- No gender predilection; may occur over a wide age range but most patients present in the fifth through seventh decades of life
- Most common complaint is hoarseness; other symptoms include dyspnea and cough.
- Can affect any portion of the larynx but most frequently seen along the true vocal cords, false vocal cords, and ventricle
- May be nodular or diffuse; single or multiple deposits
- May be associated with laryngocele

Lingual Amyloidosis

- In contrast to laryngeal amyloidosis, lingual amyloidosis is frequently a target organ as part of primary (systemic) amyloidosis:
 - Diagnosis of lingual amyloidosis should prompt clinical evaluation for systemic amyloidosis.
 - Approximately 15% of patients with primary (systemic) amyloidosis have underlying multiple myeloma.
- More common in men than in women; occurs over a wide age range with median age in the seventh decade of life
- Marked enlargement of the tongue (macroglossia) occurs in a minority of cases:
 - Tongue may protrude from the mouth, interfering with chewing, swallowing, and speaking.
 - Tongue appears pale gray to red, is firm, and may be painful.

Pathology

Gross

- Mucosal covered, firm, tan-yellow to gray that tends to appear as a polypoid mass when involving the glottis and supraglottis or as diffuse swelling when involving the subglottis.

Histology

- Extracellular eosinophilic, acellular, amorphous material deposited randomly throughout the submucosa and generally does not alter the appearance of the surface epithelium

- The deposition is often seen around blood vessels (“angiocentric”) or within the walls of vascular spaces without producing vascular compromise.
- Submucosal deposition of amyloid results in the disappearance of the seromucous glands.
- An associated chronic inflammatory infiltrate including plasma cells, lymphocytes, and histiocytes may be seen and often a foreign body type giant cell reaction is identified.
- Histochemistry:
 - Stains for amyloid (Congo red, crystal violet, thioflavin T) are positive.
 - Apple-green birefringence is seen under polarized light with Congo red staining.
- Immunohistochemistry:
 - Laryngeal amyloid is of light chain origin (AL):
 - Lambda light chain greater than kappa light chain
 - Negative for amyloid A protein, transthyretin (prealbumin), and B₂-microglobulin
 - Plasma cells are polyclonal.
- Electron microscopy:
 - Linear nonbranching fibrils varying in size from 50 to 150 Å in diameter, 7.5 to 10 nm in width
 - B-pleated sheet configuration

Differential Diagnosis

- Vocal cord nodules/polyps of the hyalinized type
- Lipoid proteinosis (hyalinosis cutis et mucosae):
 - Familial disorder possibly associated with autosomal recessive inheritance characterized by amorphous deposits of lipoprotein primarily in the skin and mucous membranes
 - Also known as Urbach-Wiethe disease
 - Clinical features include skin lesions, beady deposits under the eyelid margins, and intracranial (hippocampal gyrus) calcifications as seen by radiography.
 - Localized laryngeal involvement may occur, but more often widespread involvement is seen including the oral cavity and oropharynx.
 - Involvement of the larynx results in hoarseness or an abnormal cry (a common sign in infancy); dysphagia may also occur.
 - Multinodular growths may be seen in the laryngeal mucosa, which appear as a diffuse deposition of hyaline-like material in submucosal tissues by light microscopy.
 - Neutral and acid mucopolysaccharides can be demonstrated by special stains; amyloid stains are negative.
 - Endoscopic removal or tracheostomy may be necessary in cases attaining a large size, causing airway obstruction.

Treatment and Prognosis

Localized Amyloidosis

- Local endoscopic resection is usually curative.
- Persistent or recurrent local disease may occur and usually does so within 5 years of the initial treatment.

Systemic Amyloidosis

- Treatment is directed at limiting amyloid deposition by suppressing clonal proliferation of protein-producing cells:
 - Precursor-product concept is current basis of treatment aiming to decrease levels of precursor proteins in serum to normal or undetectable values, thereby stopping further growth of amyloid deposits:
 - Treatment for SAA is by complete suppression or eradication of the underlying chronic inflammatory disease.
 - Treatment for AL amyloidosis aimed at eradicating the underlying plasma cell dyscrasia by chemotherapy and returning the abnormally increased level of kappa or lambda free light chain in the blood to the normal range
 - Treatment for patients with hereditary ATTR amyloidosis has been liver transplantation with aim of removing source of 99% of the mutated TTR in the circulation:
 - Not always successful because ATTR amyloid sometimes progresses in the heart after liver transplantation
 - Treatment for patients with dialysis-associated amyloidosis is renal transplantation:
 - Amyloidosis seems to stabilize.
 - β_2 M serum levels decrease to normal.
 - Bone pain and stiffness decrease.
 - Cystic lesions do not increase further in size.
 - However, regression of amyloid deposits not reported
- Prognosis depends on the severity of organ involvement:
 - Median survival in patients with primary (systemic) amyloidosis is 1 to 2 years.
 - Survival rates are less in patients with multiple myeloma.
- Death is due to:
 - Organ failure (cardiac or renal)
 - Complications of multiple myeloma

Subglottic Stenosis (SS)

(Figs. 15-18 and 15-19)

Definition: Congenital or acquired, partial or complete narrowing of the laryngeal lumen.

Synonyms: Laryngotracheal stenosis; tracheal stenosis

Clinical

- Relatively rare condition with acquired stenosis more common than congenital stenosis
- No gender predilection; affects all age groups:
 - Idiopathic SS is more common in women than in men.
- Symptoms relate to airway obstruction and include:
 - Progressive respiratory difficulty, biphasic stridor, dyspnea, and air hunger
 - Other symptoms include hoarseness, abnormal cry, aphonia, dysphagia, and feeding abnormalities.
- In congenital stenosis, symptoms appear at or shortly after birth:
 - Congenital stenosis is the third most common laryngeal congenital disorder preceded by laryngomalacia and recurrent laryngeal nerve paralysis.
- In acquired stenosis, usually there is a history of trauma followed by a latent period of 1 month or longer prior to the manifestations of symptoms:
- Cause of acquired SS includes:
 - Trauma is most common cause:
 - Blunt or penetrating trauma, prolonged endotracheal intubation, endotracheal burns, post-surgical, postradiotherapy
 - Neoplasms (carcinoma, cartilaginous, fibrous and hematolymphoid [e.g., MALT lymphoma] neoplasms)
 - Infectious and/or inflammatory diseases:
 - Tuberculosis, syphilis, sarcoidosis, lupus erythematosus, granulomatosis with polyangiitis (formerly referred to as Wegener granulomatosis), relapsing polychondritis, amyloidosis
 - Laryngeal granulomatosis with polyangiitis:
 - Occurs much more frequently in women
 - Generally affects the larynx only when the disease already affects other more common sites (sinonasal tract, lungs, genitourinary system)
 - In active disease, elevated serum levels of antineutrophil cytoplasmic antibodies (C-ANCA) and proteinase 3
 - Even in absence of elevated ANCA levels, in presence of supporting histologic findings (e.g., geographic ischemic-type necrosis, vasculitis, mixed chronic inflammation, scattered multinucleated giant cells) diagnosis cannot be excluded
 - Chemical exposure
 - Idiopathic

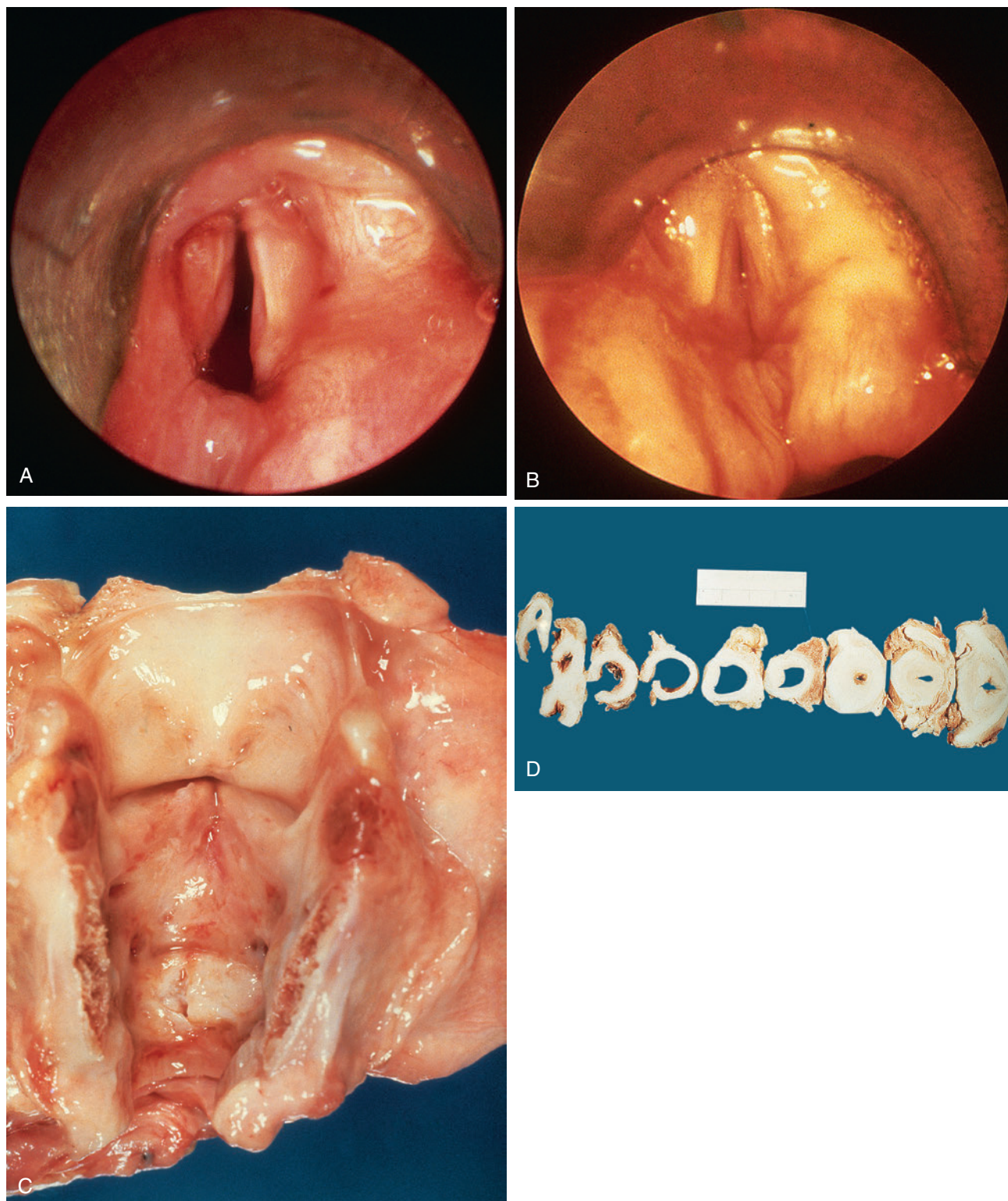


Fig. 15-18. Subglottic stenosis.

Subglottic stenosis resulting in (A) partial narrowing of the endolaryngeal luminal diameter; (B) complete narrowing of the endolaryngeal lumen; (C) laryngectomy in which a tan-white mass bulging into the endolaryngeal lumen at the lower subglottic region is identified; (D) resection specimen showing progressive narrowing (*left to right*) of the endolaryngeal lumen.

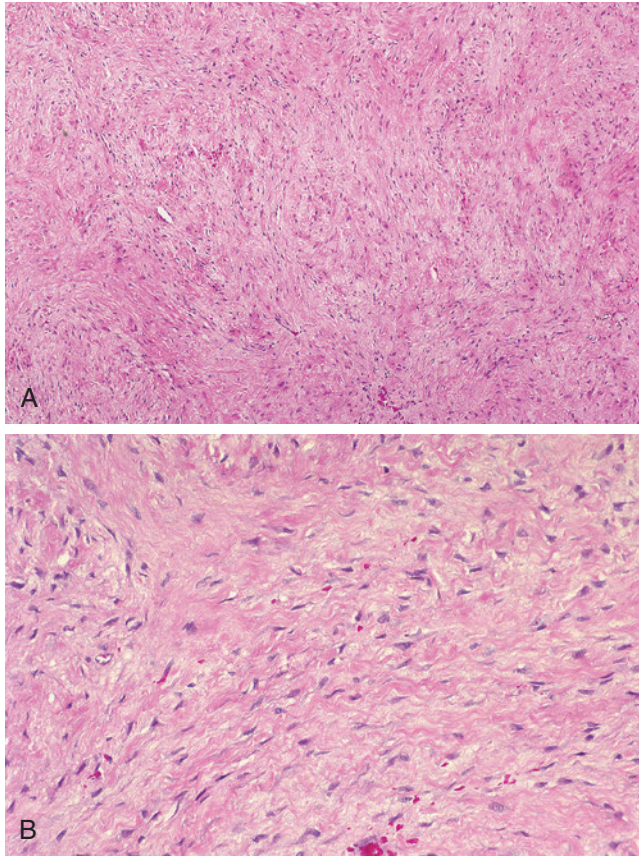


Fig. 15-19. Histology of SS.

Despite the impressive clinical picture of subglottic stenosis, the histology is remarkably bland as seen by the presence of a variably cellular fibroblastic proliferation with associated collagenized stroma.

- In children and adults, trauma is most common cause of stenosis.
- Complete physical evaluation of the entire upper aerodigestive tract is indicated to rule out separate congenital anomalies or other acquired injuries:
 - Concomitant pseudotumor of the orbit may occur in association with idiopathic subglottic stenosis.
 - Both lesions display identical histologic features.

Pathology

Gross

- Partial or complete narrowing of the endolaryngeal luminal diameter:
 - Tendency for process to be circumferential
 - Stenosis tends to begin just below the true vocal cord with progressive narrowing toward the cricoid cartilage.
 - Maximum stenosis tends to occur at the level of the cricoid cartilage and upper trachea.
- Depending on the cause a mucosal or submucosal mass or submucosal bulging may be seen.

Histology

- Histologic picture dependent on the cause of the stenosis:
 - In idiopathic stenosis:
 - Submucosal fibrous proliferation with associated nonspecific chronic inflammation
 - Fibrosis tends to be dense (keloid type) and hypocellular.
 - Cellular component includes spindle-shaped fibroblasts.
 - Variable chronic inflammatory cell infiltrate is present.
 - Overlying epithelium unchanged or may show squamous metaplasia
 - Histologic picture is similar to that of fibromatosis identified in the sinonasal tract and may, in fact, represent the same pathologic process.
 - Infections:
 - Granulomatous inflammation may be present.
 - Microorganisms may be identified.
 - Sarcoidosis:
 - Noncaseating granulomatous inflammation

Differential Diagnosis

- Infectious disease(s)
- Collagen vascular disease(s)
- Neoplasms

Treatment and Prognosis

- Treatment is based on the age of the patient, degree of stenosis, and underlying pathology.
- In general, cases of acquired stenosis initially require tracheotomy to establish an airway followed by endoscopic dilatation, laser excision, or external surgical (open excision with reconstruction) management.
- Prognosis is dependent on multiple factors with the etiology probably the most important:
 - Congenital subglottic stenosis is less severe than acquired types and many patients outgrow their condition, making surgical reconstruction often unnecessary with management by conservative methods.
- Subglottic stenosis remains a treatment challenge:
 - Patients often symptomatically improved after endoscopic dilation but recurrence rates remain high.

Teflon Granuloma

(Figs. 15-20 through 15-22)

Definition: Foreign body granulomatous reaction to extravasation of injected Teflon used in the treatment of vocal cord paralysis.

Synonym: Teflonoma

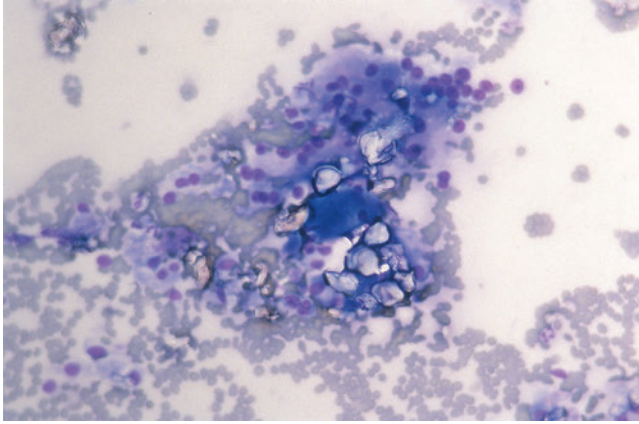


Fig. 15-20. Aspirated foreign material.

Fine-needle aspiration biopsy of a neck mass in a patient with past history of Teflon injection shows the presence of giant cells with associated glassy-appearing foreign material.

- Intracordal fluorocarbon (Teflon; polytef) injection has been used for decades to correct paralytic dysphonia, a result of unilateral laryngeal paralysis.
- Vocal cord paralysis, treated by Teflon injection, may be caused by primary laryngeal carcinoma or metastatic carcinoma (e.g., breast, lung) involving the recurrent laryngeal nerve, surgical trauma to the recurrent laryngeal nerve, or postviral neuritis.
- Cord paralysis may result in aspiration problems secondary to open glottic incompetence during deglutition, an ineffective cough, and poor voice production.
- To correct these deficits and restore glottic competence intracordal injection of Teflon paste is used as the preferred treatment.
- Injection of Teflon paste into the vocal cord causes a localized foreign body reaction walled off by surrounding fibrosis:
 - Teflon swells the paralyzed vocal cord and brings it nearer to the midline so that the functioning vocal cord can more easily approximate it and effectively close the glottis, thereby alleviating the resulting symptoms.
- Infrequently, Teflon extravasates and infiltrates into the soft tissues of the neck and larynx; depending on the error, Teflon paste:
 - May be deposited through the cricothyroid space and outside the larynx, resulting in a neck mass
 - Be placed between the mucosa and the conus elasticus causing a subglottic bulge
 - May infiltrate into the vocalis portion of the medial thyroarytenoideus muscle, causing immobilization of this area rather than medial displacement of the vocal cord

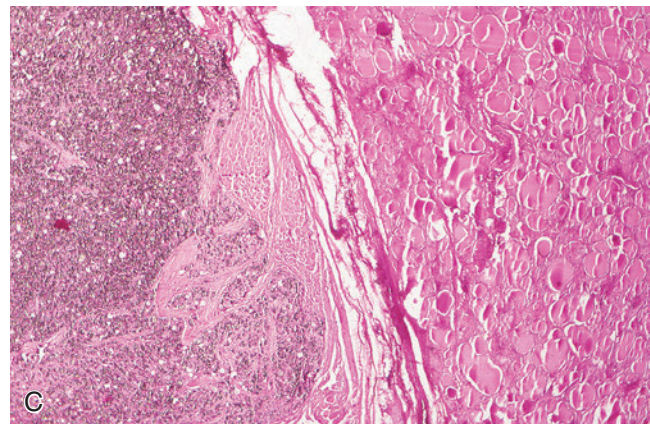
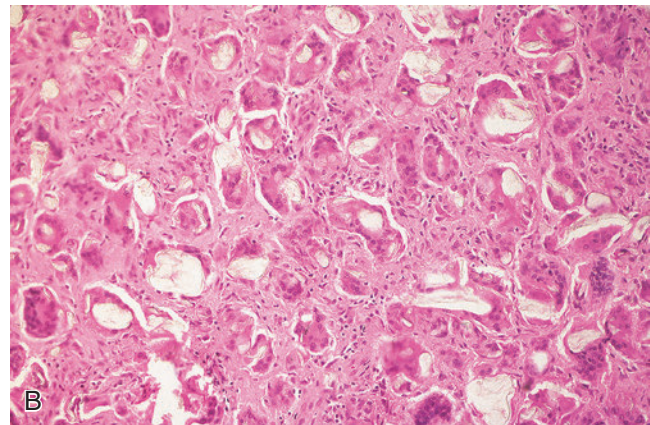
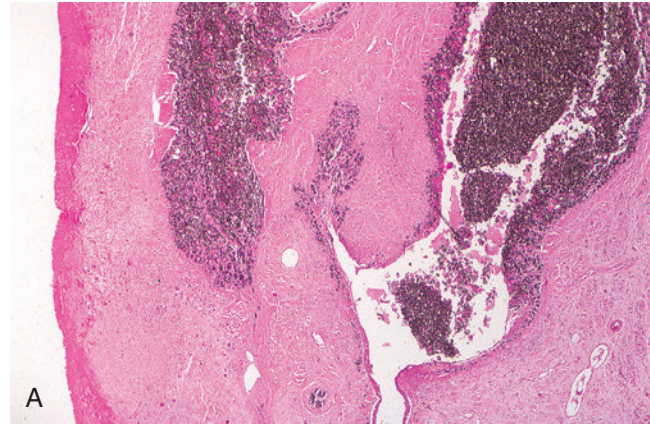


Fig. 15-21. Histology of Teflon granuloma.

The histologic features of Teflon granuloma include (A) submucosal deposition/accumulation of foreign (glassy appearing) material in the vocal cord; (B) associated foreign-body giant cell reaction; (C) extension to the soft tissues (i.e., skeletal muscle) of the neck region (*left*).

- Resulting iatrogenically induced mass may clinically be mistaken for a neoplastic process.

Clinical

- Use of Teflon to correct vocal cord paralysis is generally limited to the adult population; therefore the

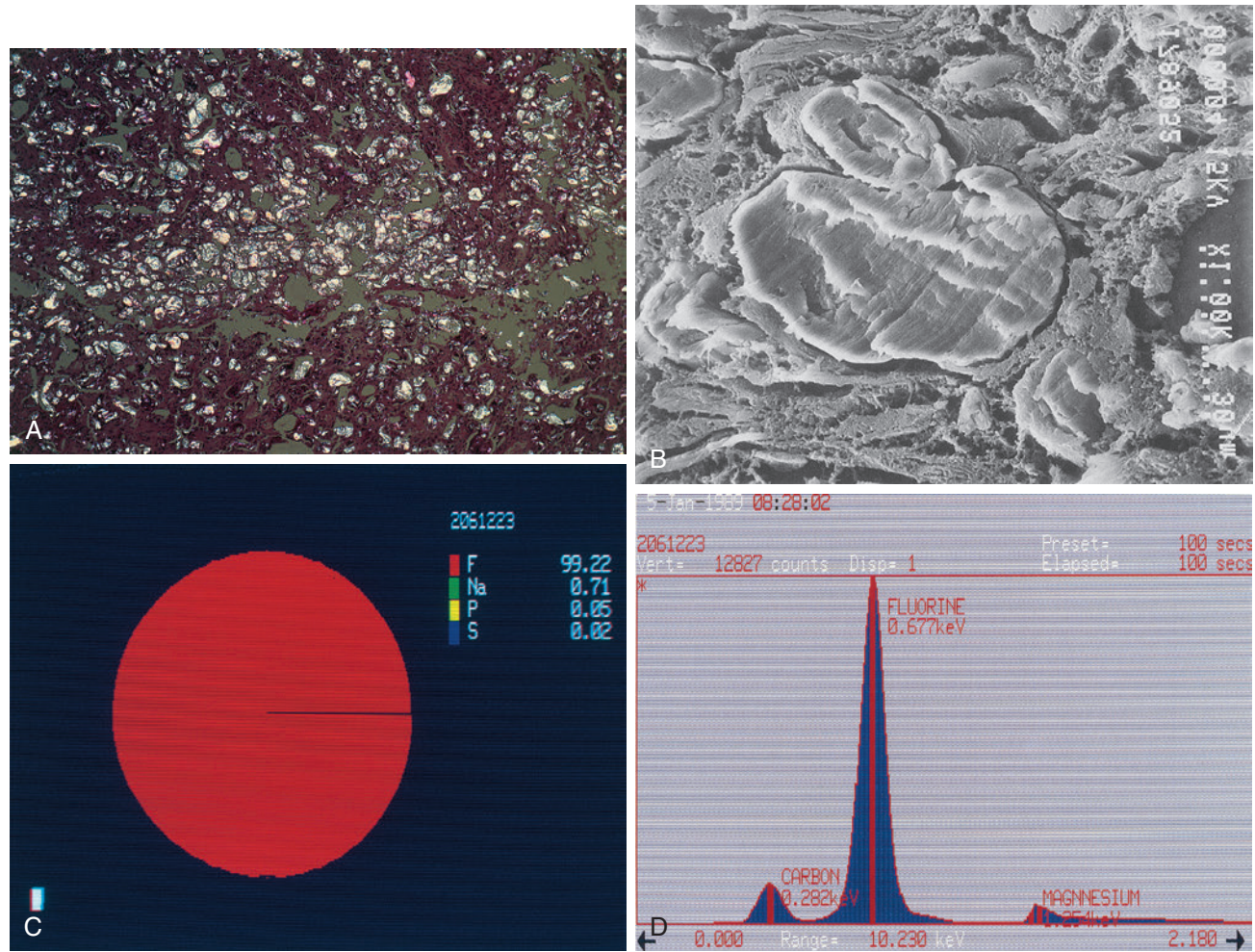


Fig. 15-22. Properties of Teflon.

The Teflon material is (A) birefringent under polarized light; (B) appears “flake-like” by scanning electron microscopy; (C) virtually entirely of fluorocarbon derivation as determined by infrared absorptive spectrophotometry (IAS), and (D) unequivocally identified by the presence of a major peak for fluorine at 0.68 keV by energy-dispersive x-ray analysis (EDXA).

development of a “teflonoma” is almost always seen in adults.

- No gender predilection
- Symptoms related to extravasation of the Teflon include a neck mass, airway obstruction, or persistent hoarseness:
 - Symptoms may manifest from as short as a month after injection to as late as many years (decade or more) after injection.
- Positron emission tomography with ^{18}F -fluorodeoxyglucose (^{18}F FDG) may show increased (false-positive) uptake, suggesting the presence of a malignant neoplasm.

Pathology

Gross

- In the larynx, tumors may appear as polypoid lesions within the submucosal compartment of the vocal

cord area or may be well-delineated, firm masses when identified in the soft tissues of the neck.

- Lesions vary from a few millimeters to 2 cm.

Fine-Needle Aspiration Biopsy

- Diagnosis can be made by fine-needle aspiration smears, which show clusters of giant cells with associated glassy-appearing foreign material.

Histology

- Submucosal or soft tissue foreign body giant cell reaction
- In vocal cord region:
 - Foreign body giant cell reaction is submucosal with extension to underlying muscle and cartilage.

- In neck:
 - Foreign body reaction can infiltrate into all soft tissue structures, including skeletal muscle, and can involve the thyroid gland.
- A glassy-appearing material is seen within the multinucleated giant cells:
 - Material is birefringent under polarized light.
- Special analysis
 - Adjuncts to conventional light microscopic analysis include evaluation by scanning electron microscopy (SEM), infrared absorptive spectrophotometry (IAS), and energy dispersive X-ray analysis (EDXA):
 - SEM shows a nonspecific “flake-like” appearance to the foreign material.
 - IAS and EDXA demonstrate the foreign material to be of fluorocarbon derivation.
 - The infrared spectrum of polytetrafluoroethylene (PTFE) exhibits a pair of intense bands in the 8- to 9-micron region in which the C-F bonds strongly absorb.
 - EDXA allows for unequivocal identification of Teflon in the tissue sections as seen by the major peak for fluorine at 0.68 keV.

Treatment and Prognosis

- Because Teflon is a permanent implant that is not absorbed, surgical resection remains the only way to remove the Teflon-induced granulomatous reaction.
- Once excised, patients experience improvement or disappearance of all related symptoms.
- Results of intracordal Teflon injection for vocal cord paralysis, in general, have been excellent with minimal complications.
- Teflon injection remains the preferred treatment in a select group of patients for alleviation of the symptoms associated with intractable unilateral vocal cord paralysis; although this is a safe and beneficial procedure, it may infrequently be associated with complications, the results of which may clinically mimic a neoplasm.

Tracheopathia Osteoplastica (TPO) (Figs. 15-23 and 15-24)

Definition: Segmental degenerative disorder of the tracheobronchial tree characterized by multiple, variable-sized submucosal osseous (and cartilaginous) nodules that may result in respiratory obstruction.

Synonym: Tracheobronchiopathia osteochondroplastica

- In contrast to aging larynx, in which there is often calcification of laryngeal cartilage, the tracheal cartilage does not calcify as readily and thereby retains its flexibility and functional integrity.

Clinical

- Uncommon disorder
- More common in men than in women; usually occurs in individuals over 50 years of age
- Patients may present with chronic cough, hemoptysis, dyspnea, stridor, and pulmonary infections; non-specific signs and symptoms may be present.
- There is an overall rigidity to the trachea.
- Endoscopically, irregular submucosal nodules can be seen protruding into the tracheal lumen:
 - Prominent sites of occurrence include the lower two thirds of the trachea and occasionally in the cervical trachea.
 - Posterior tracheal wall tends to be spared.
- Endoscopic appearance of multiple submucosal nodules often is diagnostic but an isolated or localized submucosal mass may be present, which can be clinically considered to represent a neoplasm resulting in tissue sampling:
 - Diagnosis confirmed by pathologic examination (see below)
- Radiology:
 - Sometimes the radiographic appearance demonstrates calcifications if there has been ossification within the nodules.
 - CT scan can reveal nodular thickening and irregularity of the anterior and lateral walls of the trachea; small calcified nodules along the inner aspect of the tracheal cartilage can be identified protruding into the tracheal lumen.
- Cause can possibly be linked to:
 - Chronic inflammation:
 - Many cases occur in patients with chronic inflammatory conditions, suggesting chronic inflammation as a possible cause.
 - Trauma
 - Suggestion that it is end stage of tracheal amyloidosis but there is no support for this contention

Pathology

Histology

- Submucosal irregular bony nodules with thin lamellar bony walls and fatty marrow:
 - Hematopoietic elements are not usually present.
 - Cartilage may be present in the nodules:
 - Calcifications may be present and usually are seen in limited (small) foci; rarely, extensive calcification is present.
- Continuity between the osseous or cartilaginous nodules with the tracheal cartilage may or may not be identified:
 - Absence of continuity has prompted the suggestion that the nodules are exostoses.
 - Continuity has prompted the suggestion that the nodules are metaplastic.

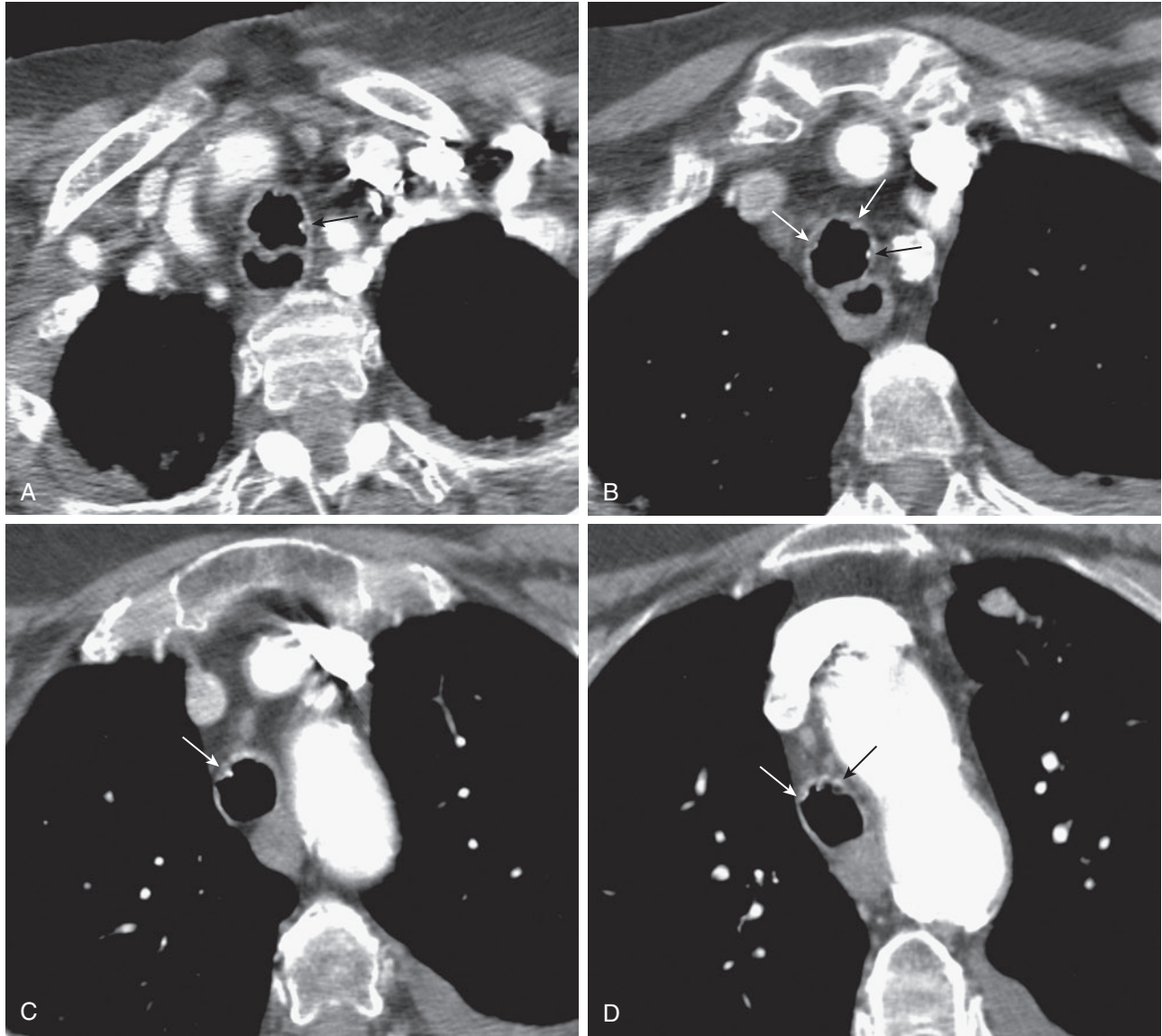


Fig. 15-23. Tracheopathia osteochondroplastica.

Contrast-enhanced axial images from a CT scan of the thorax demonstrate multiple osseous nodules and thickening of the anterior and lateral walls of the trachea (*arrows*), with sparing of the posterior membranous tracheal wall. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 32-31, p 2069.)

- The overlying mucosa is intact and may appear normal or metaplastic.
- Patients with significant narrowing may require laser removal and dilatation.

Differential Diagnosis

- Laryngeal myositis ossificans:
 - Zonal phenomenon of a highly cellular inner zone with a well-formed bone in the outer zone helps to distinguish this lesion from tracheopathia osteoplastica.
- Spindle cell squamous carcinoma

Treatment and Prognosis

- Localized disease may not require treatment.

Infectious Diseases of the Larynx and Trachea (Figs. 15-25 and 15-26)

- Larynx and trachea are subject to a wide variety of infectious disease, including bacterial, mycobacterial, viral, fungal, protozoal, and other infections.
- For a more complete discussion on specific microorganisms, see Section 1, Sinonasal Tract and Section 2, Oral Cavity.

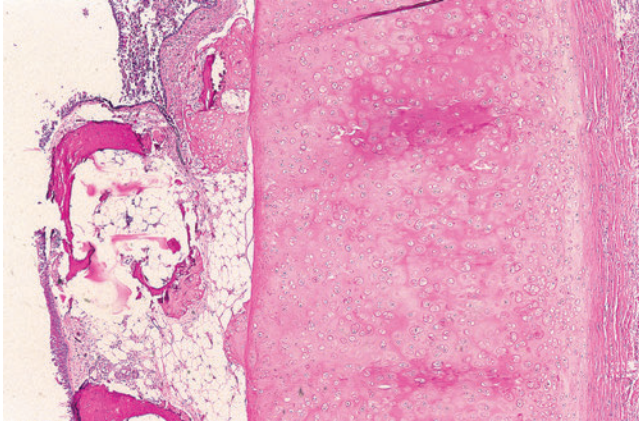


Fig. 15-24. Histology of TPO.

Tracheopathia osteoplastica showing submucosal cartilaginous nodules with associated ossification. One of the nodules is in continuity with the underlying tracheal cartilage.

- This section provides a general overview of select infectious diseases.
- Acute laryngitis:
 - Designation used for an inflammatory disorder of usually short duration, lasting hours to days and affecting an otherwise healthy patient
 - Infectious causes are usually viral and bacterial.
 - Early in the disease course there is edema, a function of increased vascular dilatation, increased blood flow, and vascular stasis, resulting in increased vascular permeability and subsequent edema.
 - Larynx appears erythematous and there is associated pain
 - Acute viral laryngitis:
 - Usually result of viral inflammation of the upper respiratory tract
 - Rhinovirus and influenza virus are common (but not the only) pathogens.
 - Usually associated with other respiratory symptoms, including coryza, rhinorrhea, cough
 - Sore throat may herald the presence of pharyngitis and laryngitis.
 - Symptoms include voice changes, fever, pain on swallowing:
 - Onset of voice changes often delayed
 - Voice quality worse during resolution stages
 - Fever is low grade.
 - Vocal symptoms usually clear within 4 to 6 days, except in the immunocompromised patient, in whom acute laryngitis may persist and become chronic laryngitis:
 - Herpes simplex virus may be the cause of chronic laryngitis in this setting.



Fig. 15-25. Acute epiglottitis.

Postmortem specimen of acute epiglottitis in a pediatric patient showing the epiglottis, normally a well-defined structure, appearing beefy red and edematous with a rounded, thumb-like appearance.

- Most patients with viral laryngitis have a self-limiting course.
- Prognosis for return of voice is excellent.
- Acute bacterial (suppurative) epiglottitis:
 - Inflammation of epiglottitis caused by bacteria *Haemophilus influenzae*
 - Typically a pediatric-related disease referred to as pediatric epiglottitis or supraglottitis
 - Patients have high fever and epiglottitis.
 - May involve entire supraglottis but most often involves epiglottis and aryepiglottic folds
 - Epiglottis normally a well-defined structures appears cherry-red, edematous, enlarged, and less well-defined with a rounded, thumb-like density:
 - Edema may encroach on the vallecula and may rarely extend to the posterior pharyngeal wall.

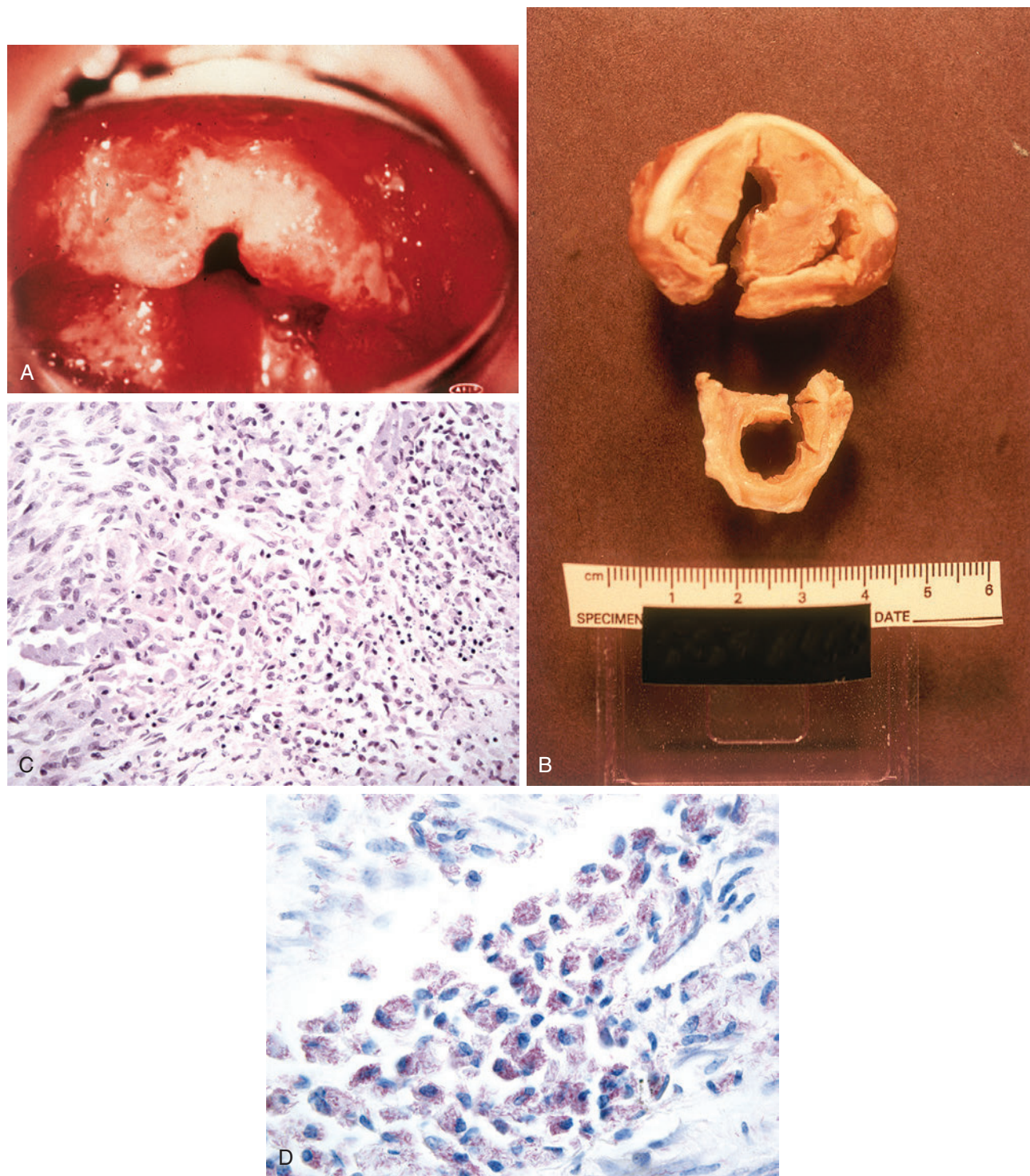


Fig. 15-26. Mycobacterial laryngitis.

A, Endoscopic appearance of mycobacterial laryngitis in which the lesion has a granular, white appearance. **B**, Postmortem sections of the larynx in an immunocompromised patient with disseminated mycobacterial disease, including laryngeal involvement appearing as circumferential submucosal thickening. **C**, Histologically, there is diffuse infiltration of the laryngeal submucosa by vacuolated histiocytes rather than the classic caseating granulomas with multinucleated giant cells seen in immune-competent patients. **D**, Numerous mycobacteria are present within the vacuolated histiocytes (acid fast bacilli [AFB] staining; oil immersion).

- Hypopharynx, including the piriform sinus, may be involved.
- Subglottic extension and narrowing may rarely occur, particularly in children.
- May progress to airway compromise and require emergency airway management
- Supraglottitis in adults is usually different from that of children:
 - Most adults with supraglottitis do not develop airway obstruction typical of *Haemophilus influenzae* infection; rather the clinical presentation is mild with a benign course and with no definable pathogen.
 - A minority of adults may have a fulminant clinical course with acute respiratory compromise and blood cultures positive for *Haemophilus influenzae*.
- Infections associated with chronic laryngitis may include fungi, bacteria, viruses, and protozoa:
 - Fungal chronic laryngitis may include infection with *Candida*, *Blastomyces*, *Cryptococcus*, *Histoplasma*.
 - May be associated with pseudoepitheliomatous hyperplasia
 - Bacterial chronic laryngitis may include *Staphylococcus*, *Treponema pallidum*
 - *Helicobacter pylori* (HP) may be associated with chronic laryngitis as well as vocal fold minimal lesions (e.g., polyps, nodules, contact ulcers).
 - HP can be detected by immunohistochemical staining or reverse transcriptase polymerase chain reaction (RT-PCR).
 - Mycobacterial chronic laryngitis includes *M. tuberculosis* and atypical mycobacteria:
 - In immune intact patient the inflammatory reaction includes granulomatous inflammation with necrosis.
 - In immunocompromised patients unable to mount a granulomatous response there is a diffuse infiltration by vacuolated histiocytes, which contain the acid-fast microorganisms; mature lymphocytes and plasma cells may be present.
 - Viral chronic laryngitis may be caused by herpes simplex virus and cytomegalovirus.
 - Protozoa that may infect the larynx include *Leishmania* and *Trichinella* species.
- Other diseases that may be associated with chronic laryngitis include:
 - Sarcoidosis, a disease of uncertain cause, may also occur in the larynx and trachea and is associated with a noncaseating granulomatous inflammation (see Section 4, Pharynx).
 - Autoimmune diseases and connective tissue diseases, including:
 - Granulomatosis with polyangiitis (see above under [Subglottic Stenosis](#)):
 - Predilects to women
 - Tends to be localized to the subglottic region
 - Associated with elevated c-ANCA levels
 - Rheumatoid arthritis:
 - Laryngeal involvement is uncommon.
 - Most often involves the cricoarytenoid; less often the cricothyroid joint
 - Cricothyroid arthritis is usually bilateral.
 - Rheumatoid nodules develop in approximately 25% of patients with rheumatoid arthritis.
 - Nodules typically involve the true vocal cords; other sites of involvement may include the false vocal cords, epiglottis, or soft tissues around the cricoarytenoid joint.
 - Patients present with hoarseness, dysphonia, and dysphagia.
 - In acute phase of laryngeal involvement there may be inflammation, joint effusion, and a synovial proliferation.
 - Over time, joint destruction and ankylosis may develop.
 - Nodules are soft and often appear yellow.
 - Histologically, rheumatoid nodules are located within the submucosa and include the presence of granulomas characterized by fibrinoid necrosis of collagen surrounded by palisading histiocytes with associated fibrosis and inflammatory cells.
 - Surgical intervention (i.e., tracheotomy) may be required in the presence of ankylosis of the joints that may result in airway compromise.
 - Relapsing polychondritis (see Section 7, Ear and Temporal Bone)
 - Systemic lupus erythematosus
 - Sjögren syndrome:
 - Individuals with Sjögren syndrome predisposed to laryngopharyngeal reflux
 - High index of suspicion for laryngopharyngeal reflux should be maintained in all individuals with Sjögren syndrome.
 - Other systemic diseases that may involve the larynx include:
 - Crohn disease, IgG4-related disease, Rosai-Dorfman disease, others
 - Cutaneous-type dermatoses of the larynx may include:
 - Pemphigoid, pemphigus, epidermolysis bullosa, Darier disease (keratosis follicularis), Stevens-Johnson syndrome

Necrotizing Sialometaplasia

(Fig. 15-27)

- Represents benign, self-healing (reactive) inflammatory process of salivary gland tissue that clinically and histologically may be mistaken for a malignant neoplasm
- For a more complete discussion see Section 6, Salivary Glands.
- Most commonly involves the intraoral minor salivary glands particularly involving the palate; however, major salivary glands, as well as the minor salivary glands of virtually every site in the upper aerodigestive tract can be affected.
- Larynx and trachea may rarely be affected.
- Pathogenesis felt to be iatrogenically induced after an operative procedure, trauma, or radiotherapy:
 - Inciting event primarily but not exclusively thought to be due to ischemia
 - Mean duration of 18 days from the time of the insult to the development of lesion
- May occur de novo unassociated with a traumatic event or it may occur in association with a neoplasm (benign or malignant)
- Self-limiting usually healing by secondary intention:
 - Depending on the size of the lesion, the healing process in most cases occurs from 3 to 12 weeks.

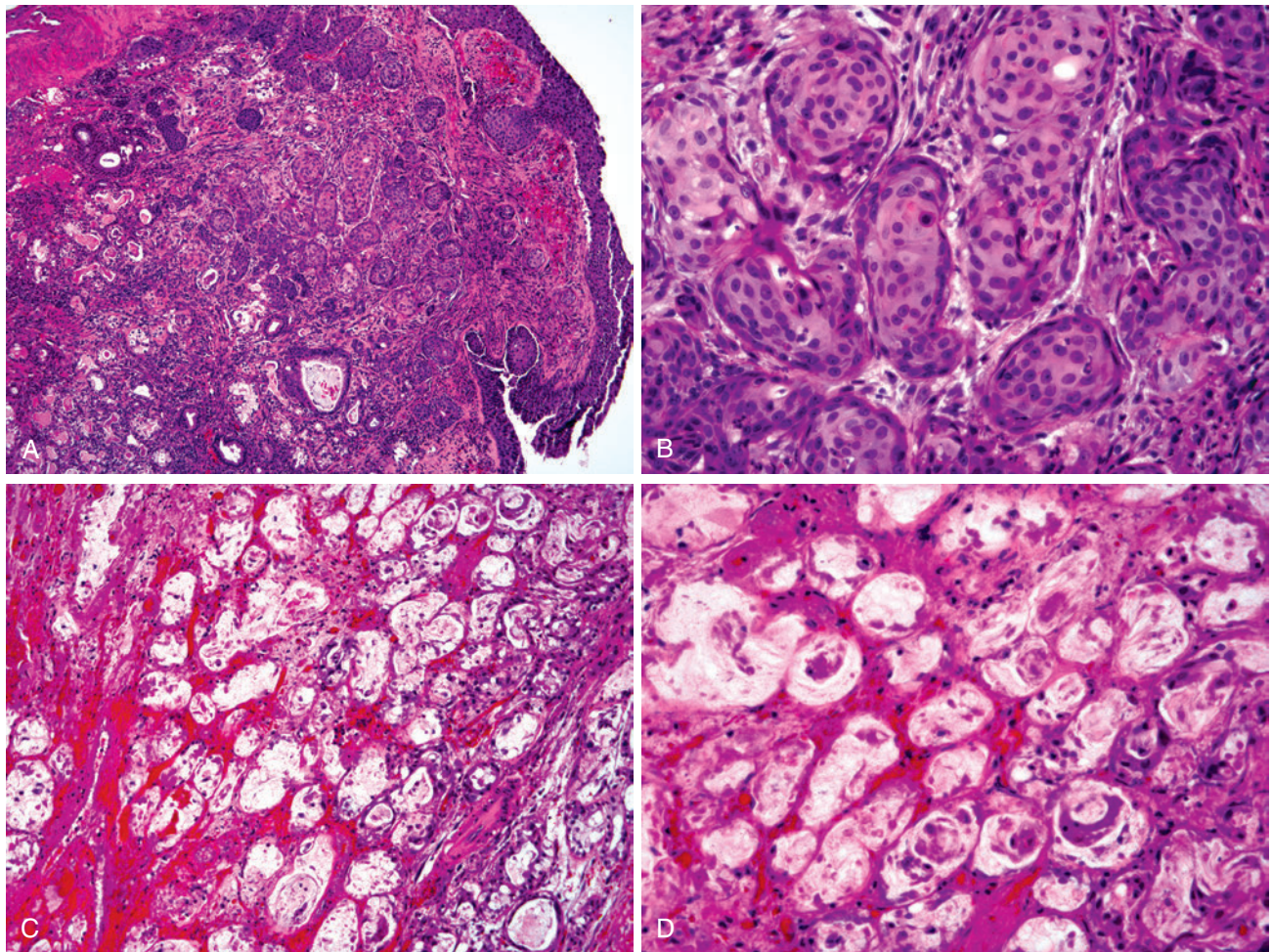


Fig. 15-27. Laryngeal necrotizing sialometaplasia.

A, Necrotizing sialometaplasia of the supraglottic larynx characterized by the presence of submucosal rounded nests with preservation of the lobular architecture of seromucous glands; squamous metaplasia of the overlying epithelium is present. **B**, At higher magnification the sialometaplastic changes include replacement of the normal seromucous glands by benign squamous epithelium; the sialometaplastic nests are round with smooth contours. **C** and **D**, Foci of necrotic lobules showing retention of the rounded architecture of glands with complete necrosis of the epithelial components.

- Debridement and saline rinses may aid in the healing process.
- Recurrences do not usually occur.

Radiation-Associated Changes

(Fig. 15-28)

- Radiation-associated injury to the upper aerodigestive tract (UADT), including the larynx (and pharynx), is fairly common owing to the use of radiation treatment as primary therapy for mucosal-based carcinomas, especially squamous cell carcinoma, of these sites.

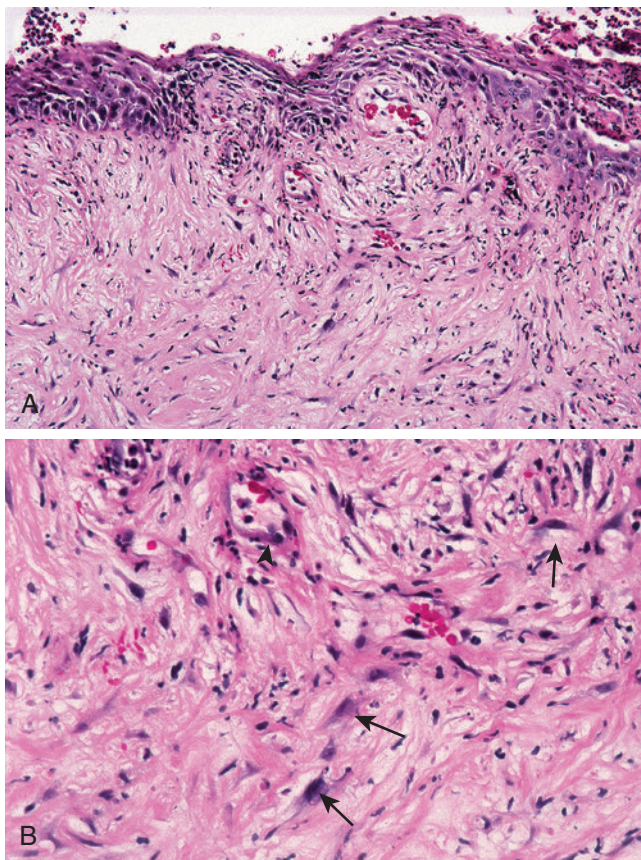


Fig. 15-28. Radiation-associated changes.

Chronic radiation-associated alterations of the laryngeal mucosa may include (A) thinning and reactive atypia of the surface squamous epithelium with submucosal stromal edema, telangiectatic capillaries showing the presence of prominent (plump) endothelial cells, and scattered individual atypical appearing fibroblasts; (B) at higher magnification, the atypical fibroblasts (arrows) have “smudged”-appearing nuclei and an absence of cohesive cellular groupings; these findings assist in distinguishing radiation change from (residual/recurrent) squamous cell carcinoma.

- Radiation injury to mucosal sites includes alterations in the surface epithelium, minor salivary glands, fibroblasts, skeletal muscle, and endothelial cells.
- Radiation-induced changes may be acute or chronic:
 - Acute changes occur from days to weeks (usually 6 weeks) after treatment.
 - Chronic changes are seen from 6 to 7 weeks after therapy to years later.
- Biopsies are taken after radiation therapy to primarily exclude the possibility of (recurrent) carcinoma:
 - Not uncommonly, may be requested as an intra-operative consultation (i.e., frozen section)
- Postradiation histomorphologic alterations include:
 - Acute postirradiation phase (days to weeks) biopsies are seldom obtained:
 - Degeneration and focal necrosis of basal zone epithelium
 - Submucosal edema with dilation of capillaries and associated swelling of endothelial cells
 - Glandular and acini distention containing mucus
 - Superficial erosions with pseudomembranes (3 to 4 weeks postradiation)
 - Approximately 1 month after initiation of therapy squamous epithelium usually shows complete restoration although thinner than normal.
 - Chronic postirradiation histologic changes are variable and may include:
 - Thinner-than-normal surface epithelium
 - Surface ulceration
 - Squamous epithelial atypia; may be so pronounced as to suggest carcinoma but in the chronic postirradiation phase most such examples are usually not indicative of carcinoma
 - Atrophy of minor salivary gland acini
 - Squamous metaplasia (sialometaplasia) of minor salivary glands:
 - May include marked cytologic atypia, suggesting a possible diagnosis of squamous cell carcinoma
 - In contrast to invasive squamous cell carcinoma that typically results in effacement of lobular architecture of minor salivary glands, retention of the lobulated outline of the minor salivary glands supports a diagnosis of sialometaplasia.
 - Submucosal fibrosis
 - Vascular alterations characterized by telangiectatic capillaries often with prominent (plump) endothelial cells, myointimal proliferation, foamy histiocytes within the intima, and thrombosis
 - Atypical (bizarre) fibroblasts:
 - Generally appear as individual cells with “smudged”-appearing nuclei in association

with other histologic alterations of radiation changes

- Absence of cohesive cellular grouping as may be seen in invasive carcinoma
- Immunohistochemical staining for epithelial markers (e.g., cytokeratins, p63, others) may be required to differentiate squamous cell carcinoma (positive staining) from radiation-induced atypical fibroblasts (negative staining)
- Bizarre striated muscle degeneration
- For a more complete discussion of radiation-related injury see Section 2, Oral Cavity.

LARYNGEAL BENIGN (NON-NEOPLASTIC) EPITHELIAL CHANGES (Figs. 15-29 through 15-32)

Benign epithelial changes include clinical and histopathologic terms, including:

Clinical terms:

- Leukoplakia:
 - Any white lesion on a mucous membrane
 - Associated with increased risk of underlying significant dysplasia but not necessarily indicative of underlying significant dysplasia (i.e., moderate or severe) or carcinoma
- Erythroplakia:
 - Any red lesion on a mucous membrane
 - Often indicative of an underlying significant dysplasia (i.e., moderate or severe) or carcinoma
- Speckled erythroplakia:
 - Mixed red and white lesion on a mucous membrane
 - Often indicative of an underlying significant dysplasia (i.e., moderate or severe) or carcinoma

Histopathologic terms:

- Hyperplasia:
 - Thickening of an epithelial surface as a result of an absolute increase in the number of cells
- Pseudoepitheliomatous hyperplasia (PEH):
 - Exuberant reactive or reparative overgrowth of squamous epithelium (hyperplasia) displaying no cytologic evidence of malignancy:
 - May be mistaken for an invasive squamous cell carcinoma
 - May be seen in association with certain tumors (e.g., granular cell tumor) or in setting of an infectious disease (e.g., fungus, others)
- Keratosis:
 - Abnormal presence and/or excessive keratin on an epithelial surface
 - Use of the term *hyperkeratosis* is redundant and unnecessary as it applies to the larynx because

under normal conditions the resting laryngeal epithelium is nonkeratinizing.

- Parakeratosis:
 - Presence of nuclei in keratin layer
- Orthokeratosis:
 - Absence of nuclei in keratin layer
- Dyskeratosis:
 - Abnormal keratinization of epithelial cells
 - Applies to cells located away from the superficial aspects of the surface epithelium
- Ulceration:
 - Erosion and/or loss of the surface epithelium
- Metaplasia:
 - Change from one histologic tissue type to another and generally occurs as a result of tissue insult or injury
- Koilocytosis
 - Descriptive term for cytoplasmic vacuolization of squamous cells
 - Morphologic change suggestive of viral (human papillomavirus) infection
- Atypia:
 - Vague term that has been liberally used spanning alterations, including those that are reactive as well as those that are dysplastic
 - In the presence of bona fide dysplastic changes, preference should be to use the designation dysplasia rather than atypia to exclude reactive changes typically not requiring further therapy and to indicate potentially irreversible cytomorphic findings typically requiring additional therapy
- Above morphologic changes may be identified in an array of pathologic lesions and are not necessarily specific for any single disease (Table 15-1).

Histomorphologic changes in a malignant (irreversible) direction include:

- Dysplasia:
 - Abnormal maturation and cellular aberrations
 - Graded as mild, moderate, or severe
- Carcinoma in situ (CIS):
 - Full-thickness intraepithelial dysplastic change in the presence of an intact basement membrane
 - Any violation of the basement by dysplastic cells generally equates to invasive carcinoma.
 - Involvement of seromucous glands by dysplastic cells represents extension of the intraepithelial dysplasia and not invasive carcinoma.
- Superficially invasive or microinvasive (squamous cell) carcinoma
 - Squamous carcinoma in which there is violation of the basement membrane with invasion into the underlying stroma:
 - No clear definition of what constitutes invasion with some authorities advocating invasion to no greater than 0.5 mm as measured from

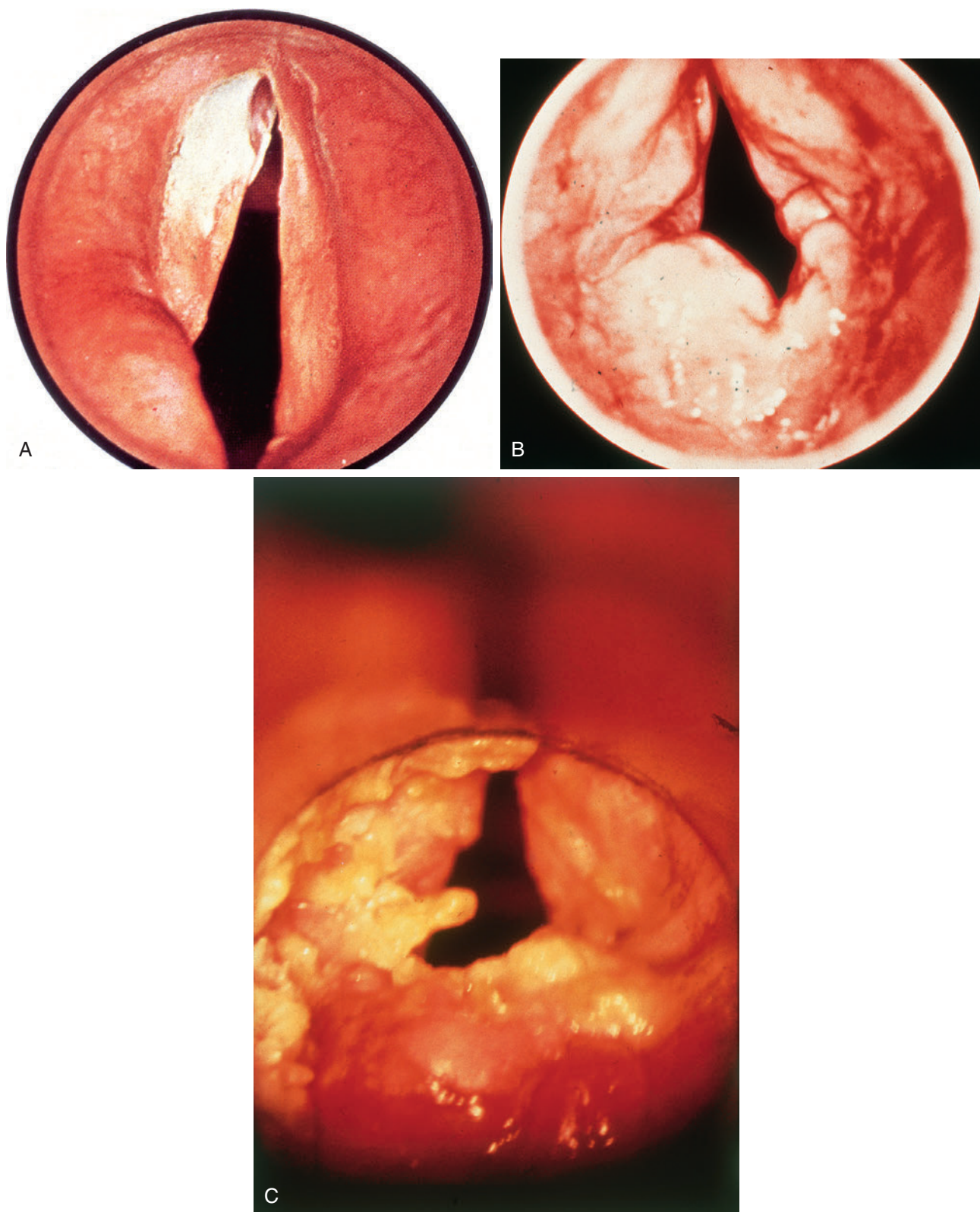


Fig. 15-29. Laryngeal leukoplakia.

A, Focal flat, white lesion along the anterior true vocal cord. **B**, In contrast to the previous example this lesion is raised and more diffuse in its extent (pachyderma larynges). **C**, Another example of laryngeal leukoplakia with a papillary or verrucoid appearance.

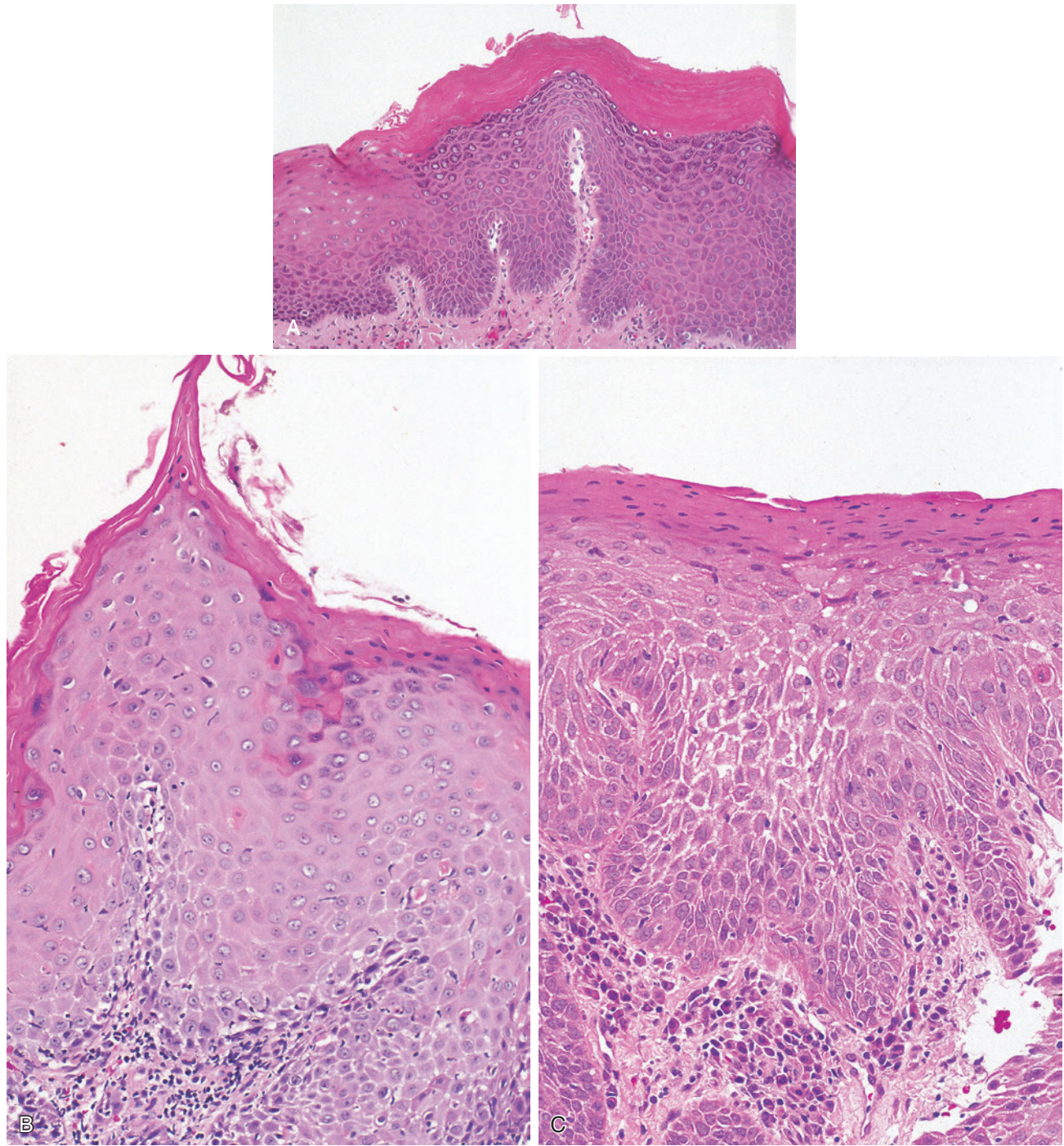


Fig. 15-30. Laryngeal keratosis without dysplasia.

A, Orthokeratotic epithelium with hypergranulosis. **B**, Papillary or verrucoid keratosis with parakeratosis. **C**, Flat keratosis with parakeratosis. All of these examples show irregular epithelial hyperplasia without dysplasia. A variable chronic inflammatory cell reaction is seen in the submucosa.

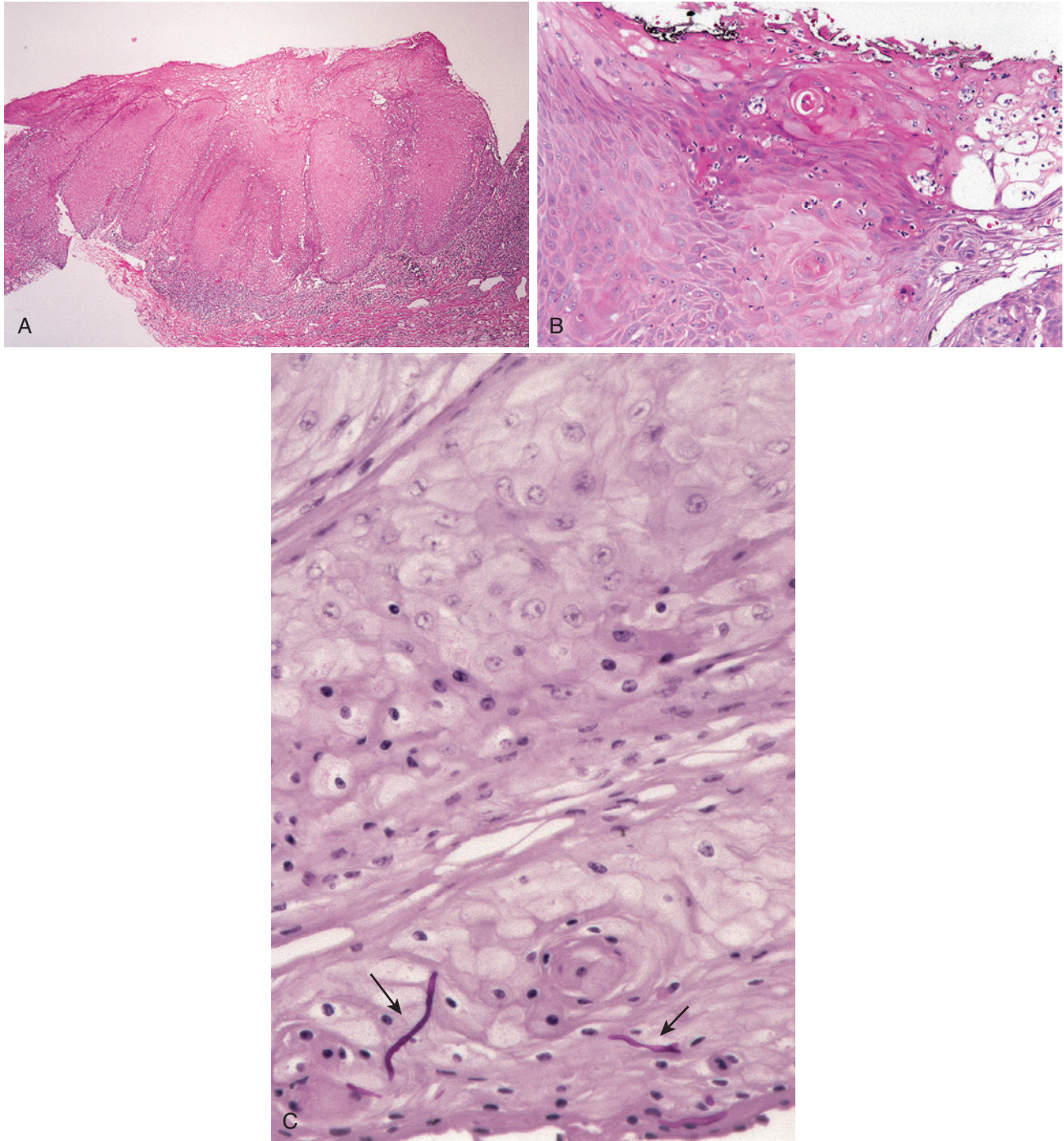


Fig. 15-31. Pseudoepitheliomatous hyperplasia due to fungal infection.

This laryngeal leukoplakic lesion was clinical suspicious for a carcinoma. **A**, At low magnification there is a keratotic epithelial proliferation with downward extension of the rete pegs, raising concern for a possible diagnosis of carcinoma. **B**, At higher magnification there is dyskeratosis, as well as neutrophilic infiltrate along the surface epithelium and within the deeper epithelial layers. **C**, Periodic acid Schiff staining shows the presence of fungal hyphae within the depth of the epithelium indicative of fungal (*Candida*) infestation with secondary pseudoepitheliomatous hyperplasia. In contrast, fungal colonization may or may not have associated neutrophilic infiltrate, but the fungal forms (spores and hyphae) are limited to the surface and/or superficial squamous epithelium rather than within the depth of the surface epithelium.

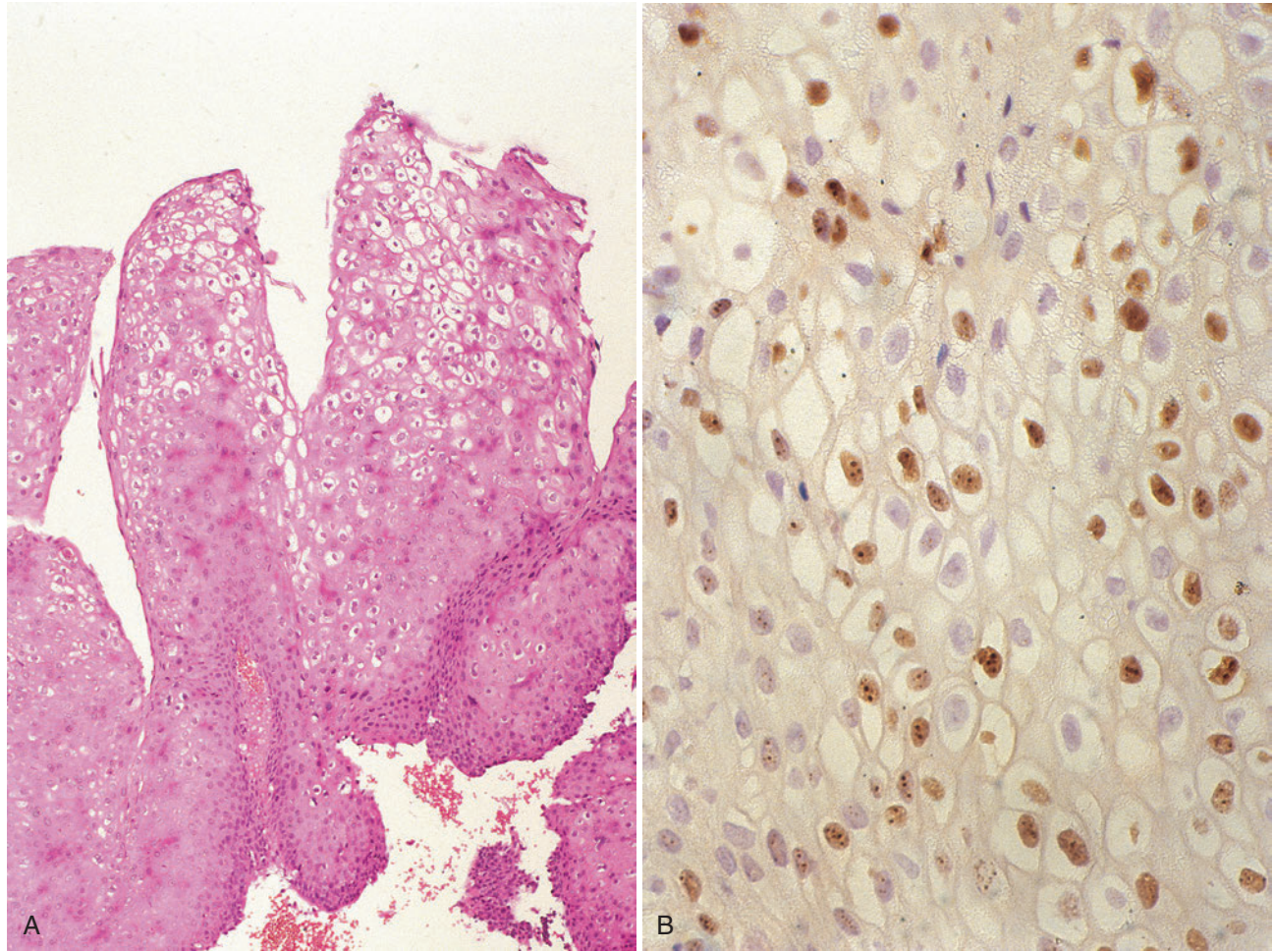


Fig. 15-32. Viral cytopathic changes.

Human papillomavirus (HPV)-associated changes in a biopsy performed for a leukoplakic laryngeal lesion and a histologic diagnosis of keratosis without dysplasia (not shown). **A**, Tissue fragment showing papillary keratosis with cytopathic viral changes (i.e., koilocytes). **B**, Immunostaining confirming the presence of HPV 6/11.

TABLE 15-1 Pathologic Abnormalities of the UADT Mucosal Surface Epithelium

Morphologic Change	Pathologic Lesion(s)
Hyperplasia/acanthosis	Benign reactive processes, infectious diseases, papillomas, intraepithelial dysplasias, carcinoma
Keratosis/parakeratosis/orthokeratosis	Benign reactive processes, infectious diseases, papillomas, intraepithelial dysplasias, carcinoma
Ulceration and/or necrosis	Benign reactive processes, infectious diseases, polyps, papillomas, other benign neoplasms, intraepithelial dysplasias, carcinoma
Pseudoepitheliomatous hyperplasia	Benign reactive processes, infectious diseases, polyps, papillomas, granular cell tumor, intraepithelial dysplasias, carcinoma
Papillary/verruroid growth	Benign reactive processes, infectious diseases, intraepithelial dysplasias, carcinoma
Koilocytosis	Benign reactive processes, verrucae, papillomas, carcinoma
Dyskeratosis	Benign reactive processes, infections/inflammatory conditions, papillomas, intraepithelial dysplasias, carcinoma
Metaplasia	Benign reactive processes, radiation-associated, intraepithelial dysplasias, carcinoma

UADT, Upper aerodigestive tract.

the epithelial basement membrane and other authorities advocating invasion limited to 1 to 2 mm from the epithelial basement membrane

- Identification of superficial or microinvasive carcinoma is significant given the presence of vascular spaces high in the lamina propria so that access to vessels may occur in the face of limited invasion, potentially resulting in metastatic disease.

Hyperplastic Epithelial Changes

Definition: Potentially reversible reactive or reparative benign process reflecting the epithelial response to a stimulus or to injury.

Synonyms: Keratosis without dysplasia; hyperplasia without dysplasia

Clinical

- More common in men than in women; generally limited to the adult population with a mean age at diagnosis in the sixth decade of life
- May occur anywhere in the larynx but identified mainly along the true vocal cord:
 - Typically unilateral proliferation but may be bilateral in up to 30% of cases
- Most frequent symptom is hoarseness.
- Causes may include:
 - Tobacco smoking
 - Excess alcohol use
 - Chronic infections, including (but not limited to) fungal infection
 - Less commonly secondary to voice abuse, environmental/industrial exposure, laryngopharyngeal reflux, and vitamin A deficiency

Pathology

Gross

- Array of appearances including a flat (most common), papillary, or verrucoid lesion with a white (leukoplakic) or red (erythroplakic) appearance
- May be localized to a small area of the vocal cord or may be diffuse, involving virtually the entire larynx (pachyderma laryngis)

Histology

- Variably include:
 - Thickening of the surface epithelium by an absolute increase in the number of cells (simple epithelial hyperplasia)
 - Presence of a superficial keratin layer (keratosis) or nuclei in the superficial keratin layer (parakeratosis)
 - Overall appearance or configuration may include papillary, exophytic, or verrucoid.

- Presence of keratohyaline granules in granulosal cell layer
- Absence of significant cytologic atypia
- Dyskeratosis may be present.
- Koilocytosis may or may not be present.
- Nonspecific chronic inflammatory cell reaction may be present in the submucosa with extension into the surface epithelium.
- An acute inflammatory cell reaction (i.e., neutrophils) may be seen in the superficial layers of the surface epithelium and/or within the depths of the surface epithelium:
 - Presence of neutrophils should prompt consideration for a possible infectious cause, specifically the presence of fungal forms (spores and/or hyphae).
 - Presence of neutrophils and/or microorganisms does not exclude a possible diagnosis of a coexisting significant dysplasia and/or carcinoma.
- Special stains for fungi including periodic acid Schiff (PAS) and/or Gomori methenamine silver (GMS) may be required to identify fungal forms (spores and/or hyphae):
 - Fungal infestation may result in epithelial changes that clinical and morphologically raise concern for a diagnosis of squamous cell carcinoma.
 - Fungal forms should be identified within the depth of the epithelium to diagnose fungal infestation.
 - Presence of fungal forms on the surface or within the superficial keratin layer represents colonization and not infestation.
- Viral-related changes (i.e., koilocytosis) may be identified:
 - Presence of koilocytosis can be seen in a variety of lesions, including in association with hyperplastic (reactive) epithelial changes.
 - Koilocytosis is not necessarily a premalignant finding or an indicator of potential progression to a malignancy.
 - Presence of koilocytosis correlates to low-risk human papillomavirus (HPV), including types 6/11.
 - To date, high-risk HPV not associated with intraepithelial dysplasia, papillomas, and/or carcinomas of the laryngeal (and tracheal) mucosa:
 - No diagnostic or therapeutic utility to using immunohistochemical staining (i.e., p16) and/or molecular diagnostic testing (in situ hybridization, polymerase chain reaction) to evaluate for the presence of HR HPV
- Immunohistochemistry, cytogenetic and molecular genetics:
 - p53 overexpression may be present:
 - Not a discriminator between keratosis without dysplasia from premalignant lesions

- Matrix metalloproteinases (MMPs) is a family of proteolytic zinc-containing enzymes, responsible for breakdown of the extracellular matrix components in pathologic and physiologic conditions.
 - MMPs involved in basement membrane disruption, stroma and blood vessel penetration, metastasis, and more evidence of their participation in tumor growth and angiogenic events
 - MMP9 belongs to the gelatinases, a subgroup of MMPs having the capacity to degrade the triple helix–type IV collagen of basal lamina of the basement membrane.
 - MMP9 expression significantly higher in dysplastic laryngeal lesions as compared with benign lesions, including keratosis without dysplasia
- Close clinical follow-up of patients advised
- Cessation of potentially contributing causes (e.g., smoking, excessive alcohol use, other) strongly advocated
- If associated etiologic factors are identified then attempts to control the inciting cause should be attempted:
 - For fungal infestation antimicrobial therapy is indicated.
- Risk of development of an invasive carcinoma in the face of a hyperplastic process without significant dysplasia is minimal:
 - Incidence of invasive carcinoma developing in lesions diagnosed as keratosis without dysplasia approximately 5%
 - Approximately 7% of cases showing keratosis without dysplasia will progress to keratosis with dysplasia:
 - Risk of developing an invasive carcinoma in lesions diagnosed as keratosis with dysplasia approximately 18%
 - Risk for progression to invasive carcinoma in lesions diagnosed as keratosis with dysplasia varies depending on the degree of dysplasia:
 - For mild dysplasia: approximately 6%
 - For moderate dysplasia: approximately 23%
 - For severe dysplasia: approximately 28%
 - For those lesions that progress to invasive carcinoma the average latency period from the diagnosis of keratosis with atypia to invasive carcinoma is 3.8 years.

Differential Diagnosis

- Contact ulcer
- Verruca vulgaris
- Keratosis with dysplasia:
 - Demographics and clinical features similar to those of keratosis without dysplasia
 - In contrast to keratosis without dysplasia, these lesions show variable dysplasia ranging from mild to moderate to severe.
 - See Chapter 16 on premalignant lesions for a more complete discussion.
- Well-differentiated (“conventional”) squamous cell carcinoma
- Papillary (exophytic) squamous cell carcinoma
- Verrucous carcinoma

Treatment

- Excisional biopsy by vocal cord stripping or by forceps is the preferred treatment.
 - Potentially reversible process
 - Lesions that qualify as keratosis without dysplasia require no additional therapy.

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Neoplasms of the Larynx and Trachea

CLASSIFICATION OF NEOPLASTIC LESIONS OF THE LARYNX AND TRACHEA (Box 16-1)

BOX 16-1 Classification of Laryngeal and Tracheal Neoplasms

Benign

Epithelial

- Papilloma/papillomatosis (recurrent respiratory papillomatosis)
- Minor salivary gland tumors

Mesenchymal/Neuroectodermal

- Granular cell tumor
- Nodular fasciitis
- Inflammatory myofibroblastic tumor
- Chondroma
- Rhabdomyoma
- Hemangioma
- Neurilemoma/neurofibroma
- Leiomyoma
- Fibrous histiocytoma
- Lipoma
- Paraganglioma
- Others

Premalignant Epithelial Lesions

- Dysplasias, keratinizing and nonkeratinizing

Malignant

Epithelial

- Squamous cell carcinoma:
 - Carcinoma in situ
 - Microinvasive carcinoma
 - Invasive squamous cell carcinoma
- Papillary (exophytic) squamous cell carcinoma

- Verrucous carcinoma
- Spindle cell squamous carcinoma
- Basaloid squamous carcinoma
- Adenosquamous carcinoma
- Lymphoepithelial-like carcinoma
- Giant cell carcinoma
- Minor salivary gland tumors:
 - Adenoid cystic carcinoma
 - Mucoepidermoid carcinoma
 - Others

Neuroectodermal

- Neuroendocrine carcinomas:
 - Carcinoid tumor
 - Atypical carcinoid tumor
 - Small cell undifferentiated neuroendocrine carcinoma
 - Large cell neuroendocrine carcinoma
- Mucosal malignant melanoma

Mesenchymal

- Chondrosarcoma
- Synovial sarcoma
- Liposarcoma
- Rhabdomyosarcoma
- Angiosarcoma/Kaposi sarcoma
- Leiomyosarcoma
- Hematolymphoid
- Others

Secondary Tumors

GENERAL CONSIDERATIONS

- Similar to tumors of other upper aerodigestive tract sites, most common tumors of the larynx are of epithelial origin:
 - Most common benign neoplasm is a (squamous) papilloma
 - Most common malignant neoplasm is squamous cell carcinoma or variant thereof, accounting for greater than 95% of all malignant neoplasms of the larynx

- Primary tumors of the trachea are rare and ratio of benign to malignant tumors varies per age of the patient:
 - In pediatric ages benign tumors > malignant tumors:
 - 60% to 90% of tumors are benign:
 - Most common are squamous papillomas, hemangioma, granular cell tumor
 - 10% to 40% are malignant:
 - Most common is mucoepidermoid carcinoma

- In adult ages malignant tumors > benign tumors:
 - 90% of tumors are malignant:
 - Most common (95% of total) are squamous cell carcinoma and its variants
- Most common benign neoplasm is a (squamous) papilloma
- For more detailed discussion on a variety of factors related to laryngeal and tracheal carcinoma, see later in this chapter under site-specific squamous cell carcinoma.

BENIGN NEOPLASMS OF THE LARYNX AND HYPOPHARYNX

LARYNGEAL PAPILOMA/ PAPILLOMATOSIS; RECURRENT RESPIRATORY PAPILLOMATOSIS

(Figs. 16-1 through 16-6)

Definition: Benign, exophytic epithelial neoplasm composed of branching fronds of squamous epithelium with fibrovascular cores that may be single or multiple and may be associated etiologically with low-risk human papillomavirus types 6 and 11.

Synonyms: Squamous papilloma; laryngeal papillomatosis; recurrent respiratory papillomatosis, juvenile papillomatosis, adult papillomatosis; nonkeratinized papilloma; keratinized papilloma; papillary keratosis

- At present, the preferred terminology for viral-associated papillomas that are nonkeratinizing, tend to persist or recur, and show a degree of resistance to treatment is recurrent respiratory papillomatosis.
- Most common benign neoplasm occurring in this anatomic region
- Due to distinct clinical and histopathologic findings, papillomas can be separated by:
 - Age: juvenile versus adult forms
 - Number of lesions: solitary versus multiple
 - Histology: nonkeratinizing and keratinizing

Recurrent Respiratory Papillomatosis (Nonkeratinizing Papilloma) (Table 16-1)

Clinical

- Divided into:
 - Lesions that occur in early years referred to as juvenile-onset recurrent respiratory papillomatosis (JO-RRP)
 - Lesions that occur in older ages referred to as adult-onset recurrent respiratory papillomatosis (AO-RRP)
 - Age separating juvenile versus adult onset not established and different studies cite different ages

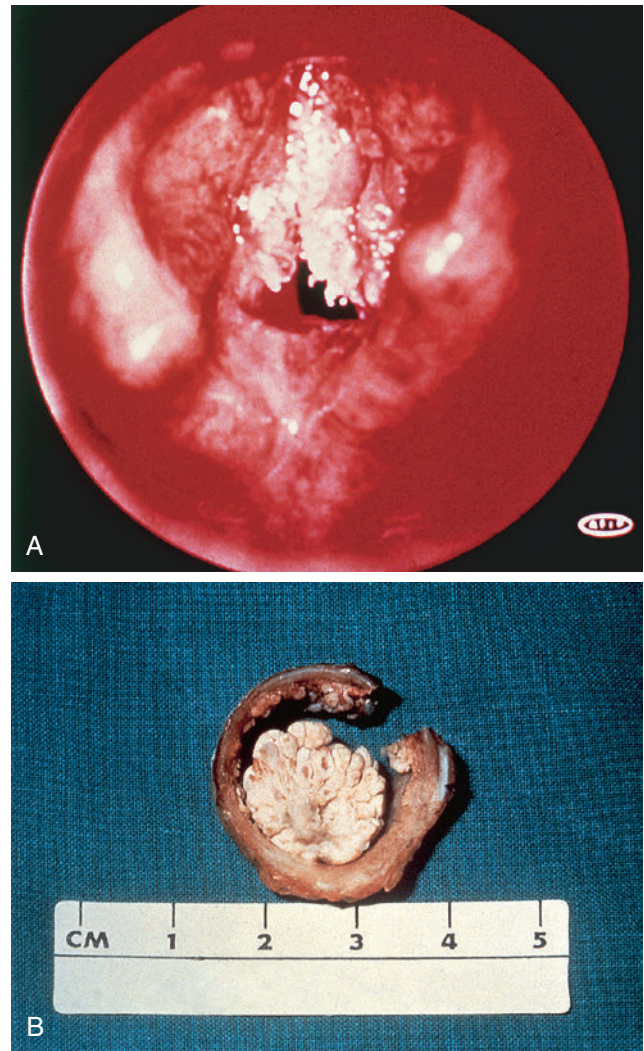


Fig. 16-1. Recurrent respiratory (laryngeal) papillomatosis.

A, The lesion is characterized by an exophytic, warty, tan-white appearance. **B,** Resected portion of larynx showing characteristic papillary appearance with intraluminal growth.

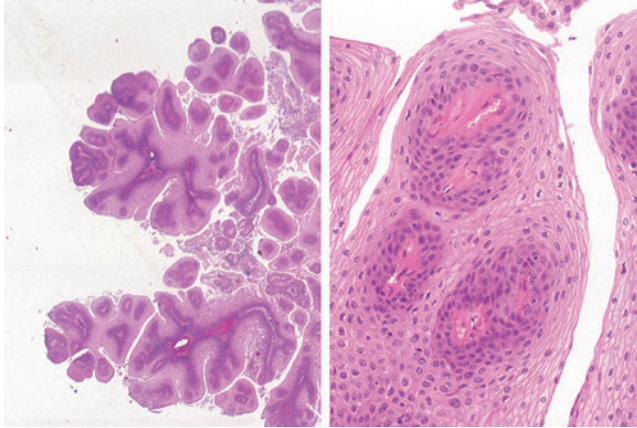


Fig. 16-2. Recurrent respiratory (laryngeal) papillomatosis.

Left, Histologic appearance is characterized by papillary fronds of multilayered squamous epithelium containing fibrovascular cores. *Right*, Benign epithelium of the papilloma is seen; the majority of these lesions lacks keratinization.

- Although not universally accepted, 20 years of age can serve as a potential dividing line between JO-RRP and AO-RRP.

JO-RRP

- No gender predilection; most patients become symptomatic at an early age, including 2 to 5 years of age.
- Clinical presentation includes changes in phonation (e.g., abnormal crying, hoarseness), dyspnea, cough, dysphagia, stridor.
- Majority are multiple (rather than a single lesion) with extensive growth and rapid recurrence:
 - May remit spontaneously or persist into older ages

AO-RRP

- More common in men than in women; affects all age groups but most common from ages 20 to 40
- Clinical presentation includes changes in phonation (e.g., hoarseness).
- Majority are single (rather than multiple) and tend to recur less often.

JO-RRP and AO-RRP

- Primarily a disease of the larynx:
 - May occur anywhere in the larynx but most often involve the true and false vocal cords, ventricles, and subglottis
 - Spread to nearby (extralaryngeal) areas may occur and include oral cavity and tracheobronchial tree:

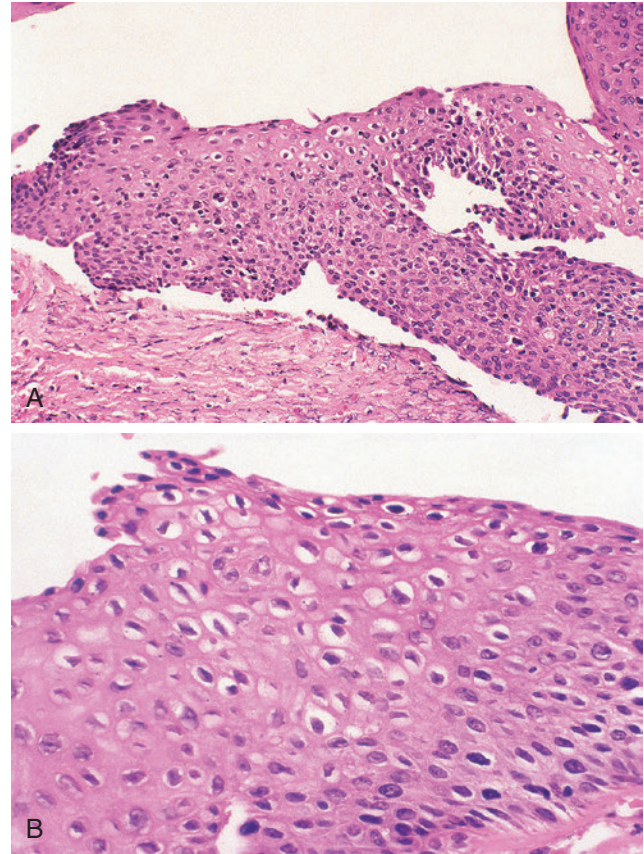


Fig. 16-3. Dysplasia in laryngeal papilloma.

The dysplastic changes occurred over time and only after multiple recurrences. **A**, Dysplastic features include the presence of immature-appearing cells with nuclear hyperchromasia, pleomorphism, increased nuclear-to-cytoplasmic ratio, and loss of cell polarity. **B**, HPV cytopathic changes (i.e., koilocytes) are seen; immunostaining confirmed the presence of HPV 6/11 (not shown).

- Extralaryngeal spread occurs more commonly in children than in adults.
- Extension into and down tracheobronchial tree occurs in approximately 5% of patients.
- RRP tends to localize to those junctional areas where ciliated respiratory epithelium meets squamous epithelium referred to as squamous epithelial-ciliary respiratory epithelial junction (SCJ) and include:
 - Histologically normal junctional mucosa (e.g., supraglottic-glottic junction or glottic-subglottic junction)
 - Areas in which there is metaplastic alteration secondary to an injury with squamous epithelium replacing ciliated respiratory epithelium creating a new squamous epithelial-ciliated respiratory epithelial junction

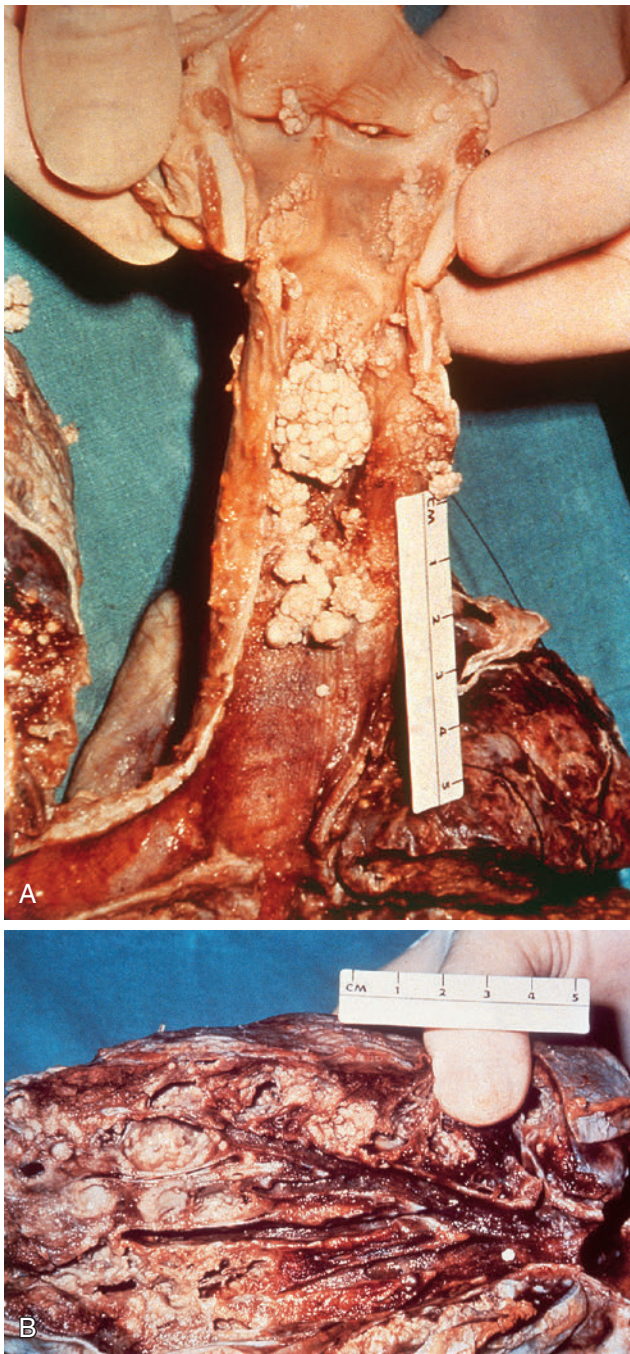


Fig. 16-4. Spread of papillomatosis.

Progression of recurrent respiratory (laryngeal) papillomatosis may include **(A)** extension of the papillomas from the glottic region into the subglottis and down the tracheobronchial tree; **(B)** extension into the lungs. The histology of all of these papillomata was that of typical (benign) papilloma without dysplasia or evidence of carcinoma.

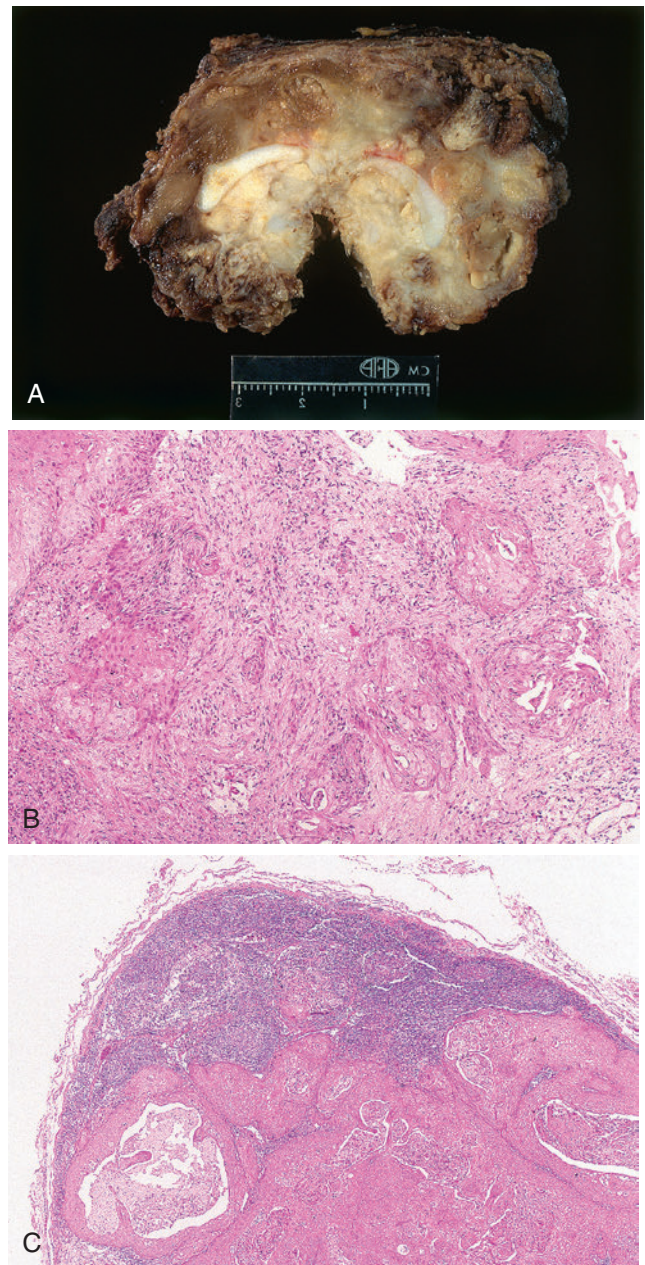


Fig. 16-5. Malignant transformation.

Rare example of malignant transformation of recurrent respiratory (laryngeal) papillomatosis that occurred in a teenage girl. **A**, Laryngectomy specimen showing the neoplasm invading into and through cartilage. **B**, The histology of the carcinoma was that of a well-differentiated squamous cell carcinoma. **C**, The carcinoma metastasized to paratracheal and cervical neck lymph nodes.

- Cause:
 - Virally induced caused by low-risk human papillomavirus (HPV)
 - HPV types 6 and 11 most frequent types identified:

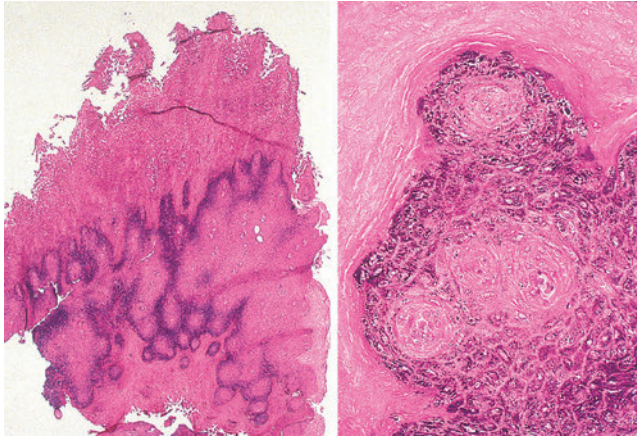


Fig. 16-6. Laryngeal verruca vulgaris.

Laryngeal verruca vulgaris characterized by verrucoid growth, marked keratosis, prominent granular cell layer, and coarse, irregular keratohyaline granules.

- Rarely, HPV 16, 18, 31, 33, and 35 identified
- Mode of transmission:
 - In JO-RRP a significant percentage of patients (up to 70%) born to women with uterine cervical condylomas with transmission related to maternal-genital infection:
 - JO-RRP has been correlated to the triad of (1) first-born child, (2) vaginal delivery, and (3) teenage mother.
 - Vaginal condyloma in pregnancy is strongly predictive of JO-RRP.
 - Cesarean section rather than vaginal delivery has been advocated in this clinical setting but cesarean section has not been entirely protective from infection and the development of RRP.
 - In AO-RRP the mode of transmission remains uncertain; considerations include:
 - Possibility of maternal transmission during delivery with the virus remaining dormant until adulthood when there is activation of virus
 - Orogenital contact with an infected individual

TABLE 16-1 Laryngeal Papillomas: Clinical-Pathologic Features

	JO-RRP	AO-RRP	Keratinizing Papilloma
Age	Less than 20 years*	20 years and older*	Occurs in adults
Gender	No gender predilection	Much more common in men than in women	No gender predilection
Symptoms	Changes in phonation, stridor, dysphagia, cough	Hoarseness	Hoarseness
Sites	SCJ includes supraglottic-glottic junction or glottic-subglottic junction	SCJ includes supraglottic-glottic junction or glottic-subglottic junction	True vocal cord is the most common location
Lesions	Majority are multiple (80% to 98%)	Majority are single (65% to 75%)	Usually single
Pathology	Papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores with little or no keratin	Papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores with little or no keratin	Papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores with associated keratinization (parakeratosis or orthokeratosis); kerato-hyaline granules may be present
HPV	Present usually 6 and 11 rarely high-risk types	Present usually 6 and 11 rarely high-risk types	Absent
Treatment	Surgical excision	Surgical excision	Surgical resection
Prognosis	Variable often with recurrent disease	Variable	Usually cured after excision
Malignant transformation	2% in nonirradiated cases 14% irradiated cases	2% in nonirradiated cases 14% irradiated cases	Rare

AO-RRP, Adult-onset recurrent respiratory papillomatosis; JO-RRP, juvenile-onset recurrent respiratory papillomatosis; SCJ, squamous epithelial-ciliary respiratory epithelial junction.

*Not universally accepted as the dividing age limit.

Pathology

Gross

- Single or multiple exophytic, warty, friable, tan-white to red growth(s)
- Characteristic feature is ease of bleeding after minor trauma.

Histology

- Papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores
- Little or no surface keratin production although an occasional case may have keratinization (parakeratosis or orthokeratosis)
- Stroma well vascularized; variable amount of inflammatory cells are present
- A certain degree of cellular atypia may be seen especially in those lesions that recur over short periods of time:
 - Generally the degree of dysplasia is limited and the risk of progression to a more significant dysplastic lesion or carcinoma is low.
 - Atypical features include basal zone hyperplasia with nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, loss of cell polarity, prominent nucleoli, and increased mitotic activity; dyskeratosis may also be identified.
 - Presence of severe atypia may be indicative of the development of squamous carcinoma arising in papillomatosis or may in fact represent an exophytic squamous cell carcinoma.
 - In presence of dysplasia majority are positive for low-risk HPV subtypes so that high-risk HPV subtypes do not predispose patients with laryngeal papilloma to dysplasia
- Viral-induced changes (i.e., koilocytosis) may be seen.
- Immunohistochemistry:
 - Immunostains for HPV may be positive:
 - When virus is present majority are HPV 6/11.
 - p16 typically negative:
 - Patchy p16 reactivity may be present but such reactivity does not represent positive staining.
 - Positive staining requires diffuse and strong nuclear and cytoplasmic staining in at least 75% of the lesions.
 - p53 negative
- Cytogenetics and molecular genetics:
 - Identification of viral antigens or genomes by in situ hybridization and polymerase chain reaction
 - In situ hybridization for angiogenic growth factor VEGF-A has shown strong expression in the epithelium of squamous papillomas in RRP, as well as strong expression of VEGFR-1 and VEGFR-2

mRNAs by underlying vascular endothelial cells, suggesting a role for VEGF-A in the pathogenesis of RRP.

Differential Diagnosis

- Verruca vulgaris:
 - Typically occurs in cutaneous sites
 - Infrequently occurs in mucosal sites, including lips
 - Etiologically linked to HPV:
 - HPV 2 and 4 typically associated with VV of the skin, lips, and oral cavity
 - HPV 6 and 11 identified in laryngeal VV
 - Rare lesion of the larynx:
 - Much more common in men than in women; disease of adults
 - Most common on the true vocal cord
 - Hoarseness is the most common symptom.
 - Exophytic, demarcated warty-appearing white lesion usually measuring less than 1 cm
 - Histologically similar to verruca vulgaris of the skin and includes:
 - Verrucoid appearance
 - Keratosis
 - Prominent granular cell layer
 - Coarse and irregular keratohyaline granules
 - Thin, pointy rete pegs
 - Presence of koilocytes
 - Simple excision is curative.
 - Recurrence may rarely occur.
- Verrucous carcinoma
- Papillary or exophytic squamous cell carcinoma

Treatment and Prognosis

- Because of the unpredictable nature of disease, which may be characterized by periods of active growth and remission, best mode of treatment and the efficacy of treatment remain uncertain:
 - Presently recommended treatment for RRP is surgery, including microlaryngeal excision with CO₂ laser surgery
 - Adjunctive drugs used in treatment with varying success include interferon, various virostatics (e.g., acyclovir, valacyclovir, and cidofovir), and indole-3-carbinol
 - Vaccination with a quadrivalent vaccine against HPV types involved most commonly in RRP may provide the best hope to prevent severe forms of this disease.
- In general, treatment should be as conservative as possible with the primary aims of therapy to include:
 - Airway maintenance
 - Voice preservation
 - Reduction of tumor burden with the goal of disease eradication
 - Avoidance of tracheotomy:

- Tracheotomy may be required to maintain a functional airway in as high as 65% of patients.
- On average tracheotomy is required in approximately one third of patients.
- If tracheotomy is required, then the maintenance of airway patency and use of the shortest tracheotomy tube are advised.
- Complications of surgery may include:
 - Laryngoceles
 - Scarring
 - Stenosis
 - Arytenoid fixation
- Radiotherapy is contraindicated because of its associated complications, including:
 - Laryngeal destruction, scarring, and laryngeal stenosis and the risk of inducing malignant transformation
 - 16-fold increased risk of developing carcinoma in patients who have been irradiated
- Recurrence of tumor is common, requiring long-term and repeated management:
 - Recurrence correlates with persistence of HPV.
 - HPV can be identified in nonpapillomatosis mucosa adjacent to the papilloma in as many as 75% of patients:
 - Identification of HPV in nondiseased mucosa by in situ hybridization and polymerase chain reaction
- Variability of disease course is reflected in the unpredictable nature of recurrent tumor:
 - Some patients experience one or two recurrences over a few-year period followed by spontaneous remission.
 - Other patients have frequent recurrences over very short periods of time (weeks), necessitating multiple operative procedures.
 - Other patients may have repeated recurrences over short periods of time and then remain disease free for decades only to have multiple recurrent diseases later in life, necessitating multiple operative procedures.
 - Appears that patients with RRP are at risk throughout their lives for the possibility of local recurrence
 - In approximately 80% of patients disease persists for 5 years or longer.
 - Effect of puberty and pregnancy on the course of disease remains controversial:
 - In some patients the disease resolves or becomes less aggressive in puberty or pregnancy.
 - In some patients the disease progresses/becomes more aggressive in puberty or during pregnancy.
- Overall mortality rate varies from 2% to 14%:
 - Extension into the tracheobronchial tree occurs in 2% to 15% and involvement of lower respiratory tract parenchyma is associated with increased mortality rates.
- Death may be caused by asphyxiation, superimposed infection, and malignant transformation.
- Carcinoma developing in RRP may occur in nonirradiated and in irradiated patients:
 - Overall incidence of developing carcinoma in nonirradiated patients is 2%.
 - Overall incidence of developing carcinoma in irradiated patients is 14%.
 - Carcinoma developing in the setting of RRP is squamous cell carcinoma.
 - Transformation of RRP to squamous cell carcinoma may:
 - Be spontaneous, not characterized by histologic progression, through dysplasia over time
 - Develop through a continuum of dysplasia over time
 - Transformation to squamous cell carcinoma may result in loss of HPV expression.
 - Carcinoma developing in RRP may develop in larynx or in the lung.
 - Laryngeal carcinomas developing spontaneously (i.e., in nonirradiated patients) tend to:
 - Occur in JO-RRP
 - Develop decades after disease onset
 - Have lower mortality rates
 - Laryngeal carcinomas developing in irradiated patients tend to:
 - Occur in JO-RRP
 - Develop in shorter interval periods (decade or less) after disease onset
 - Have higher mortality rates
 - Lung carcinomas developing in nonirradiated and nonsmoking patients tend to:
 - Have early onset of RRP ranging in age from 1 to 6 years with an average age of onset of 2½ years
 - Have disease extension down the tracheobronchial tree into the lungs
 - Develop carcinoma approximately 25 years after laryngeal disease
 - Often have metastatic disease (regional lymph nodes and distant)
 - Have high mortality rates usually over short periods of time following the diagnosis of carcinoma
 - Factors in RRP reported to be associated with increased risk of aggressive behavior with spread to lower airway passages, malignant transformation, and death include:
 - Patients with HPV type 11:
 - Malignant transformation reported solely for HPV 11-associated RRP in 2% to 4% of all RRP cases

- Malignant transformation not reported to be associated with HPV 6; however, a patient with HPV 6 expressing E6 and E7 oncogenes shown to follow similar aggressive clinical course as patients with HPV 11
 - These patients developed disease at a younger age and expressed higher levels of E6 and E7 oncogenes compared with the patients with more indolent course.
- Alterations of aldo-keto reductase 1C3 gene (AKR1C3) on chromosome 10p15.1 may be implicated in carcinogenesis.
- Severity score of greater than 4:
 - Includes functional assessment of clinical parameters and an anatomic assessment of disease distribution
 - Anatomic score can then be used in combination with the functional score to measure an individual patient's clinical course and response to the therapy over time.
- A high number of surgical procedures prior to interferon-alpha therapy

Keratinizing Papilloma (Papillary Keratosis) (see Table 16-1, Fig. 16-7)

Clinical

- No gender predilection; disease of adults but may occur over a wide age range, including patients younger than 50 years of age
- Tend to occur on the true vocal cord
- Patients usually present with hoarseness.
- Cause:
 - Not etiologically linked to human papillomavirus (unlike nonkeratinizing papillomas)
 - Reported to occur in patients with smoking history

Pathology

Gross

- Exophytic or papillary lesion with a white appearance, usually does not exceed 2 cm in greatest dimension.

Histology

- Papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores with associated keratinization
- Keratinization may be in the form of parakeratosis or orthokeratosis.
- Keratohyaline granules can be identified.
- In most examples there is an absence of cytologic dysplasia (i.e., keratinizing papilloma or papillary keratosis without dysplasia):

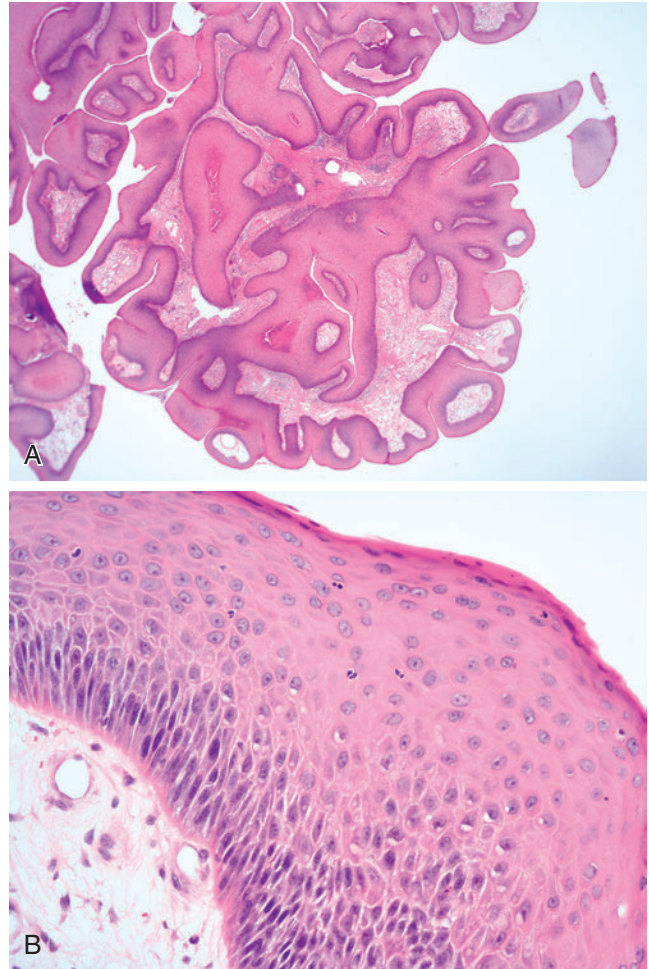


Fig. 16-7. Keratinizing papilloma.

A, B, Laryngeal keratinizing papilloma composed of papillary fronds of multilayered benign squamous epithelium containing fibrovascular cores and associated surface keratosis and parakeratosis; a sparse neutrophilic cell infiltrate is present.

- Dysplasia can be seen ranging from mild to moderate to severe and should be reported as such (i.e., keratinizing papilloma or papillary keratosis with mild, moderate, or severe dysplasia).
- In general, a high threshold should be maintained to diagnose dysplasia because laryngeal papillomas in general and squamous papillomas of the entire upper aerodigestive tract tend to be resistant to developing high-grade intraepithelial dysplasia (i.e., moderate to severe dysplasia).
- A variable mixed inflammatory cell infiltrate may be present in the stroma.

Differential Diagnosis

- Verrucous carcinoma
- Papillary or exophytic squamous cell carcinoma

Treatment and Prognosis

- Surgical resection is usually curative.
- Usually do not recur but occasionally may recur
- Rarely undergo malignant transformation to a carcinoma

BENIGN SALIVARY GLAND TUMORS

- Laryngeal benign salivary gland tumors are extremely rare:
 - Laryngeal malignant salivary gland tumors are more common than benign ones.
- Most common tumor type is pleomorphic adenoma.
- Most often occur in supraglottic larynx
- Histology is identical to pleomorphic adenomas of more common locations (i.e., salivary glands).
- Another category of salivary gland lesions include oncocytic papillary lesions:
 - Controversial category
 - Various designated oncocytic cyst, oncocytic papillary cystadenoma
 - Likely do not represent true neoplasms but metaplastic reaction
 - See Chapter 15 under Laryngeal Cyst for a more complete discussion.

BENIGN NONEPITHELIAL TUMORS

- Benign mesenchymal tumors of the larynx and trachea are rare.
- In this category, tumor types include:
 - Hemangiomas
 - Benign peripheral nerve sheath tumors (neurilemoma; neurofibroma), including granular cell tumor
 - Lipoma
 - Paraganglioma
 - Leiomyoma (conventional leiomyoma, vascular leiomyoma, and epithelioid leiomyoma)
 - Chondroma
 - Rhabdomyoma
 - Giant cell tumor (osteoclastoma)
- For more complete discussion of some of these tumor types see other sections.
- This section includes discussion of the following lesions: inflammatory myofibroblastic tumor, granular cell tumor, lipoma, paraganglioma, and chondroma.

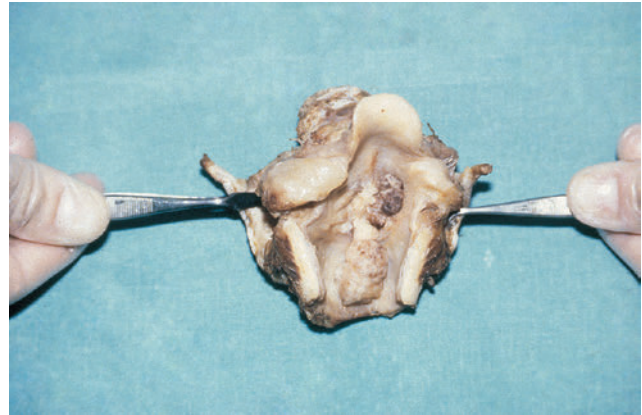


Fig. 16-8. Laryngeal inflammatory myofibroblastic tumor (IMT).

Laryngectomy specimen showing a polypoid and nodular-appearing transglottic lesion. In general, aggressive surgery is not indicated for laryngeal (or other mucosal-based) IMTs, but this is an unusual example of a multiply recurrent lesion necessitating more radical treatment.

Inflammatory Myofibroblastic Tumor (IMT) (Figs. 16-8 through 16-11)

Definition: Distinctive lesion composed of myofibroblastic and fibroblastic cells with a variable admixture of inflammatory cells, including mature lymphocytes, plasma cells, and/or eosinophils.

- Predominantly soft tissue and visceral tumor that may occur in mucosa of upper aerodigestive tract

Synonyms: Inflammatory (myofibroblastic) pseudotumor, plasma cell granuloma, plasma cell pseudotumor, pseudosarcomatous (myofibroblastic) lesions/tumors

Clinical

- IMT of upper aerodigestive tract are rare:
 - Aside from scattered case reports there are very few comprehensive studies detailing the clinicopathologic features of IMT in upper aerodigestive tract sites.
- Male predominance; contrasting to soft tissue and visceral IMT, which occur predominantly in children and young adults, IMT of the upper aerodigestive tract occur over a wide age range that includes the pediatric population but is more common in adult populations:
 - Relative to laryngeal IMT, median age of 59 years reported

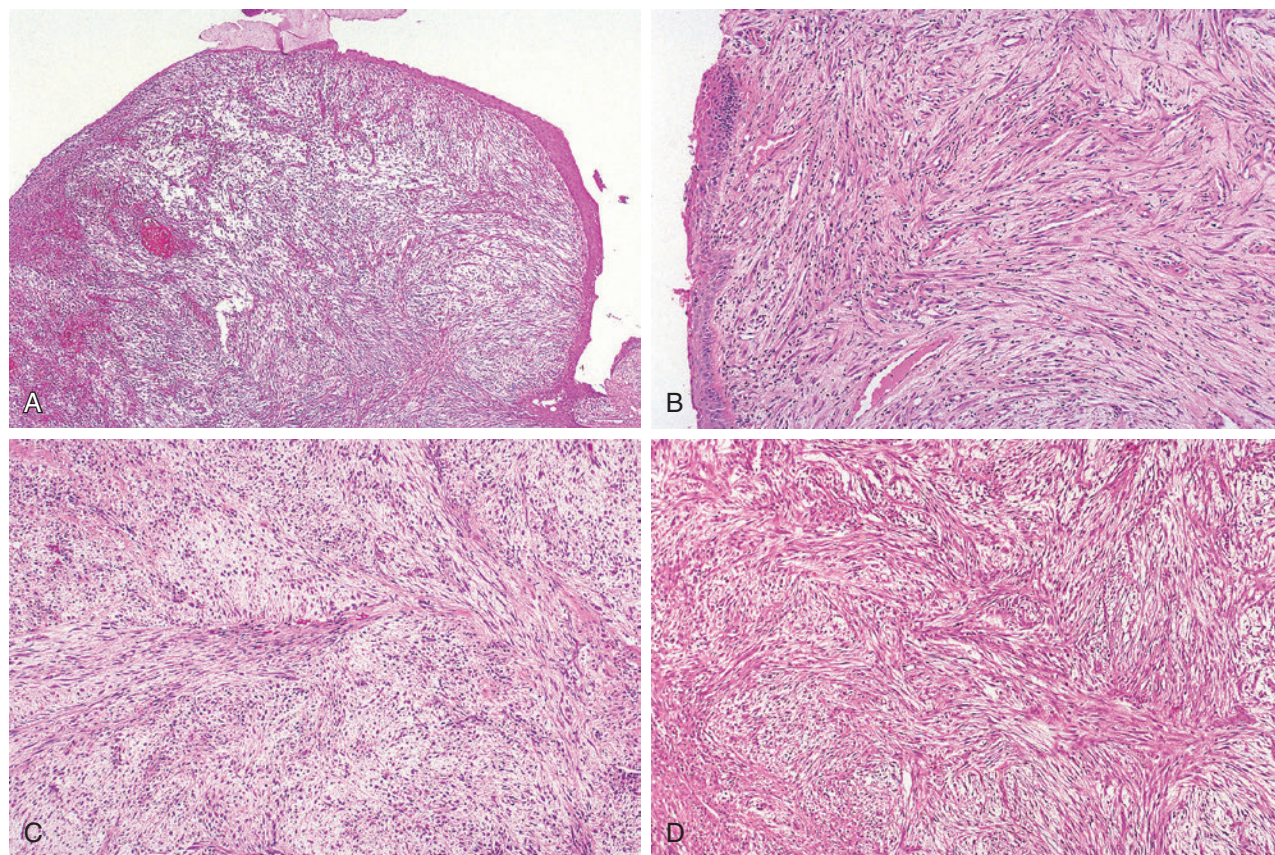


Fig. 16-9. Laryngeal IMT.

Histology of (laryngeal) IMT may include **(A, B)** polypoid-appearing lesions characterized by the presence of a submucosal loosely cellular proliferation of spindle-shaped to stellate cells with variably admixed inflammatory cells; surface squamous epithelium is intact but may be ulcerated; **(C, D)** cellular proliferation is loosely arranged with a storiform to fascicular growth pattern and an edematous myxoid stroma. The overall histologic appearance can be similar to that seen in nodular fasciitis.

- In upper aerodigestive tract, IMT most commonly occur in the larynx:
 - Laryngeal sites of involvement include glottis, supraglottis, and subglottis.
 - Most common site of occurrence is the true vocal cord
 - Nonlaryngeal sites of occurrence include oral cavity, tonsil, parapharyngeal space, sinonasal tract, salivary glands, and trachea.
- Clinical presentation varies per site of occurrence:
 - Larynx: hoarseness, stridor, dysphonia, and/or a foreign body sensation in the throat; duration of symptoms range from as short as 10 days up to 4 months
 - Other aerodigestive tract sites may present as painless mass, ulcerative painful mass, nasal obstruction, epistaxis, headaches, and dysphagia.
 - Constitutional and/or systemic signs and symptoms such as fever, weight loss, pain, malaise, anemia, thrombocytosis, polyclonal hyperglobulinemia, and elevated erythrocyte sedimentation rate seen in association with soft tissue and visceral IMT are not usually a component of upper aerodigestive tract IMT. High fever, anemia and weight loss may be present.
- IMT of the upper aerodigestive tract present as solitary (isolated) lesions, typically without lesions of other upper aerodigestive tract sites or evidence of myofibroblastic lesions of other sites of the body.
- Cause of IMT in general and upper aerodigestive tract in specific is unknown:
 - No specific link to tobacco smoking, trauma (e.g., traumatic intubation), human herpesvirus-8 (HHV-8), or Epstein-Barr virus (EBV)

Pathology

Gross

- Polypoid, pedunculated, or nodular firm lesion with a smooth appearance and fleshy to firm consistency

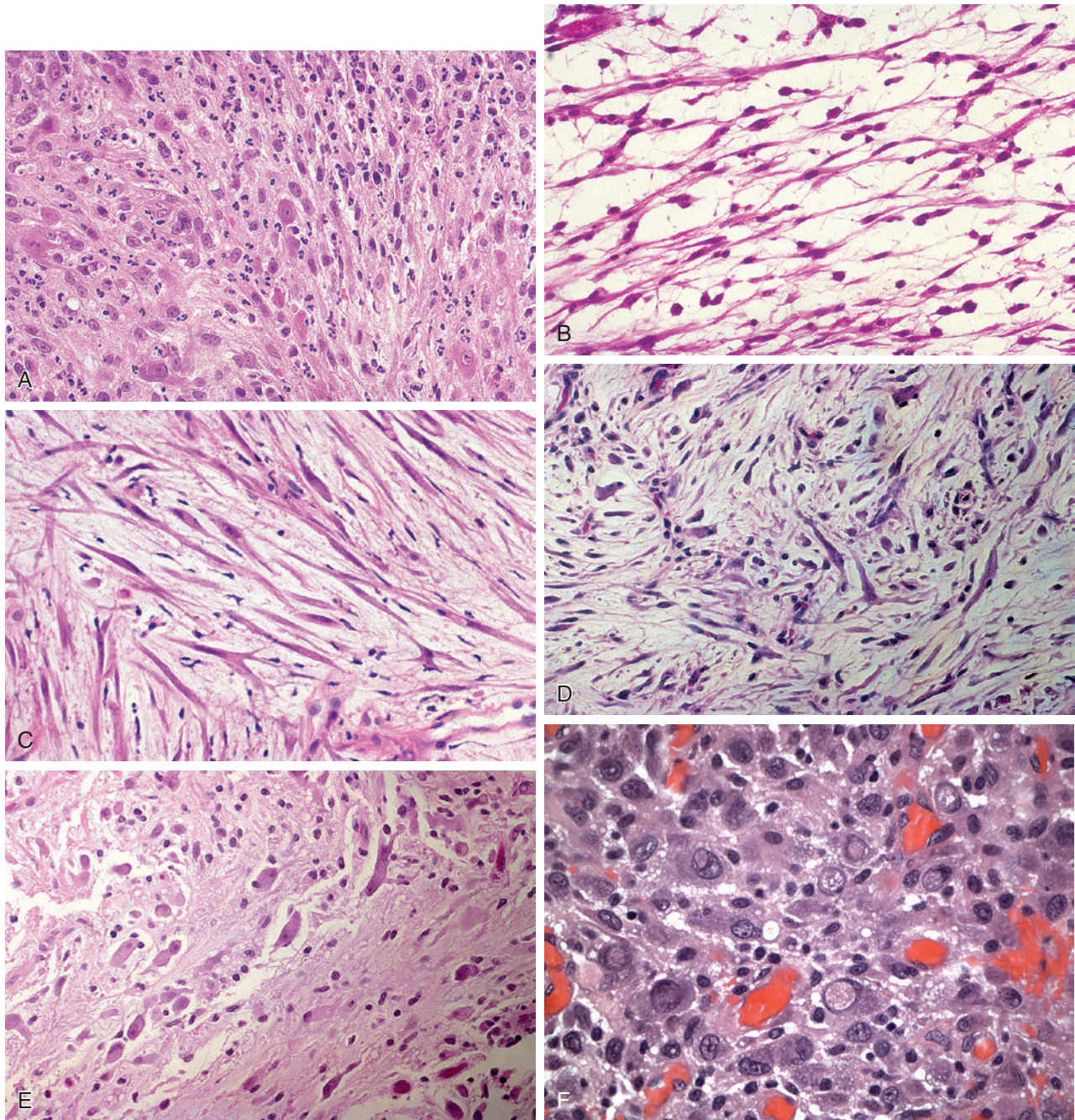


Fig. 16-10. Myofibroblasts in IMT.

The myofibroblasts in IMT may have a varied appearance including **(A)** epithelioid or histiocytoid characterized by round to oval nuclei, prominent nucleoli, and ample basophilic to eosinophilic granular cytoplasm; **(B through D)** spindle-shaped to stellate-appearing cells with enlarged round to oblong nuclei, inapparent to prominent eosinophilic nucleoli, and abundant basophilic to eosinophilic-appearing fibrillar cytoplasm; axonal-appearing (spider-like) cells with long cytoplasmic extensions creating cells with a bipolar-to-multipolar (tadpole-like) appearance are seen; **(E)** the stroma in this example has a neurofibrillar-like appearance; GFAP staining was negative (not shown). **F**, Intranuclear eosinophilic inclusions may be seen and may represent a clue to the diagnosis of IMT.

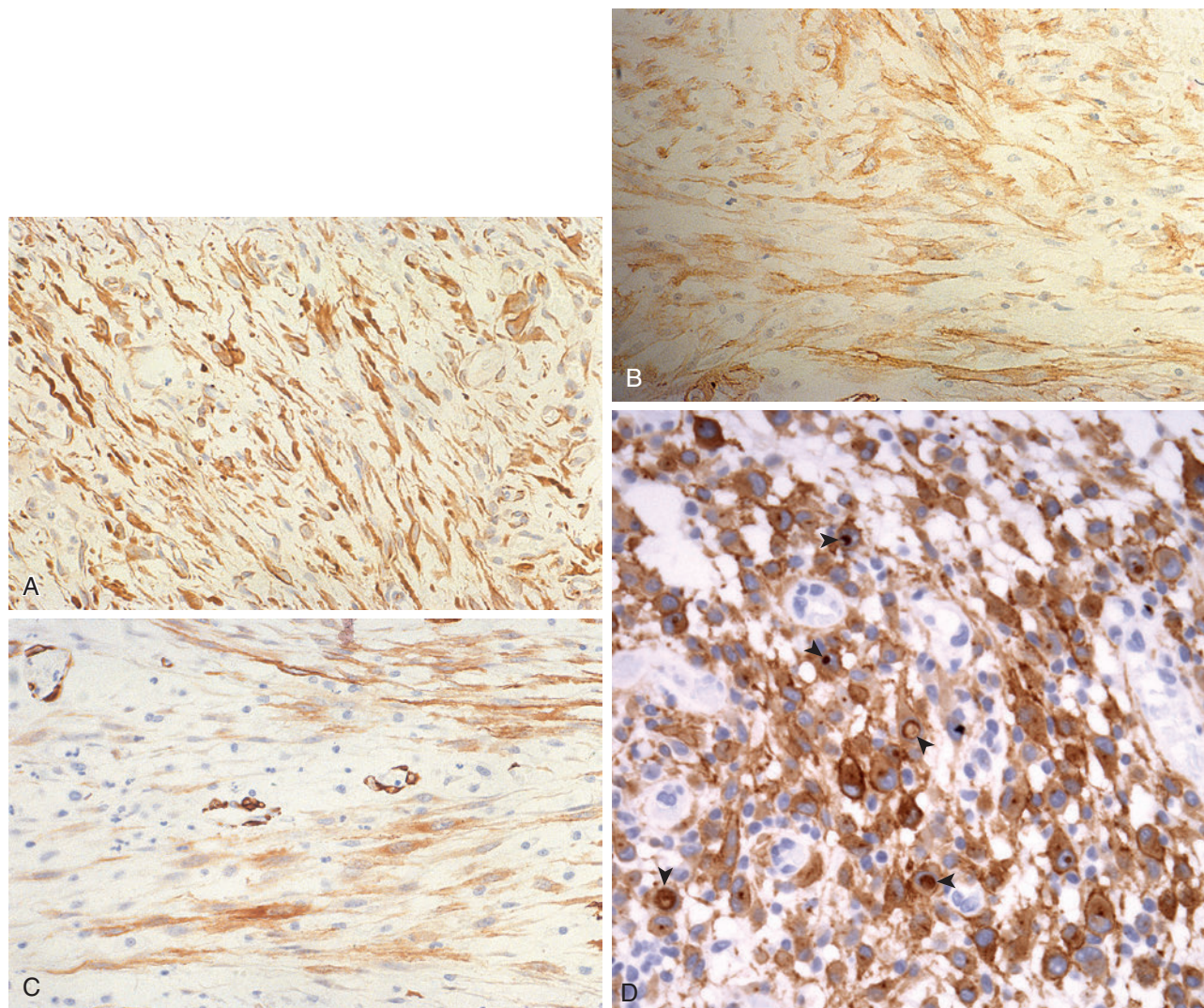


Fig. 16-11. Immunohistochemistry of IMT.

Immunohistochemical staining of the myofibroblasts in IMT may include **(A)** vimentin; **(B)** muscle-specific actin; **(C)** smooth muscle actin; **(D)** anaplastic lymphoma kinase (ALK) reactivity including cytoplasmic staining and staining of the intranuclear inclusions (*arrowheads*).

- Range in size from 0.4 to 3 cm in greatest dimension

Histology

- Polypoid and unencapsulated characterized by the presence of a submucosal loosely cellular proliferation of spindle-shaped to stellate cells with variably admixed inflammatory cells
- Cellular proliferation loosely arranged with a storiform to fascicular growth pattern and an edematous myxoid to fibromyxoid stroma, prominent vascularity, and an inflammatory cell infiltrate composed of mature plasma cells, mature lymphocytes, eosinophils, histiocytes, and scattered polymorphonuclear leukocytes:

- Overall appearance is similar to a reactive process resembling granulation tissue and nodular fasciitis.

Myofibroblasts

- Primarily spindle-shaped or stellate with enlarged round to oblong nuclei, inapparent to prominent eosinophilic nucleoli, and abundant eosinophilic to basophilic-appearing fibrillar cytoplasm:
 - In some cases myofibroblasts may appear more epithelioid or histiocytoid, including round to oval nuclei, prominent nucleoli, and ample cytoplasm.
 - Myofibroblasts may also appear as slender axonal (spider-like) cells with elongated nuclei,

inapparent nucleoli, and long cytoplasmic extensions creating cells with a bipolar-to-multipolar (tadpole-like) appearance.

- In all their histologic forms myofibroblasts maintain a low nuclear-to-cytoplasmic ratio.
- A helpful feature may be the presence of intranuclear eosinophilic inclusions:
 - Not unique to IMT but represent a rather characteristic feature especially in the context of histologic findings associated with IMT
- Focal nuclear pleomorphism may be present; marked nuclear pleomorphism and necrosis not usually present
- Mitotic figures are present and may be numerous but atypical mitoses are not usually seen.

Stroma

- Stromal component varies from an edematous myxoid background to fibromyxoid and more fibrous (collagenized); rarely, a fibrillar appearing stroma resembling neurofibrillary matrix may be seen.
- Vascular component varies from widely dilated medium-sized vascular channels to narrow, slit-like blood vessels that can be obscured by the myofibroblasts and inflammatory cells; vascular thrombosis not present

Inflammatory Cells

- Admixture of different cell types, including mature lymphocytes, mature plasma cells, eosinophils, histiocytes, and scattered polymorphonuclear leukocytes:
 - Degree of inflammatory cell infiltrate may vary from case to case
 - Prominent mature plasma cell infiltrate may be present:
 - Previous designation for IMT was plasma cell granuloma.
 - In conjunction with sclerotic stroma as well as increased numbers of IgG4-positive plasma cell and IgG4/IgG ratio ≥ 0.10 may suggest a possible diagnosis of IgG4-related disease (see Differential Diagnosis below).

Surface Epithelium

- Surface epithelium may be intact and unremarkable to ulcerated to hyperplastic.
- Myofibroblastic proliferation may approximate surface epithelium but usually there is a separation between the myofibroblasts and surface epithelium.
- Reactive epithelial atypia may be seen but significant epithelial dysplasia (i.e., moderate to severe dysplasia), carcinoma in situ, and invasive squamous carcinoma are not present.

- Histochemistry:
 - Essentially noncontributory to the diagnosis
- Immunohistochemistry:
 - Strong diffuse cytoplasmic immunoreactivity for vimentin
 - Smooth muscle actin and/or muscle specific actin typically present but may vary from focal to diffuse
 - Desmin staining may be present.
 - CD68 may be focal in histiocytic-appearing cells.
 - Epithelial markers (cytokeratins, EMA, others) typically absent but staining for cytokeratins may be present in up to 33% of cases:
 - When present cytokeratin staining tends to be focal rather than diffuse.
 - No immunoreactivity for S100 protein, p63, HMB-45, myoglobin, myogenin (myf-4), MyoD1, CD34, CD117
 - Reactivity for anaplastic lymphoma kinase (ALK) can be seen corresponding to the presence of ALK rearrangements (see Cytogenetics later):
 - ALK reactivity is cytoplasmic.
 - Intranuclear inclusions may be ALK positive.
 - Wide range of ALK positivity reported varying from 36% to 60% of cases
 - ALK lacks specificity and sensitivity.
 - Imperfect correlation to ALK mutations
 - Different fusion partners (see Cytogenetics later) may result in different patterns of ALK immunoreactivity
- Electron microscopy:
 - IMTS show features of myofibroblastic and fibroblastic differentiation:
 - Cytoplasmic organelles include well-developed, prominent rough endoplasmic reticulum, Golgi complexes, bundles of microfilaments arranged in parallel along the long axis of the cells with focal densities (“stress fibers”), fragmented basal lamina, pinocytotic vesicles, and fibronexus junctions.
 - Fibronexus junctions represent foci on the cell surface in which intracellular myofilaments and extracellular fibronectin filaments converge.
 - Rarely, junctional complexes can be seen.
- Cytogenetics and molecular genetics:
 - In children and young adults from 50% to 70% of cases often contain clonal cytogenetic rearrangements involving chromosome band 2p23 that fuse 3' kinase region of ALK gene with various partner genes including:
 - *TPM3*, *TPM4*, *CLTC*, *RANBP2*, and *ATIC*
 - Such rearrangements are uncommon in adults >40 years of age.

- Rearrangement restricted to myofibroblastic cell component whereas inflammatory cell component is normal without gene rearrangements or expression of ALK protein
- Presence of immunohistochemical expression of the ALK C-terminal end in myofibroblastic component of IMT and low to absent detection of ALK protein in nonneoplastic myofibroblasts represent strong evidence for oncogenic activation mechanism in IMT

Differential Diagnosis

- Contact ulcer of the larynx
- Pyogenic granuloma
- Nodular fasciitis:
 - Myofibroblastic dominant proliferation
 - Typically a lesion of soft tissue but rarely may be mucosal based, originating in mucosal sites of upper aerodigestive tract, including the larynx and pharynx
 - For a more complete discussion, see Section 4, Neck.
- IgG4-related disease:
 - Although there may be some overlap in histologic findings and presence of increase IgG4 plasma cells between IgG4-related disease and IMT, these two entities have distinct clinical and pathologic findings:
 - IgG4-related disease is typically systemic but may be localized, whereas IMT are generally localized.
 - Histologic findings often seen in IgG4-related disease include obliterative phlebitis and lymphoid aggregates, features not seen in IMT.
 - IgG4-related disease is ALK negative.
 - IgG4-related disease responds to steroid treatment.
 - For a more complete discussion of IgG4-related disease see Section 6, Salivary Glands.
- Spindle cell squamous carcinoma:
 - Overtly malignant cell infiltrate that may be associated with intraepithelial dysplasia and/or invasive squamous cell carcinoma
 - Reactivity may be seen for epithelial markers (cytokeratins, others) and p63.
 - Consistently reactive for vimentin and may be reactive for mesenchymal markers including actins and desmin
 - ALK negative
 - Spindle cell squamous carcinomas, especially those with associated surface ulceration and reactive changes, may have coexisting (reactive) myofibroblasts, the latter representing part of the wound healing process.
- Myofibrosarcoma

Treatment and Prognosis

- Laryngeal IMT are treated by conservative surgical resection, including local excision by laser removal or via laryngoscopic techniques.
- Conservative resection usually curative:
 - Rarely, recurrent tumor may occur after conservative surgical resection necessitating laryngectomy.
- Targeted therapy using ALK inhibitor crizotinib has shown promising results in ALK-translocated IMT
- Recurrence rate of approximately 25% has been reported for extrapulmonary IMT.
- Rare examples of extrapulmonary (not head and neck) IMT metastasize (less than 2%):
 - May be linked to presence of *RANBP2* and round cell morphology
 - ALK-negative IMT may have higher risk of metastasis.
- Difficult to predict on the basis of pathologic features which IMTs may behave more aggressively:
 - No correlation between behavior and tumor size, nuclear atypia, mitotic activity, necrosis
 - Aggressive behavior may correlate to round cell transformation characterized by:
 - Sheets of round to epithelioid cells with vesicular nuclei, prominent nucleoli, amphophilic to eosinophilic cytoplasm, increased mitotic activity including atypical mitoses, myxoid stroma, and prominent neutrophilic infiltrate
 - Distinct nuclear membrane or perinuclear pattern of ALK staining
 - *RANBP2*-ALK fusion detected by reverse transcription polymerase chain reaction
 - To date, such changes reported in IMT located within the abdomen arising from omentum or mesentery
 - Terminology of epithelioid inflammatory myofibroblastic sarcoma suggested for this lesion conveying malignant behavior

Granular Cell Tumor

(Figs. 16-12 through 16-14)

Definition: Benign tumor of neurogenic (Schwann cell) origin characterized by lysosome-rich cells with abundant granular eosinophilic-appearing cytoplasm.

Synonyms: Granular cell myoblastoma; granular cell neuroma; granular cell schwannoma; granular cell neurofibroma; Abrikossoff tumor; granular cell schwannoma

- Two forms can occur:
 1. Mucosal granular cell tumor
 2. Congenital granular cell epulis (see Section 2, Oral Cavity, for detailed discussion)

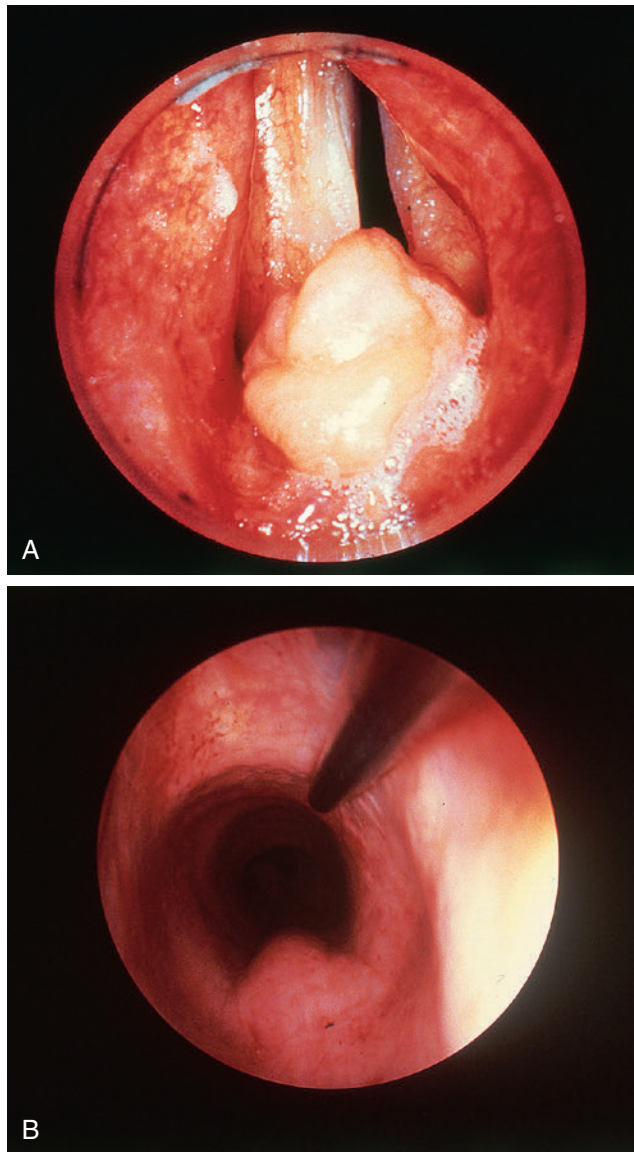


Fig. 16-12. Endoscopic appearance of granular cell tumor.

A, Laryngeal granular cell tumor appearing as a large, solitary tan-yellow mass along the posterior aspect of the true vocal cord. **B**, Tracheal granular cell tumor appearing as a mucosal-covered nodular intraluminal protrusion.

Mucosal Granular Cell Tumor

Clinical

- Can occur in virtually any organ but most frequent sites of occurrence include:
 - Skin > tongue > breast > larynx > gastrointestinal tract > bronchus, trachea
 - Except for the larynx, granular cell tumors are more common in women than in men
 - See Section 2 on the Oral Cavity for a discussion of lingual granular cell tumor and congenital granular cell epulis.

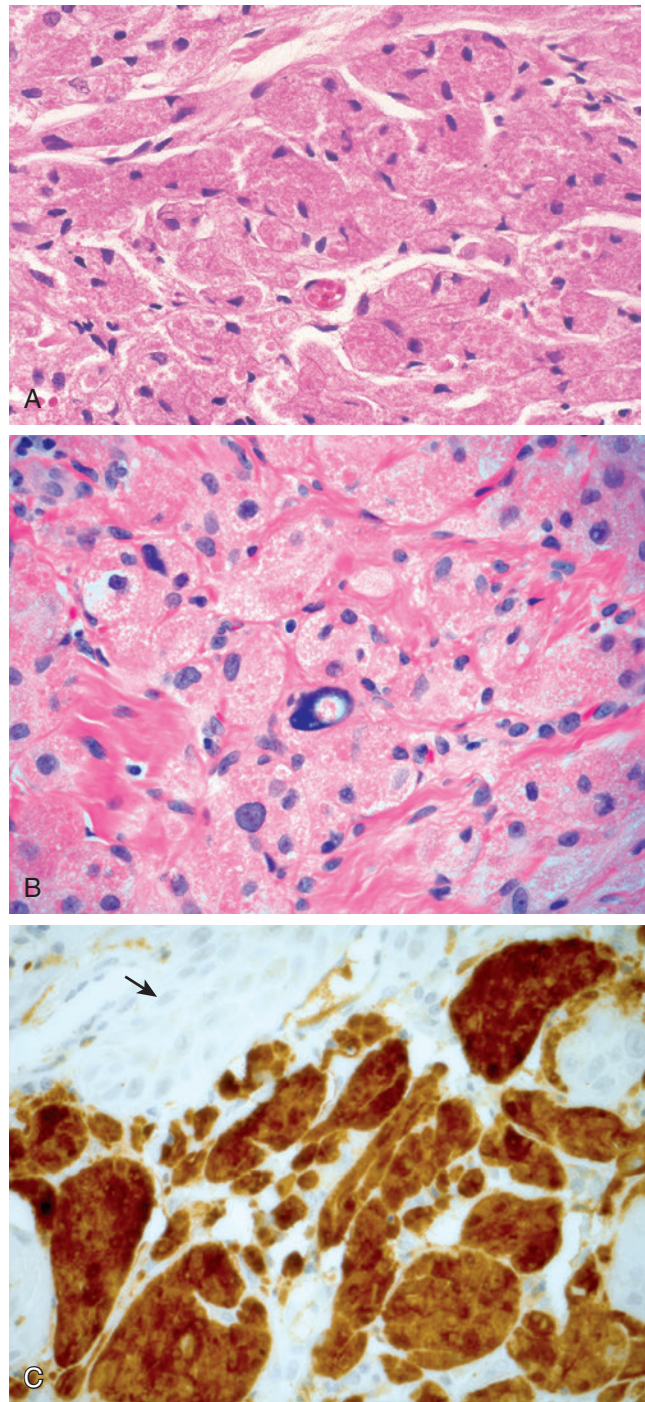


Fig. 16-13. Granular cell tumor.

A, Histologically, granular cell tumors are characterized by the presence of round to polygonal shaped cells with round to oval, vesicular nuclei, coarse granular cytoplasm, and ill-defined cell borders. **B**, Markedly pleomorphic and hyperchromatic nuclei may be identified, which are not diagnostic for malignancy. **C**, Granular cells are immunoreactive for S100 protein, which is negative in the squamous epithelium (*arrow*).

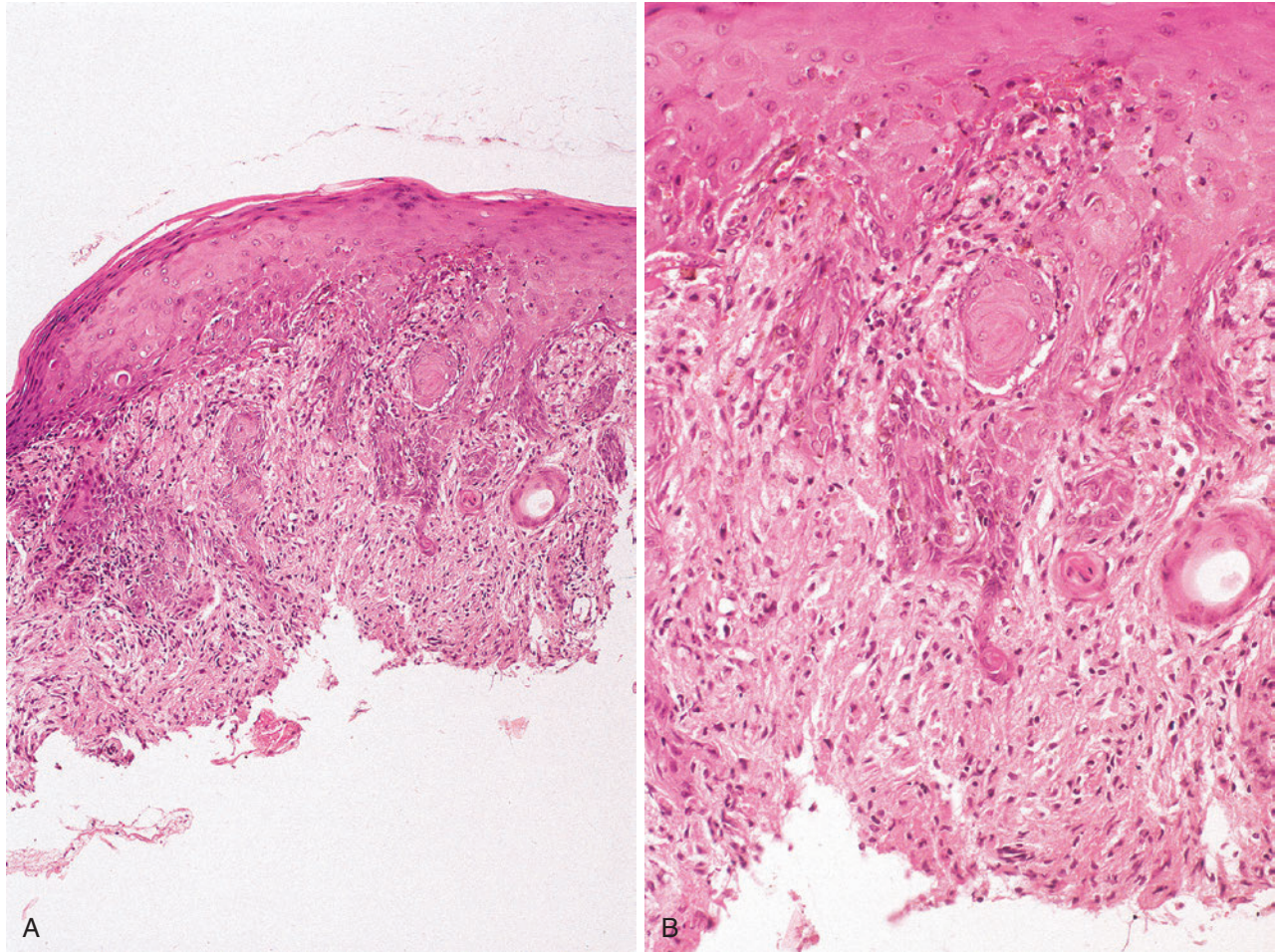


Fig. 16-14. Pseudoepitheliomatous hyperplasia and granular cell tumor.

A, B, Pseudoepitheliomatous hyperplasia of the larynx with associated granular cell tumor. The epithelial proliferation may be misinterpreted as an invasive squamous carcinoma unless attention is paid to the presence of granular cells deep to and intermingled with the hyperplastic squamous epithelium.

- For laryngeal tumors:
 - No gender predilection; primarily affects adults in third to fifth decades of life; uncommon in children
 - Hoarseness is most common complaint.
 - Most frequently identified along the posterior aspect of the true vocal cord (posterior one third) but can also be seen in the supraglottic and subglottic areas:
 - Vocal cord > arytenoids > false cord > anterior commissure > subglottis > postcricoid area
- For tracheal tumors:
 - More common in women than in men
 - Wide age range but peak incidence is in the fourth decade
 - Symptoms include stridor and airway obstruction.
 - Most often arise in the cervical trachea
- Regardless of site, most GCTs are single lesions but multiple tumors may be found:
 - May occur synchronously or metachronously
 - Multiple granular cell tumors may occur in LEOPARD syndrome and Noonan syndrome associated with mutations in *PTPN11*.
- No known cause
- Granular cell tumors felt to be of neural (Schwann cells) origin supported by:
 - Involvement of small to medium nerves
 - S100 protein, CD57, and neuron-specific enolase positive
 - Presence of myelinated and nonmyelinated axon-like structures by ultrastructural analysis
 - Presence of residual axons in many granular cell tumors

Pathology

Gross

- Often solitary, polypoid, or sessile, tan-white to yellow, measuring from 0.3 to 3.0 cm in diameter; occasionally may have papillary or cystic areas

- Most are submucosal with an intact overlying surface epithelium, although rarely may be associated with epithelial ulceration.

Histology

NOTE: Regardless of location, histology is the same.

- Unencapsulated or poorly circumscribed subepithelial lesion with a syncytial, trabecular, or nested growth pattern
- Neoplastic cells are round to polygonal with round to oval, vesicular to hyperchromatic, centrally located small nuclei, and the presence of coarsely granular eosinophilic-appearing cytoplasm with poorly delineated cell borders.
- Cellular pleomorphism varies but usually is minimal:
 - Uncommonly markedly pleomorphic nuclei may be present.
- Mitoses and necrosis not typically present
- Occasionally, within the collagenous tissue and in the proximity of vessels, stromal histiocytes with large refractile needle-shaped bodies may be seen:
 - Referred to as angulate bodies
- Pseudoepitheliomatous hyperplasia (PEH) may be present:
 - Exuberant epithelial hyperplasia that may be associated with granular cell tumors
 - May be so exuberant as to suggest a diagnosis of invasive squamous cell carcinoma:
 - In contrast to squamous cell carcinoma, PEH typically displays no cytologic evidence of malignancy.
 - However, some examples may be histologically identical to invasive squamous cell carcinoma:
 - A diagnosis of SCC should not be rendered in the presence of granular cell tumor unless:
 - Epithelial proliferation extends beyond/below the depth of associated granular cell tumor:
 - S100 protein and cytokeratins may be needed to determine extent of the epithelial proliferation relative to the granular cell tumor.
 - Metastatic squamous cell carcinoma (locoregional, distant) is present.
- Granular cell tumor cells may involve (“invade”) nerves:
 - Does not represent an indicator of malignancy (see below for malignant granular cell tumor)
- Histochemistry:
 - Cytoplasmic granules are diastase-resistant, PAS-positive, stain with alcian blue at pH 2.5, stain red with trichrome, and vary in size from being minute to as large as red blood cells.
 - Angulate bodies are intensely PAS positive.
- Immunohistochemistry:
 - S100 protein, calretinin, CD57 (Leu-7) positive
 - Strongly CD68 (KP-1) positive as well as alpha-1-antitrypsin and alpha-1-antichymotrypsin
 - Laminin and collagen type 4 are positive, highlighting basement membranes around groups of tumor cells.
 - Additional consistent but nonspecific staining seen for inhibin alpha-subunit and protein gene product 9.5:
 - Significance of inhibin expression with regard to cell differentiation and pathogenesis is unclear.
 - Proliferative activity as seen by Ki-67 reactivity is low.
 - Negative for cytokeratins, neurofilament protein, and glial fibrillary acidic protein
 - Interstitial cells with angulate bodies are CD68 positive and S100 protein negative.
- Electron microscopy:
 - Characterized by presence of numerous intracellular large granules (secondary lysosomes) consisting of membrane-bound, autophagic vacuoles containing mitochondria, rough endoplasmic reticulum, myelin figures, and myelinated and nonmyelinated axon-like structures
 - Interstitial cells contain membrane-bound structures with parallel arrays of microtubules representing angulated bodies as well as microfilaments and lipid material.

Differential Diagnosis

- Rhabdomyoma
- Invasive squamous cell carcinoma as a result of the PEH
- Alveolar soft part sarcoma
- Malignant granular cell tumor:
 - Rare neoplasms accounting for approximately 1% of all granular cell tumors
 - Clinically are similar to benign granular cell tumors except that they do not occur in newborns or children
 - Usually measure >4.0 cm in diameter and tend to occur in the extremities
 - Histologically, a diagnosis of malignancy can be made in the presence of three of the following criteria:
 - Necrosis
 - Spindle-shaped cells
 - Increased nuclear-to-cytoplasmic ratio
 - Vesicular nuclei with prominent nucleoli
 - Pleomorphism
 - Increased mitotic activity (greater than two mitoses per 10 high-power fields)
 - Any granular cell tumor in which one or two of the above criteria are found can be referred to as atypical.

- Transition from benign granular cell tumor to malignant granular cell tumor is frequently apparent.
- Immunohistochemical staining similar to that of benign granular cell tumors except:
 - CEA reactivity reported, significance of which is not known
 - Increase proliferation rate from 10% to 50% by Ki67 (MIB1) staining
 - Extensive p53 staining in up to 70% of cases
- Differential diagnosis includes alveolar soft part sarcoma and paraganglioma.
- Surgery is the preferred treatment (wide en bloc excision); radio- and chemotherapy are ineffective.
- Metastasize via lymphatics and blood vessels (lymph nodes, lung, liver, and bone)

Treatment and Prognosis

- Conservative but complete surgical excision is considered curative:
 - Small tumors can be excised endoscopically.
- Granular cell tumors are radioresistant.
- Local recurrence may occur in a minority of patients (less than 10%):
 - Recurrent tumor may represent a new primary lesion in patients with multifocal disease.

Laryngeal Paraganglioma

(Figs. 16-15 and 16-16)

Definition: Benign neoplasm arising from the extra-adrenal neural crest-derived paraganglia specifically located in the larynx, and believed to arise from the superior and inferior laryngeal paraganglia.

Synonym: Glomus tumor

Histoanatomy

- Laryngeal paraganglia are microscopic structures with variable anatomic distribution in relation to cricoid and thyroid cartilages.
 - Most are paired structures located in superior and inferior locations in lateral larynx.
 - Sometimes found immediately adjacent to thyroid gland or within capsule of thyroid gland
 - Described in relation to laryngeal recurrent nerve
- Physiologic role of laryngeal paraganglia unknown

Clinical

- Uncommon laryngeal tumor
- More common in women than in men; wide age range but most common in the fifth decade of life
- Vast majority (greater than 80%) predilect to the supraglottic larynx with the aryepiglottic fold and false vocal cord representing the most common sites of occurrence.

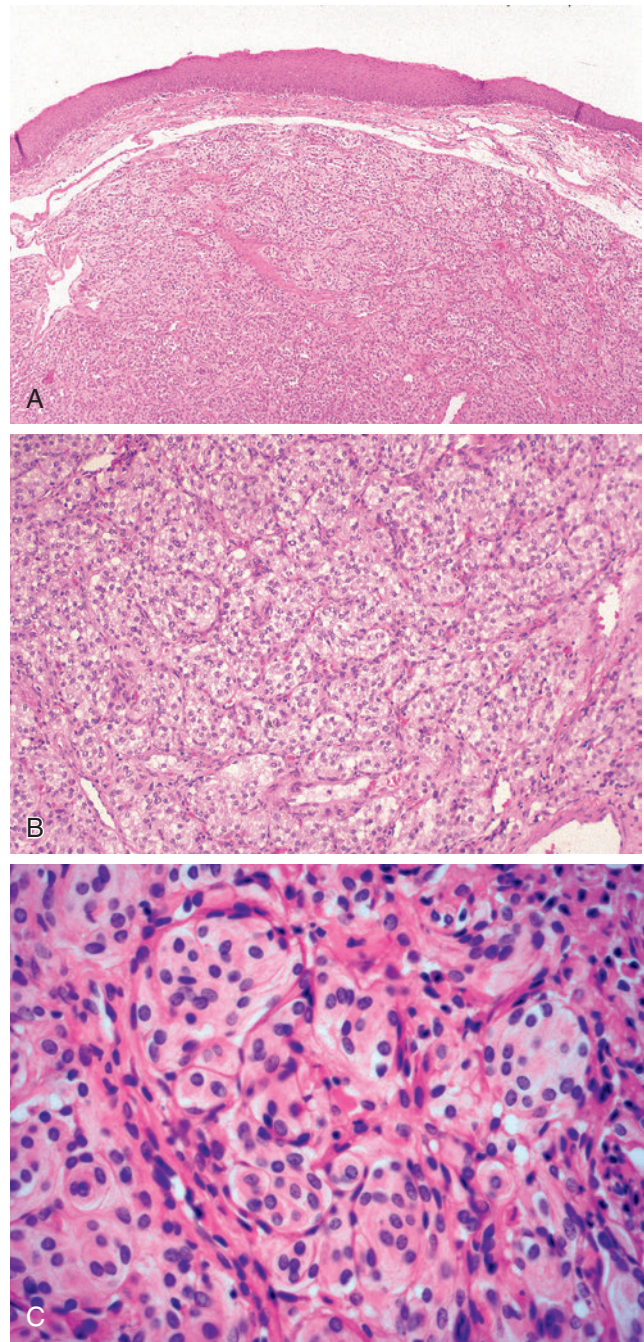


Fig. 16-15. Laryngeal paraganglioma.

A and B, The tumor is located wholly within the submucosa showing characteristic organoid or cell nest ("zellballen") growth with the cell nests separated by fibrovascular stroma. **C,** Cells nests are composed predominantly of chief cells with uniform round to oval nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm; sustentacular cells situated at the periphery of the cell nests are difficult, if not impossible, to identify by light microscopy.

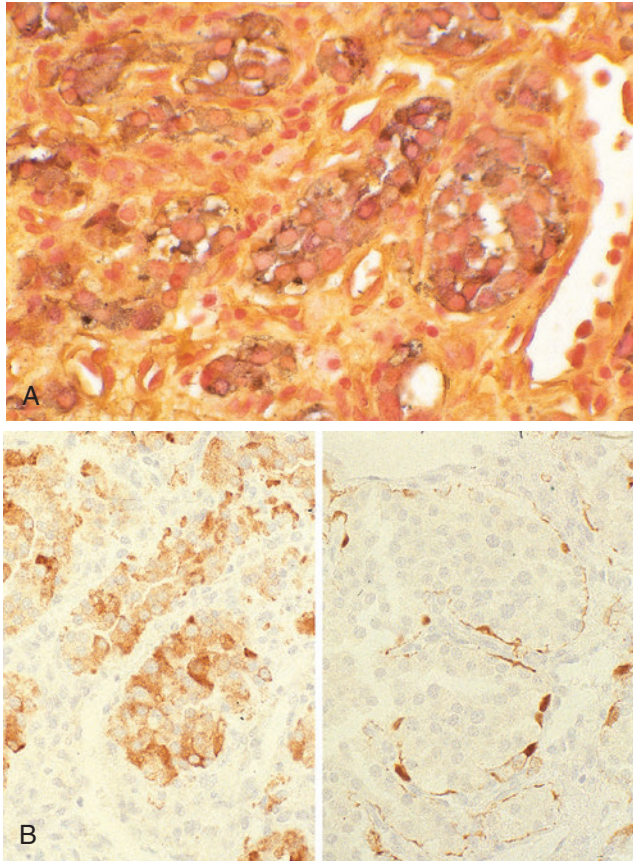


Fig. 16-16. Special stains in paraganglioma.

Special stains that can be seen in (laryngeal) paragangliomas may include **(A)** argyrophilic (Churukian-Schenk) positive intracytoplasmic granules; **(B)** dedicated chromogranin reactivity to the chief cells (*left*) and dedicated S100 protein to the sustentacular cells (*right*).

- Clinical presentation includes hoarseness, dysphagia, dyspnea, and stridor.
- Generally are not hormonally (functionally) active, although exceptional cases may be functional.
- Rarely may be multicentric with other head and neck paragangliomas
- Radiology:
 - CT: enhancing mass
 - MRI: intermediate signal intensity on T1-weighted image and high signal intensity on T2-weighted image

Pathology

Gross

- Submucosal tumors ranging in size from 0.5 to 6.0 cm

Histology

- Located in submucosa without involvement of overlying intact epithelium

- Identical to paragangliomas of more usual sites:
 - Histologic hallmark is the presence of a cell nest or “Zellballen” pattern cell nest characteristic of paragangliomas.
 - Stroma surrounding and separating the nests is composed of a prominent fibrovascular tissue
 - Neoplasm is composed predominantly of chief cells, which are round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm
 - Sustentacular cells difficult, if not impossible, to identify by light microscopy:
 - These cells represent modified Schwann cells.
 - Are located at the periphery of cell nests
 - Appear as spindle-shaped, basophilic-appearing cells
- Glandular or alveolar differentiation is not seen.
- Histochemistry:
 - Reticulin staining may better delineate the cell nest growth pattern with staining of the fibrovascular cores surrounding the neoplastic nests
 - Tumor cells are argyrophilic (Churukian-Schenk)
 - Argentaffin (Fontana-Masson), mucicarmine, and periodic acid Schiff stains are negative.
- Immunohistochemistry:
 - Chief cells:
 - Chromogranin, synaptophysin, CD56, neuron-specific enolase, neurofilaments, and a variety of peptides positive; GATA3 positive (nuclear)
 - May also be S100 protein positive
 - Sustentacular cells:
 - S100 protein positive, Sox10 positive
 - Vimentin is variably reactive in chief cells and sustentacular cells
 - In general, epithelial markers, including cytokeratins and p63, are negative:
 - Rare examples of cytokeratin-reactive paragangliomas are reported.
 - Melanocytic markers (HMB45, melan-A, tyrosinase, MITF, Sox10) negative
 - Myogenic markers (desmin, myogenin, others) negative
- Electron microscopy:
 - Abundant neurosecretory granules (100 to 250 nm)
 - Cellular junctional complexes are rarely (if ever) seen.

Differential Diagnosis

- Neuroendocrine carcinomas including carcinoid tumor and atypical carcinoid (see [Box 16-5](#) and [Table 16-6](#))

Treatment and Prognosis

- Surgery is the preferred treatment and is curative.
- Malignant paragangliomas reported in the literature more likely represent neuroendocrine carcinoma

Chondroma (Fig. 16-17)

Definition: Benign tumor of mature hyaline cartilage.

Clinical

- Cartilaginous neoplasms of the head and neck are uncommon, and those of the larynx are rare:
 - Laryngeal chondrosarcomas are more common than chondromas.
- Most common sites of occurrence of head and neck chondromas include:
 - Sinonasal tract
 - Less common sites include maxilla and mandible, larynx, palate, pharynx, nasopharynx, and ear.
- In the larynx, chondromas may originate from posterior lamina of cricoid cartilage and thyroid cartilage and less often from epiglottis and arytenoids.
 - May arise in soft tissues of the true vocal cords (Reinke space)
- May be incidentally identified or cause hoarseness:
 - A clinically significant cartilaginous tumor of the larynx is most likely a chondrosarcoma.
- Radiology:
 - Discrete soft tissue mass contiguous with its laryngeal cartilaginous origin
 - Coarse calcifications and ossification may be seen.

- Involvement of Reinke space most probably represents a metaplastic rather than a true neoplastic process with derivation from the vocal cord ligament.

Pathology

Gross

- Lobulated, firm to hard, blue-gray, submucosal mass seldom measuring greater than 1 cm:
 - Although laryngeal chondromas seldom attain sizes greater than 1 cm, occasionally they may grow to sizes up to 4 cm.

Histology

- Submucosal lobulated or nodular growth(s) composed of chondrocytes recapitulating the normal histology of cartilage.
- Absence of cellular pleomorphism, binucleate chondrocytes, or mitotic activity
- Immunohistochemistry:
 - S100 protein positive
 - Podoplanin (D2-40) positive

Differential Diagnosis

- Cartilaginous hamartoma
- Chondrosarcoma (see later in chapter)

Treatment and Prognosis

- Conservative but wide surgical excision including an adequate margin of normal tissue is the preferred treatment:
- Surgical resection is curative.

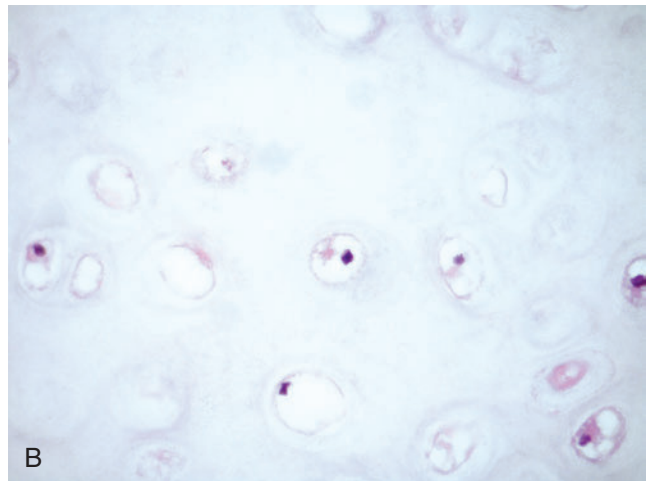


Fig. 16-17. Laryngeal chondroma.

A, Submucosal cartilaginous nodules with intact overlying squamous epithelium. **B**, At high magnification the chondrocytes are bland in appearance, lacking significant nuclear pleomorphism, binucleate chondrocytes, or mitotic activity as may be seen in low-grade chondrosarcomas.

- Recurrences are uncommon and according to most authorities do not occur in association with laryngeal chondromas.
- Recurrent chondromas of the larynx should prompt a diagnosis of a low-grade chondrosarcoma.

Lipoma (Fig. 16-18)

Definition: Benign tumor of mature adipocytes.

Clinical

- In the head and neck, most often occur in the neck region (see Section 4, Neck, for more complete discussion)
- Rare tumor of larynx (and hypopharynx)
- More common in men than in women; adult ages usually sixth decade and older
- Solitary tumors often arising in the supraglottic larynx or project into the larynx from a hypopharyngeal mass:

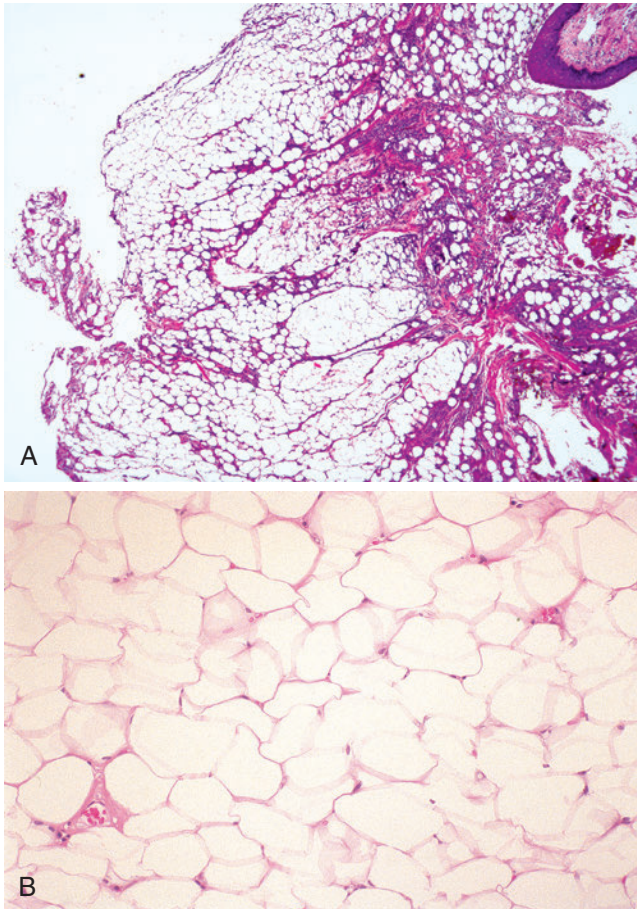


Fig. 16-18. Laryngeal lipoma.

A, B, Circumscribed submucosal tumor composed of mature adipocytes lacking evidence of cytologic atypia.

- Laryngeal sites of occurrence include aryepiglottic fold, vestibular fold, and epiglottis.
- Symptoms include dysphagia, dyspnea, acute airway obstruction, hoarseness, dysphonia, and a lump in the throat.
- Radiology:
 - CT scan: low attenuation mass:
 - Adipose tissue is the only soft tissue that has a density less than water (zero or negative Hounsfield units) so that CT scan reveals extent of the mass and also its lipomatous nature.
- No known cause:
 - Rare cases reported in association with symmetric lipomatosis (Madelung disease or Launois-Bensaude syndrome)

Pathology

Gross

- Sessile to pedunculated mass measuring from a few millimeters to 6.0 cm in greatest dimension

Histology

- Encapsulated tumor of mature adipose tissue (adipocytes):
 - Adipocytes are uniform, varying slightly in size and shape.
 - Atypical adipocytes and/or lipoblasts are not identified.
- Richly vascularized but vascularity may be difficult to appreciate due to compression by distended adipocytes.
- Secondary changes may include hemorrhage, calcification, cyst formation, fat necrosis, and infarction.
- Metaplastic bone and cartilage may be identified.
- Laryngeal (and hypopharyngeal) lipomas may include:
 - Lipomas with prominent myxoid stroma (myxolipoma) or prominent fibrous tissue component (fibrolipoma)
 - Intramuscular lipomas:
 - Also referred to as infiltrating lipoma
 - Characterized by the presence of mature adipocytes infiltrating skeletal muscle
 - Spindle cell lipoma:
 - Characterized by mature adipocytes admixed with uniform, small spindle cells, and eosinophilic collagen bundles set in a myxoid matrix with a vascular pattern varying from inconspicuous to prominent
 - Mast cells can be seen in association with the spindle cells.
 - Other types of lipomas including angiolipoma, pleomorphic lipoma, angiomyolipoma, and lipoblastoma not reported in these sites

- Immunohistochemistry (not needed for the diagnosis):
 - Adipocytes are S100 protein positive.
 - CD34 positive in spindle cell lipomas
 - MDM2 and CDK4 negative
- Hibernoma (benign tumors of brown fat)
 - Rare examples reported to occur in the larynx
- For spindle cell lipoma:
 - Various spindle cell neoplasms of these sites

Treatment and Prognosis

- Surgery is curative.
- May rarely recur:
 - May be a function of inadequate excision
 - Presence of recurrence should raise diagnosis of well-differentiated liposarcoma:
 - Does not represent transformation from a lipoma but initial lesion was a liposarcoma that went undiagnosed due to overall bland morphology lacking overt evidence of malignancy
 - In this setting staining for MDM2 and CDK4 may prove useful and diagnostic.

MALIGNANT NEOPLASMS OF THE LARYNX AND HYPOPHARYNX

GENERAL CONSIDERATIONS

- Squamous cell carcinoma or a variant thereof is most common malignant neoplasm of the larynx
- See Section 2, Oral Cavity, for a more complete discussion of the following topics related to head and neck squamous cell carcinoma (HNSCC):
 - Mutagen sensitivity
 - “Field cancerization”
 - Second primary malignancy
 - Genetics of HNSCC
 - Prognostic indicators, including:
 - Status of the surgical resection margins
 - Nodal metastasis
 - Lymph-vascular invasion
 - Invasion of soft tissue structures including nerves and cartilage
 - Distant metastasis
 - Multiple primary malignancies (second malignancy)
 - Host immunologic response

neoplasia (SIN); laryngeal intraepithelial lesion (LIN); laryngeal intraepithelial lesion (LIL); simple hyperplasia; basal/parabasal hyperplasia; atypical hyperplasia

- Recommended WHO terminology includes mild, moderate, and severe dysplasia and carcinoma in situ (Table 16-2).

Clinical

- More common in men than in women; generally limited to the adult population with a mean age at diagnosis in the sixth decade of life
- May occur anywhere in the larynx but mainly identified along the true vocal cord:
 - Typically is a unilateral lesion but may be bilateral in up to 30% of cases
- Most frequent symptom is hoarseness.
- May appear white (leukoplakia), red (erythroplakia), or mixed red and white (speckled leukoplakia):
 - See Section 2, Oral Cavity, for more complete discussion on leukoplakic and erythroplakic lesions.
- Causes may include:
 - Tobacco smoking (most common) and excess alcohol use:
 - Alcohol potentiates the effect of tobacco smoking.
 - Risk of developing dysplastic lesions increases with duration of smoking and/or alcohol use.
 - Chronic infections, including fungal infection
 - Less commonly secondary to voice abuse, environmental/industrial exposure, and vitamin A deficiency
 - Role of human papillomavirus in development of intraepithelial dysplasia of the larynx remains unproven:

LARYNGEAL EPITHELIAL DYSPLASIA

Keratinizing and Nonkeratinizing Dysplasia (Figs. 16-19 through 16-22)

Definition: Alteration in a malignant direction in the appearance of epithelial cells with an increased likelihood to progress to squamous cell carcinoma.

Synonyms: Keratosis with atypia; atypia; mild dysplasia; moderate dysplasia; severe dysplasia; squamous intraepithelial lesion (SIL); squamous intraepithelial

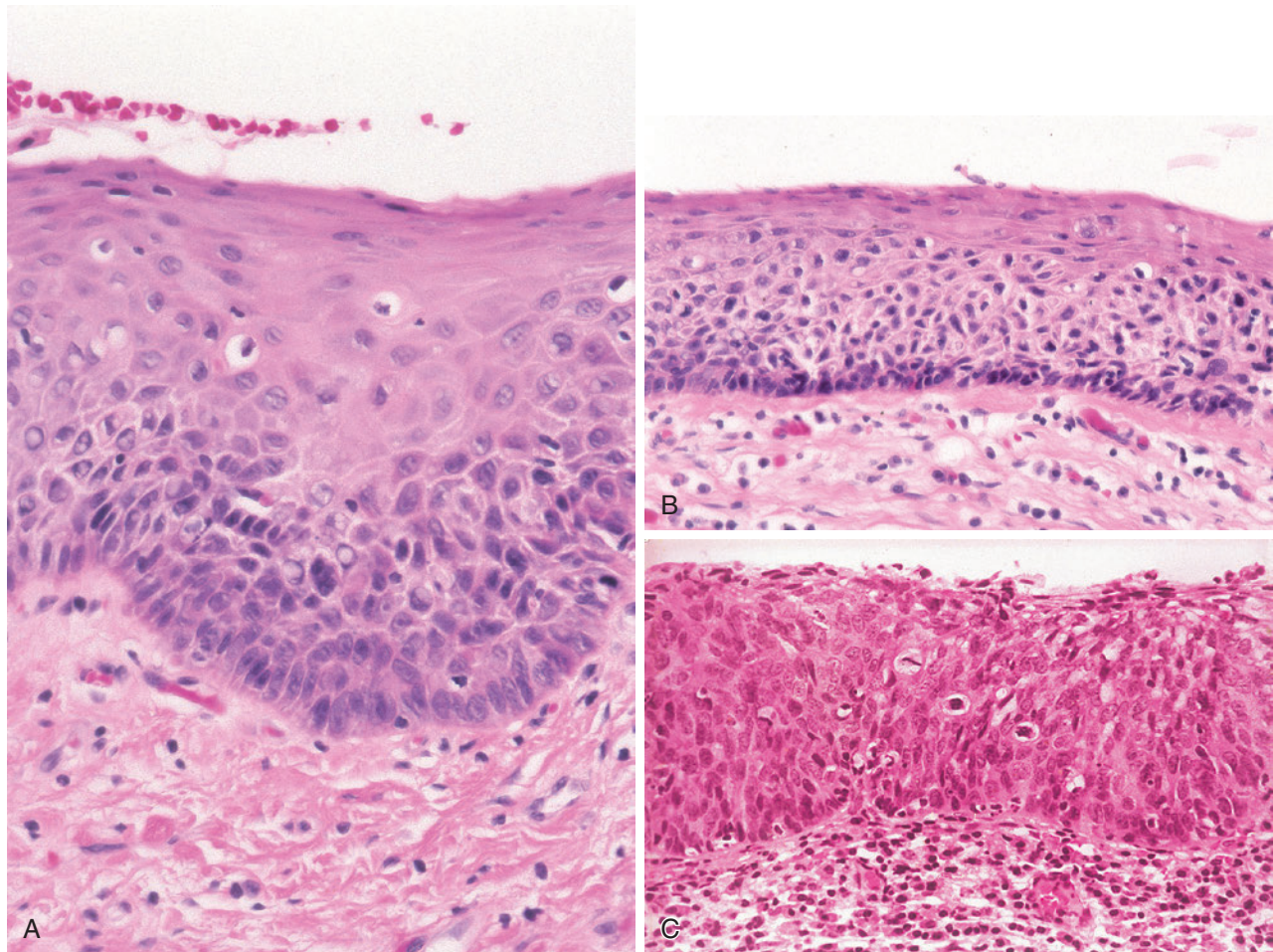


Fig. 16-19. Laryngeal nonkeratinizing dysplasia.

The grading in these dysplastic lesions is similar to that of the uterine cervix and includes **(A)** mild dysplasia when the dysplastic changes are limited to the lower third of the surface epithelium; **(B)** moderate dysplasia when the dysplastic changes involve two thirds of the surface epithelium; and **(C)** severe dysplasia (carcinoma in situ) when the dysplastic changes involve the entire surface epithelium without violation of the basement membrane.

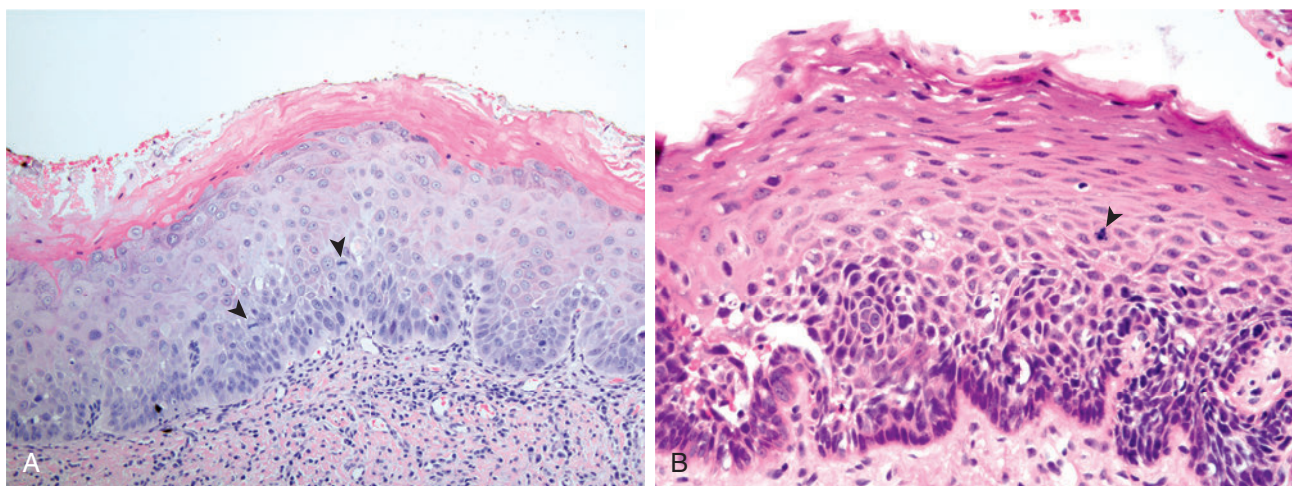


Fig. 16-20. Laryngeal keratinizing mild dysplasia.

Laryngeal keratinizing mild dysplasia (low-grade squamous intraepithelial lesion) showing squamous epithelium with associated keratosis and dysplastic cytologic changes limited to the basal zone with relatively flat-appearing epithelium without associated elongated and downwardly extending rete ridges. Mitotic figures (*arrowheads*) are seen at the junction (more or less) of the lower and mid-epithelial layers.

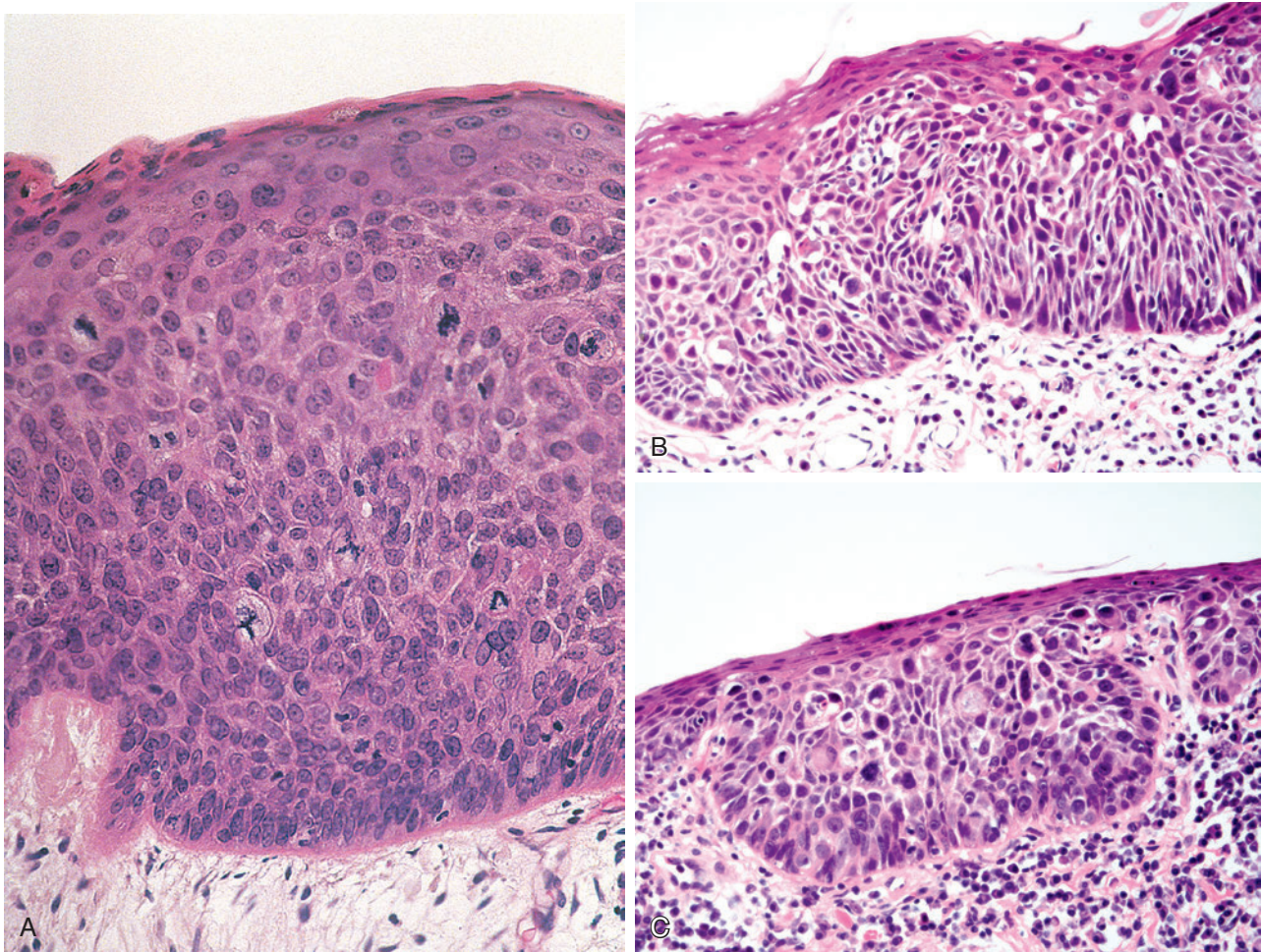


Fig. 16-21. Laryngeal keratinizing moderate dysplasia.

Laryngeal keratinizing moderate dysplasia (high-grade squamous intraepithelial lesion) showing squamous epithelium with associated keratosis and dysplastic cytologic changes involving at least two thirds of the thickness of the epithelium with relatively flat to widened and/or slightly elongated and downwardly extending rete pegs. In these images there is still maturation of the most superficial layer of the epithelium. However, given a shared risk to progression to invasive carcinoma with keratinizing severe dysplasia, a classification that includes keratinizing moderate and severe dysplasias within the category of high-grade squamous intraepithelial lesion appears justified.

TABLE 16-2 Classification Schemes for Epithelial Precursor Lesions

WHO*	SIN	Ljubljana	Modified Ljubljana	Two-Tiered
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia	LGSIL	LGSIL
Moderate dysplasia	SIN 2	Atypical hyperplasia	HGSIL	HGSIL
Severe dysplasia	SIN 3	Atypical hyperplasia	HGSIL	HGSIL
CIS	SIN 3	CIS	CIS	HGSIL

CIS, Carcinoma in situ; *HGSIL*, low-grade squamous intraepithelial lesion; *LGSIL*, low-grade squamous intraepithelial lesion; *SIN*, squamous intraepithelial neoplasia; *WHO*, World Health Organization.

*Currently recommended classification scheme.

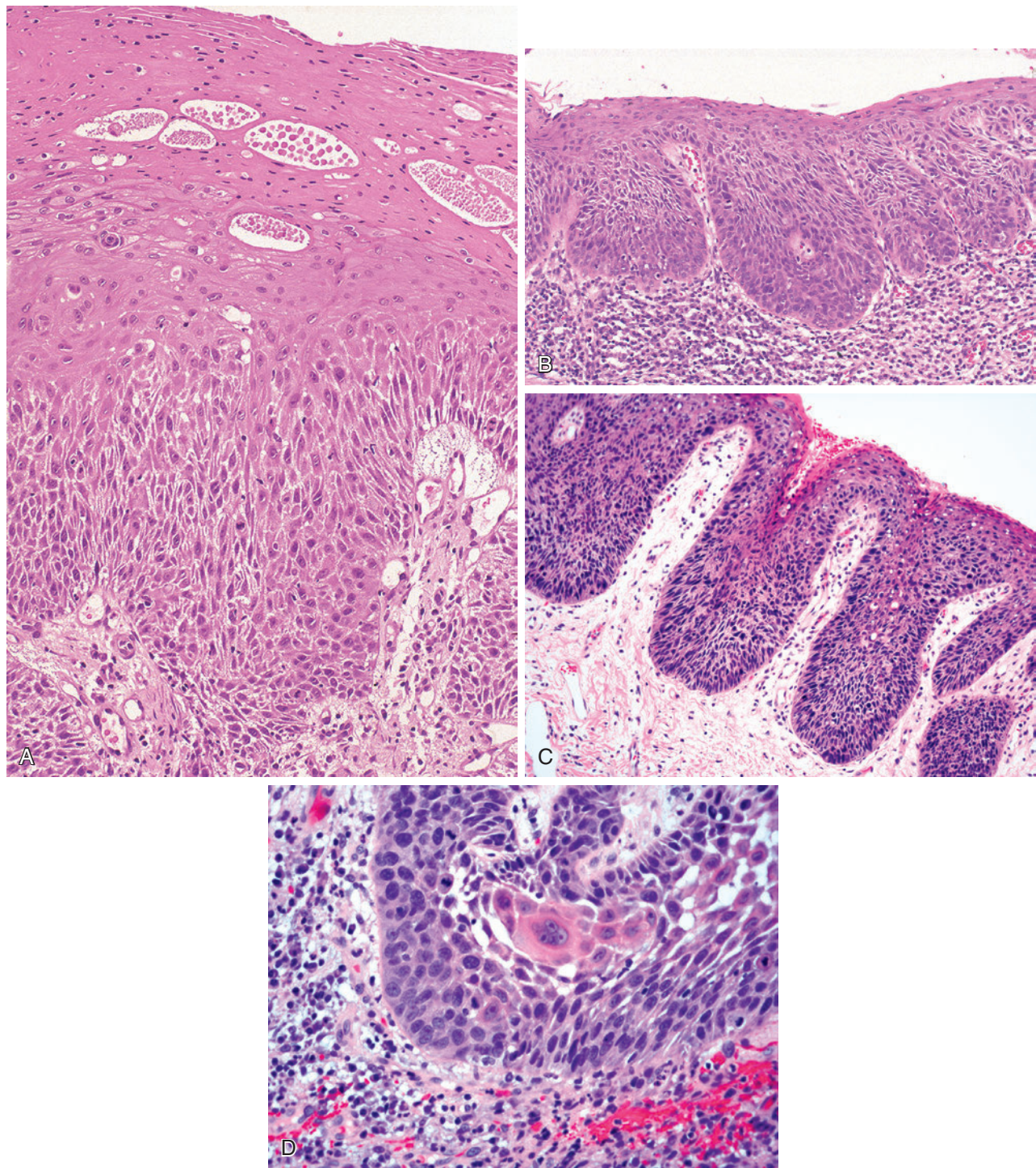


Fig. 16-22. Laryngeal keratinizing severe dysplasia.

A through **C**, Laryngeal keratinizing severe dysplasia tantamount to carcinoma in situ (high-grade squamous intraepithelial lesion) including architectural alterations with widening and elongated and downwardly growing rete ridges coupled to cytomorphic changes. All of these examples include an absence of full-thickness intraepithelial dysplasia, thereby falling short of the classic definition for carcinoma in situ. Nevertheless, these lesions all merit designation as keratinizing severe dysplasia tantamount to carcinoma in situ as the risk of progression to invasive carcinoma is similar to that of “classic” carcinoma in situ. Further, such lesions can progress to invasive carcinoma in the absence of full-thickness intraepithelial dysplasia. **D**, Paradoxical maturation characterized by abnormal keratinization in the basal zone; associated high-grade dysplastic cytomorphic features are present.

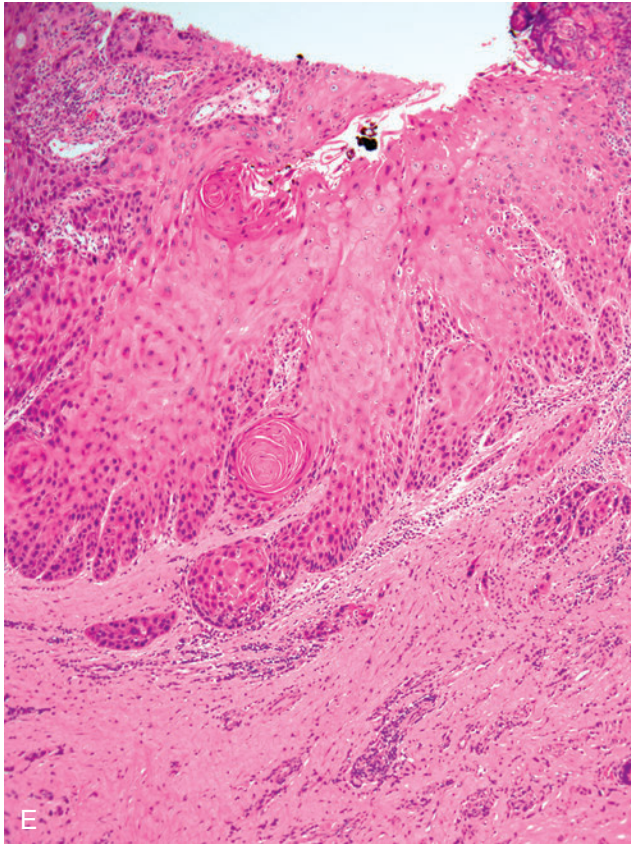


Fig. 16-22, cont'd

E, Example of laryngeal invasive carcinoma originating from dysplastic changes limited to the basal zone epithelium ("drop off" carcinoma) without full thickness intraepithelial dysplasia.

- High-risk HPV uncommon finding in head and neck squamous cell carcinoma from patients who have history of tobacco or alcohol use
- Low-risk HPV not associated with such cases
- Prevalence of HPV in precursor lesions (i.e., dysplasia) reported in approximately 12% of cases
- HPV DNA reported in 12% to 25% of normal (clinically and histologically) larynges

Pathology

Gross

- Localized, circumscribed flat, or papillary area with white (leukoplakic), red (erythroplakic), or gray appearance

Histology (Box 16-2)

- Histomorphologic changes can be separated into architectural abnormalities and cellular abnormalities and include proliferation of immature or "uncommitted" cells with process beginning in basal and parabasal area:

BOX 16-2 Histomorphologic Changes Associated with Dysplasia

Architectural Abnormalities

- Irregular epithelial stratification with elongated rete ridges extending in a downward fashion into submucosa
- Loss of maturation with increased cellularity in the superficial epithelium:
 - Normally in mature squamous epithelium there is a decrease in the cellularity from the basal zone toward the keratinizing layers.
- Crowding of cells with loss of polarity especially in the basal zone
- Increased mitotic activity, especially away from the basal zone involving the mid- and upper (superficial) portions of the surface epithelium:
 - May include atypical forms
- Abnormal keratosis (dyskeratosis) and paradoxical maturation:
 - Occurs in individual cells
 - Keratin pearls in elongated rete ridges

Cellular Abnormalities

- Abnormal variation in nuclear size (anisonucleosis)
- Abnormal variation in the nuclear shape (nuclear pleomorphism)
- Increase nuclear size relative to cytoplasm (increased nuclear-to-cytoplasmic ratio)
- Nuclear hyperchromasia with irregularities in nuclear contour
- Prominent nucleoli (not unique to dysplasia may be seen in reactive or reparative processes)

- Architectural abnormalities:
 - Irregular epithelial stratification with elongated rete ridges extending in a downward fashion into submucosa
 - Loss of maturation with increased cellularity in the superficial epithelium:
 - Normally in mature squamous epithelium there is a decrease in the cellularity from the basal zone toward the keratinizing layers
 - Paradoxical maturation (abnormal keratinization or keratin pearl formation in the basal zone)
 - Crowding of cells with loss of polarity especially in the basal zone
 - Increased mitotic activity, especially away from the basal zone involving the mid- and upper (superficial) portions of the surface epithelium:
 - May include atypical forms
 - Abnormal keratosis (dyskeratosis):
 - Occurs in individual cells
 - Keratin pearls in elongated rete pegs
- Cellular abnormalities:
 - Abnormal variation in nuclear size (anisonucleosis)
 - Abnormal variation in the nuclear shape (nuclear pleomorphism)

- Increased nuclear size relative to cytoplasm (increased nuclear-to-cytoplasmic ratio)
- Nuclear hyperchromasia with irregularities in nuclear contour
- Prominent nucleoli (not unique to dysplasia and may be seen in a reactive or reparative process)
- Histomorphologic evaluation for dysplasia is primarily predicated on the cellular abnormalities but also include architectural abnormalities especially in relationship to keratinizing dysplastic lesions.

Grading of Epithelial Dysplasia

- Grading of upper aerodigestive tract intraepithelial dysplasias is controversial and fraught with subjectivity especially for keratinizing dysplasias.
- Variety of grading schemes proposed (see Table 16-2) but at present the recommended classification scheme is three-tiered system of grading intraepithelial dysplasias advocated by the World Health Organization to include:
 - Mild dysplasia (grade I):
 - Dysplasia limited to the lower portions or inner third of the epithelium (basal zone dysplasia)
 - Moderate dysplasia (grade II):
 - Dysplasia involves up to two thirds of the thickness of the epithelium.
 - Severe dysplasia (grade III):
 - Dysplasia involves from two thirds to almost complete thickness of the epithelium.
 - Carcinoma in situ is subsumed within this grade.
- Two-tiered system of grading intraepithelial dysplasias (see Table 16-2) is advocated to include:
 - Low-grade squamous intraepithelial dysplasia includes mild dysplasia.
 - High-grade squamous intraepithelial dysplasia includes moderate and severe dysplasia/carcinoma in situ.
 - More reproducible with greater consensus among pathologists than three-tiered system:
 - Subject of Hershey Consensus Conference (unpublished data)
 - No statistical differences in risk of progression to invasive carcinoma between moderate and severe dysplasia justifying “lumping” these two lesions within a single category similar to Bethesda classification of uterine cervical squamous intraepithelial lesions
- Paradigm for grading epithelial dysplasia is one used for uterine cervix referred to as “classic” or nonkeratinizing dysplasia:
 - Absent keratosis
 - Increasing gradations of dysplasia include mild (grade I), moderate (grade II), and severe (grade III), with the latter representing full-thickness replacement of the squamous epithelium by atypical, small, immature basaloid cells and referred to as carcinoma in situ (CIS)
- Grading scheme is reproducible and is clinically useful.
- “Classic” or nonkeratinizing dysplasia is uncommon in the upper aerodigestive tract, especially in the laryngeal glottis.
- Majority of the upper aerodigestive tract lesions, especially larynx and oral cavity (see Section 2), are keratinizing dysplasias:
 - Alterations occur in the presence of surface keratinization.
 - Criteria for evaluating keratinizing dysplasias are less defined and diagnosis of severe keratinizing intraepithelial dysplasia remains controversial.
 - Definition of severe dysplasia in the setting of keratosis, especially in the laryngeal glottis, is broader than the highly reproducible pattern seen in the uterine cervix and includes a microscopically heterogeneous group of lesions.
 - In the setting of keratinizing dysplasia in which surface maturation is retained with only partial replacement of the epithelium by atypical cells, severe dysplasia includes those lesions in which epithelial alterations are so severe that there would be a high probability for the progression to an invasive carcinoma if left untreated.
 - Severe dysplasia shows presence of aberrant cell maturation with dyskeratotic cells and mitotic figures with or without atypical forms above the basal zone.
 - In the evaluation of upper aerodigestive tract dysplasia, the presence of surface keratinization is not significant; however, finding dyskeratotic cells represents an important clue to the presence of significant dysplasia.
 - In conjunction with the cytomorphologic changes, architectural alterations also factor into the evaluation and the presence of elongated and irregular-appearing rete ridges extending downward into the submucosa assists in determining the degree of dysplasia in the setting of a keratotic proliferation.
- Carcinoma in situ (CIS) as applied to the uterine cervix by histologic definition requires loss of maturation of squamous epithelium:
 - By this definition keratotic dysplastic lesions cannot be CIS owing to the presence of maturation of the squamous epithelium.
 - Use of the specific term CIS relative to keratinizing dysplasias has been questioned and is likely inappropriate in this setting.
 - More appropriate designation that of severe keratinizing dysplasia tantamount to CIS

- Histopathologic interpretation and grading of epithelial dysplastic changes in the upper aerodigestive tract are imprecise and subjective:
 - Given the complexities in the issues relative to UADT intraepithelial lesions, confusion and misunderstandings may occur between the clinician and the pathologist that may result in inappropriate management of the patient.
 - Uniformity in terminology is desirable so that there is a correlation between the pathologic diagnosis and the clinical import of that diagnosis.
 - In an attempt to standardize the terminology of upper aerodigestive tract, intraepithelial lesions using a grading system akin to that of the cervical mucosa, including terminology of squamous intraepithelial neoplasia (SIN) with SIN I equivalent to mild dysplasia, SIN II to moderate dysplasia, and SIN III to severe dysplasia
 - Similar gradations but using terminology of laryngeal intraepithelial neoplasia (LIN) and laryngeal intraepithelial lesion (LIL) have been proposed.
 - Ljubljana classification (see Table 16-2) of laryngeal precancerous lesions was proposed; in this system the terms used include:
 - Simple hyperplasia (i.e., keratosis without atypia)
 - Abnormal hyperplasia (i.e., keratosis with atypia)
 - Atypical hyperplasia (i.e., severe dysplasia)
 - Carcinoma in situ
 - More recently amended Ljubljana classification (see Table 16-2) proposed dividing squamous intraepithelial lesions (SIL) into low-grade, high-grade, and carcinoma in situ (CIS):
 - Low-grade SIL is considered to be most often benign, with low malignant potential, characterized by a spectrum of morphologic changes ranging from a simple hyperplastic process with retention of the basal layer and an increased prickle cell layer, to augmentation of basal and parabasal cells occupying up to the lower half of the epithelium, with the upper part remaining unchanged, containing regular prickle cells.
 - High-grade SIL considered to be a potentially premalignant lesion with $\geq 12\%$ of patients subsequently developing malignancy is morphologically characterized by a spectrum of changes, including augmentation of immature epithelial cells, which occupy the lower half or more of the epithelial thickness.
 - Carcinoma in situ reserved for lesions showing features of conventional carcinoma, e.g., structural and cellular abnormalities but without invasion (intraepithelial carcinoma)
 - Facilitates better interobserver agreement than previous systems, and retrospective follow-up study demonstrated highly significant difference in risk of malignant progression between low-grade and high-grade SILs
- At present preferred grading for dysplastic epithelial alterations of the upper aerodigestive tract include mild, moderate, and severe dysplasia depending on the degree and extent of cellular and maturation alterations that are present:
 - Histologic grading is evolving and as previously indicated a two-tiered system to include low grade (mild dysplasia) and high grade (moderate dysplasia and severe dysplasia/CIS) for upper aerodigestive tract epithelial dysplastic lesions may be adopted.
- Risk of progression to invasive carcinoma
 - End point for the grading of dysplasia is to convey to the clinician what is the potential biologic behavior of a given epithelial lesion.
 - Keratotic epithelium without dysplasia carries a very low risk of developing subsequent carcinoma, with reported incidences of 1% to 5%.
 - In contrast, keratotic epithelium with dysplasia is associated with an increased risk for the subsequent progression or development of premalignant or overtly carcinomatous changes varying from 11% to 18% of cases.
 - This risk of malignant transformation represents an increase of three to five times as compared with carcinoma arising in keratotic lesions without atypia.
 - The risk for progression to invasive carcinoma in lesions diagnosed as keratosis with atypia varies depending on the degree of atypia/dysplasia:
 - For mild dysplasia: approximately 6%
 - For moderate dysplasia: approximately 23%
 - For severe dysplasia: approximately 28%
 - For those lesions that progress to invasive carcinoma the average latency period from the diagnosis of keratosis with atypia to invasive carcinoma is 3.8 years
 - Histologic features seen in those dysplasias progressing to invasive carcinoma as compared with those lesions that remain stable and do not progress include:
 - Increased mitotic activity in the middle and upper portions of the epithelium
 - Presence of atypical mitoses
 - Moderate to severe nuclear pleomorphism
 - Proliferation of small uncommitted cells above the basal zone or lower third of the mucosa

- Another important point to recognize is the clinical concern attached to a diagnosis of severe keratinizing intraepithelial neoplasia:
 - Clinical concern is due to fact severe dysplasia is often multifocal and frequently occurs adjacent to or near synchronous foci of invasive carcinoma
 - This form of dysplasia has a rate of progression to invasive carcinoma that is greater than that of “classic” carcinoma in situ in setting or non-keratinizing dysplasia.
 - A diagnosis of severe dysplasia requires therapeutic intervention, as well as clinical evaluation of the entire upper aerodigestive tract to exclude the possible presence of additional foci of dysplasia or carcinoma.
- Immunohistochemistry:
 - No known reliable markers to assist in diagnosis and differential diagnosis
 - Increased proliferation rates in suprabasal epithelium by Ki67 (MIB1) staining seen in higher grade dysplasias
 - Increased p53 immunoreactivity seen in higher grade dysplasias
 - p16 not a reliable marker in determining presence or absence of dysplasia in the larynx:
 - Predominance of keratinizing dysplasia in larynx (often etiologically linked to tobacco and alcohol use) not associated with transcriptionally active virus:
 - p16 and p21 immunohistochemistry may be present in laryngeal keratinizing dysplasia but do not correlate to the presence of transcriptionally active HPV.
 - p16 should not be used as the definitive surrogate marker of HPV-driven tumors in the larynx.
- Cytogenetics and molecular genetics:
 - Loss of heterozygosity at 3p21, 5q21, 9p21, 17p13 more likely to progress to invasive carcinoma
 - Tumor suppressor gene p53 implicated in head and neck carcinogenesis:
 - p53 mutations found in >50% of invasive head and neck squamous cell carcinoma

Differential Diagnosis

- Reactive epithelial changes
- Infectious disease(s)
- Microinvasive carcinoma:
 - Diagnosis of microinvasive carcinoma should be reserved for cases in which there is definitive evidence of dissociated squamous cells at the epithelial-to-stromal interface with invasion of the lamina propria; see later in section for more complete discussion.

Treatment and Prognosis

- Excisional biopsy by vocal cord stripping or by forceps is preferred treatment.
- Close follow-up of the patient is advocated; if clinically warranted, rebiopsy may be necessary and should be performed months after any procedure to allow adequate healing and fewer surgery-associated pathologic changes that may hamper the histologic evaluation and/or obscure a neoplastic process.
- Cessation of contributing risk factors should be undertaken:
 - In general, mild and moderate dysplasias are felt to be potentially reversible alterations.
 - Circumstantial evidence supports the idea that preinvasive dysplasias are potentially reversible after cessation or removal of an instigating factor such as tobacco use.
 - Problem of predicting the malignant potential of a dysplastic lesion is greatest in cases of moderate dysplasia:
 - Virtually impossible to differentiate the moderately dysplastic lesions that are reversible from those that represent the earliest forms of neoplastic transformation
 - Diagnosis of moderate dysplasia should engender enough concern to the clinician to warrant close patient follow-up.
 - Recurrence or persistence of this dysplasia may be indicative of malignant transformation.
 - Determination of whether a mild to moderate dysplasia is reactive or neoplastic, although a desirable goal, is not always achievable; the clinically abnormal lesions that show limited cytologic and architectural abnormalities falling under the designation of reactive atypias or hyperplastic lesions represent reversible changes that rarely, if ever, progress to carcinoma:
 - These lesions are responsive to conservative management.
 - Uterine cervical moderate dysplasia (cervical intraepithelial neoplasia II) and severe dysplasia (cervical intraepithelial neoplasia III) are currently lumped in the category of high-grade squamous intraepithelial lesion (HGSIL).
 - Risk of progression to invasive carcinoma relative to upper aerodigestive tract moderate dysplasia (approximately 23%) and severe dysplasia (approximately 28%) is not statistically significant.
 - To date, grouping of upper aerodigestive tract keratinizing moderate and severe dysplasia into a single category as high-grade squamous intraepithelial lesion similar to the uterine cervix has not been adopted but may be the

recommended grading scheme in the near future to include:

- Low-grade squamous intraepithelial lesion/neoplasia for mild dysplasia
- High-grade squamous intraepithelial lesion/neoplasia for moderate and severe dysplasias

CARCINOMA IN SITU (CIS)

(Fig. 16-23)

Definition: Classically defined as cellular dysplasia involving the entire thickness of the mucosa without compromise of the basement membrane:

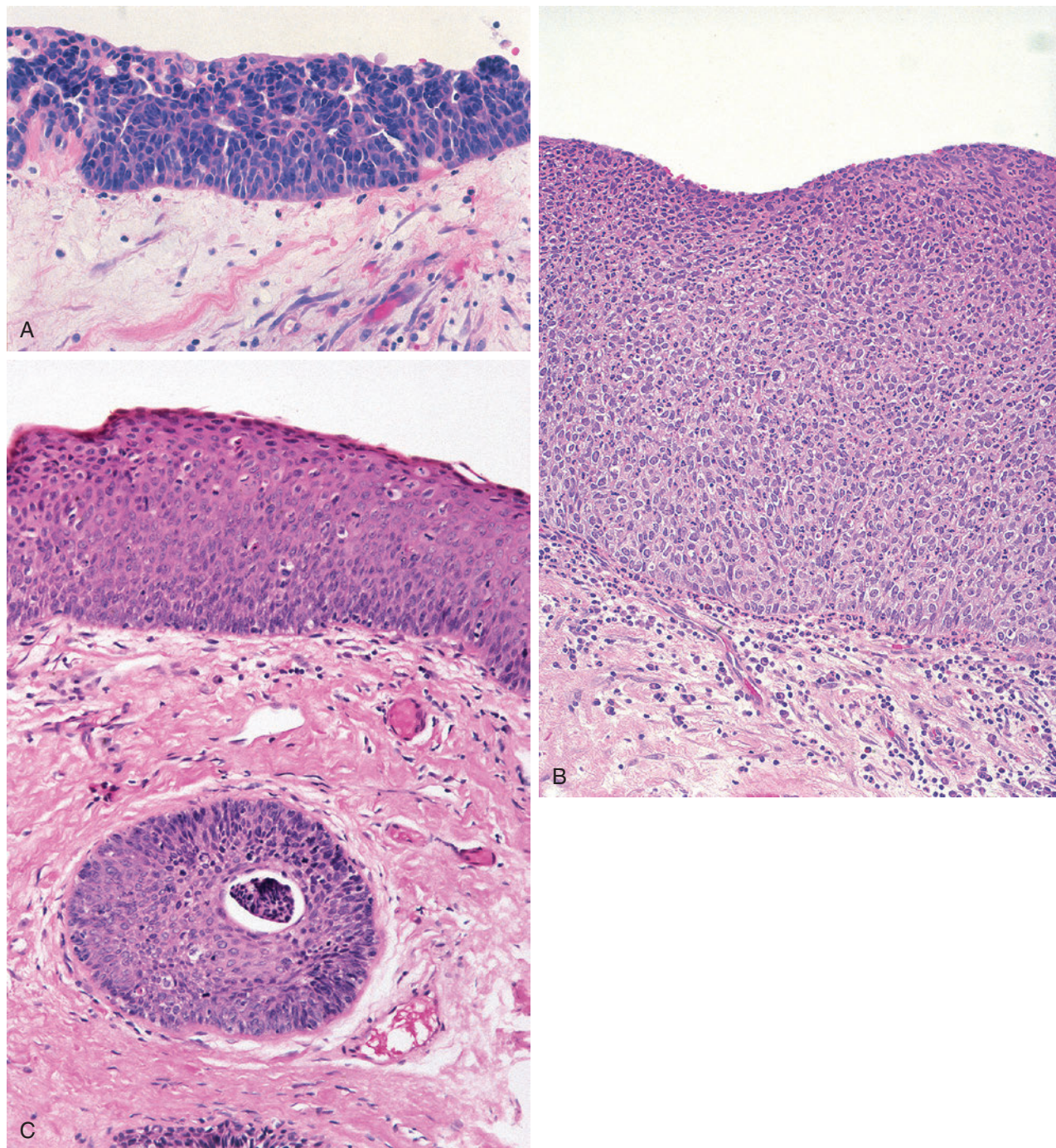


Fig. 16-23. Laryngeal “classic” carcinoma in situ (CIS).

A and **B**, Nonkeratinizing epithelium showing full-thickness intraepithelial dysplasia. **C**, CIS with extension to subadjacent minor salivary gland, a finding that still constitutes CIS and not invasive carcinoma.

- Dysplasia may extend into adjacent seromucous glands and is still considered as an in situ lesion.

Clinical

- Represents approximately 1% to 13% of all laryngeal carcinomas
- More common in men than in women; most frequently seen in the sixth to seventh decades of life
- Can occur anywhere in the larynx but most often involves the anterior one third of one or both true vocal cords:
 - May involve the entire cord
 - May be bilateral
 - Frequently associated with an invasive squamous cell carcinoma either lying adjacent to or remote from one another
 - May exist as an isolated lesion unrelated to invasive carcinoma
 - Multifocal areas can occur.
- Hoarseness is most frequent presenting complaint.
- CIS may be associated with invasive carcinoma:
 - Invasive carcinoma may occur in association with CIS or may be separate from CIS.
 - Clinically, evaluation is advised to exclude the possible presence of invasive carcinoma.
- Risk factors include:
 - Tobacco smoking (most common) and excess alcohol use:
 - Alcohol potentiates the effect of tobacco smoking.
 - Risk of developing dysplastic lesions increases with duration of smoking and/or alcohol use
 - Role of human papillomavirus in development of carcinoma in situ of the head and neck (other than oropharynx) not proven
- Presence of mitoses in all layers of the mucosa:
 - May include normal and abnormal forms
- Keratosis and dyskeratosis may be present.
- In presence of a diagnosis of CIS, the pathologist should liberally section the specimen to rule out the presence of an invasive squamous cell carcinoma.
- As previously noted under epithelial precursor lesions (see above), classic carcinoma in situ histologically defined as full-thickness intraepithelial dysplasia is uncommon relative to upper aerodigestive tract intraepithelial keratinizing dysplasias; CIS typically occur in nonkeratinizing dysplasia, which is an uncommon lesion in mucosal sites of the upper aerodigestive tract, especially the larynx and oral cavity:
 - Keratinizing dysplasias are much more common, and in such lesions full-thickness intraepithelial dysplasia (i.e., classically defined CIS) is uncommon and is not a prerequisite for development of invasive carcinoma.
 - In setting of keratinizing dysplasia, marked dysplastic alterations may be restricted to basal zone epithelium only, from which invasive carcinoma may develop.
 - Given such findings, use of diagnostic terms such as “keratinizing severe dysplasia, tantamount to carcinoma in situ” conveys to the surgeon alterations in a lesion that will behave similarly to carcinoma in situ (i.e., irreversible and likely to progress to invasive carcinoma unless adequately treated).
- Immunohistochemistry:
 - No known reliable markers to assist in diagnosis and differential diagnosis
 - Increased proliferation rates in suprabasal epithelium by Ki67 (MIB1) staining seen in higher-grade dysplasias
 - Increased p53 immunoreactivity seen in higher-grade dysplasias
 - p16 not a reliable marker in determining presence or absence of dysplasia in the larynx:
 - Predominance of keratinizing dysplasia in larynx (often etiologically linked to tobacco and alcohol use) not associated with transcriptionally active virus:
 - p16 and p21 immunohistochemistry may be present in laryngeal keratinizing dysplasia but does not correlate to the presence of transcriptionally active HPV.
 - p16 should not be used as definitive surrogate marker of HPV-driven tumors in the larynx.

Pathology

Gross

- Circumscribed or diffuse lesion with a white, red, or gray color and a smooth to granular appearance

Histology

- Dysplastic process involves the entire thickness of the squamous epithelium without violation of the basement membrane:
 - Extension into adjacent seromucous glands (particularly in the region of the anterior true vocal cord) may occur and does not constitute invasion.
- Squamous epithelium may or may not be thickened.
- Cytomorphologic changes include:
 - Increased nuclear pleomorphism and nuclear size
 - Loss of cellular maturation and polarity
 - Nuclear hyperchromasia with irregular nuclear contours
 - Increased nuclear-to-cytoplasmic ratio

Progression to Invasive Carcinoma

- Wide variation in the literature relative to the incidence of laryngeal CIS progressing to invasive carcinoma:

- Discrepant statistics ranging from approximately 3% to as high as 90% reflect inconsistencies in the diagnosis of CIS, which can be a notoriously subjective diagnosis.
- Collated incidence of laryngeal CIS progressing to invasive carcinoma is 23% to 27%.
- Latent period of 3 to 5 years from diagnosis of CIS to invasive carcinoma

Differential Diagnosis

- Reactive epithelial changes
- Microinvasive carcinoma

Treatment and Prognosis

- No standard treatment; treatment may include:
 - Vocal cord stripping
 - Laser surgery
 - Cordectomy
 - Radiation
- Diagnosis of carcinoma in situ should prompt ablative therapy followed by surveillance for recurrence or progression:
 - Surgical excision is preferred treatment.
 - Alternative therapies such as radiation may be employed in selected patients when surgical therapy is not the best option.
- Management offers a high cure rate (approximately 75%):
 - Vigilant follow-up including periodic laryngoscopic examinations should be maintained.
- Risk factor modification remains important not only as a primary prevention strategy but to reduce risk of progression to invasive carcinoma.
- Treatment failures result from:
 - Extensive and/or multifocal disease
 - Associated undetected invasive squamous carcinoma
 - Extension of CIS to subjacent seromucous glands harboring residual disease following the mucosal stripping:
 - Particularly true for CIS of the anterior commissure region, where seromucous glands may be located distant from the opening of their ducts and may lie outside area that is stripped
 - For CIS of anterior commissure additional therapy including laser ablation or irradiation may be indicated.

MICROINVASIVE CARCINOMA

(Figs. 16-24 through 16-27)

Definition: Malignant cells that have penetrated the basement membrane and infiltrate into the superficial compartment of the lamina propria.

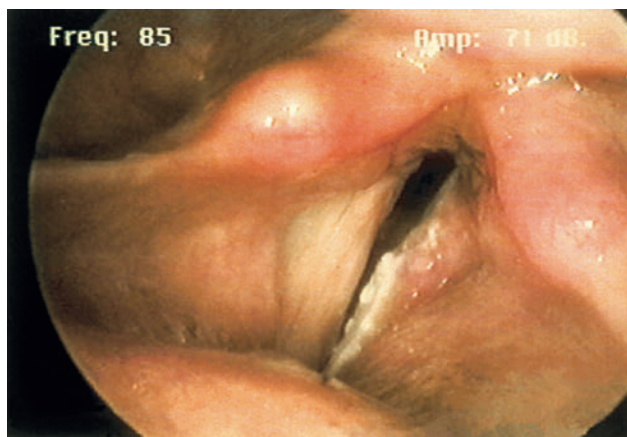


Fig. 16-24. Microinvasive carcinoma.

Endoscopic appearance of a microinvasive (T1) laryngeal (vocal cord) squamous cell carcinoma.

Synonym: Superficially invasive squamous cell carcinoma

Clinical

- Clinical manifestations are similar to those of carcinoma in situ.
- In the larynx, full cord mobility is present:
 - Any dysfunction in vocal cord mobility (fixation) by definition means muscle invasion, which excludes a diagnosis of microinvasive cancer.
- Biologically malignant lesion capable of metastasizing either via lymphatic or vascular channels

Pathology

Gross

- Similar to carcinoma in situ

Histology

Diagnostic Criteria for Microinvasive Carcinoma

- Definition of features constituting microinvasion varies in literature:
 - Presence of scattered malignant cells within the submucosa just below the basement membrane
 - Presence of malignant cells limited to 2 mm of invasion
 - Presence of malignant cells within 1 to 2 mm of the basement membrane without angioinvasion
 - Presence of tongues or discrete foci of malignant epithelium invading through the basement membrane
 - Invasive carcinoma extending into the stroma no more than 0.5 mm measured from the epithelial basement membrane and without angioinvasion
 - Represents preferred definition
- Regardless of specific definition, diagnosis of microinvasive carcinoma excludes those lesions that are

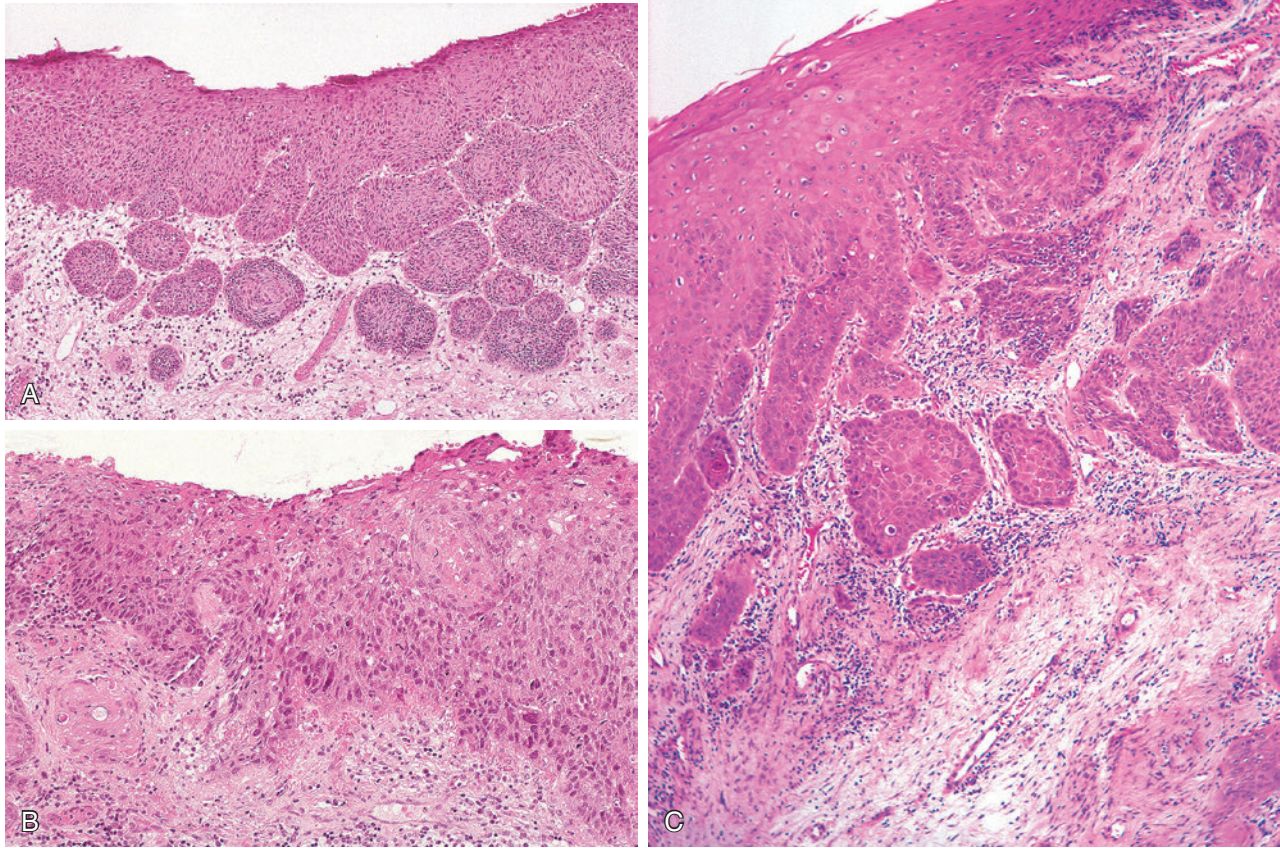


Fig. 16-25. Invasive squamous cell carcinoma.

A, Nonkeratinizing severe dysplasia (carcinoma in situ) with development of microinvasive carcinoma; note the invasive tumor nests that, while well-rounded, are below the level of submucosal small vascular spaces. **B**, Keratinizing dysplasia with downward extension of the rete ridges and disruption (penetration) of basement membrane; in addition, a separate nest of invasive carcinoma with associated dyskeratosis is present (left of center). **C**, "Drop-off" or "drop-down" carcinoma in which invasive carcinoma originates from the basal zone of the surface epithelium which otherwise shows bland cytomorphology without dysplasia.

restricted to the surface epithelium or carcinoma in situ (CIS) and those carcinomas that are deeply invasive into muscle and cartilage, and extralaryngeal structures (T2 or greater tumors).

- Microinvasive carcinoma can occur in two unrelated phases:
 - Development from (and as a continuum of) carcinoma in situ:
 - Typically occurs in a setting of nonkeratinizing dysplasia with full-thickness intraepithelial dysplasia:
 - Not a common occurrence relative to dysplastic lesions of the larynx (and oral cavity)
 - Invasion from an epithelium demonstrating dysplastic alterations representing severe dysplasia but lacking full-thickness intraepithelial dysplasia:

- Typically occurs in the setting of a keratinizing high-grade dysplasia (i.e., moderate to severe) in which the (micro)invasive carcinoma is seen originating from dysplastic epithelial changes limited to the basal zone epithelium with the remainder of the more superficially located epithelium lacking dysplastic change:
 - Such invasive carcinomas are referred to as "drop off" or "drop down" carcinoma.
 - Reinforces the fact that in the upper aerodigestive tract, particularly in the larynx and oral cavity, "classic" carcinoma in situ is not a prerequisite for the development of a (micro)invasive squamous cell carcinoma
- In invasive carcinoma:
 - Tumor nests have an irregular outline with infiltrative borders.

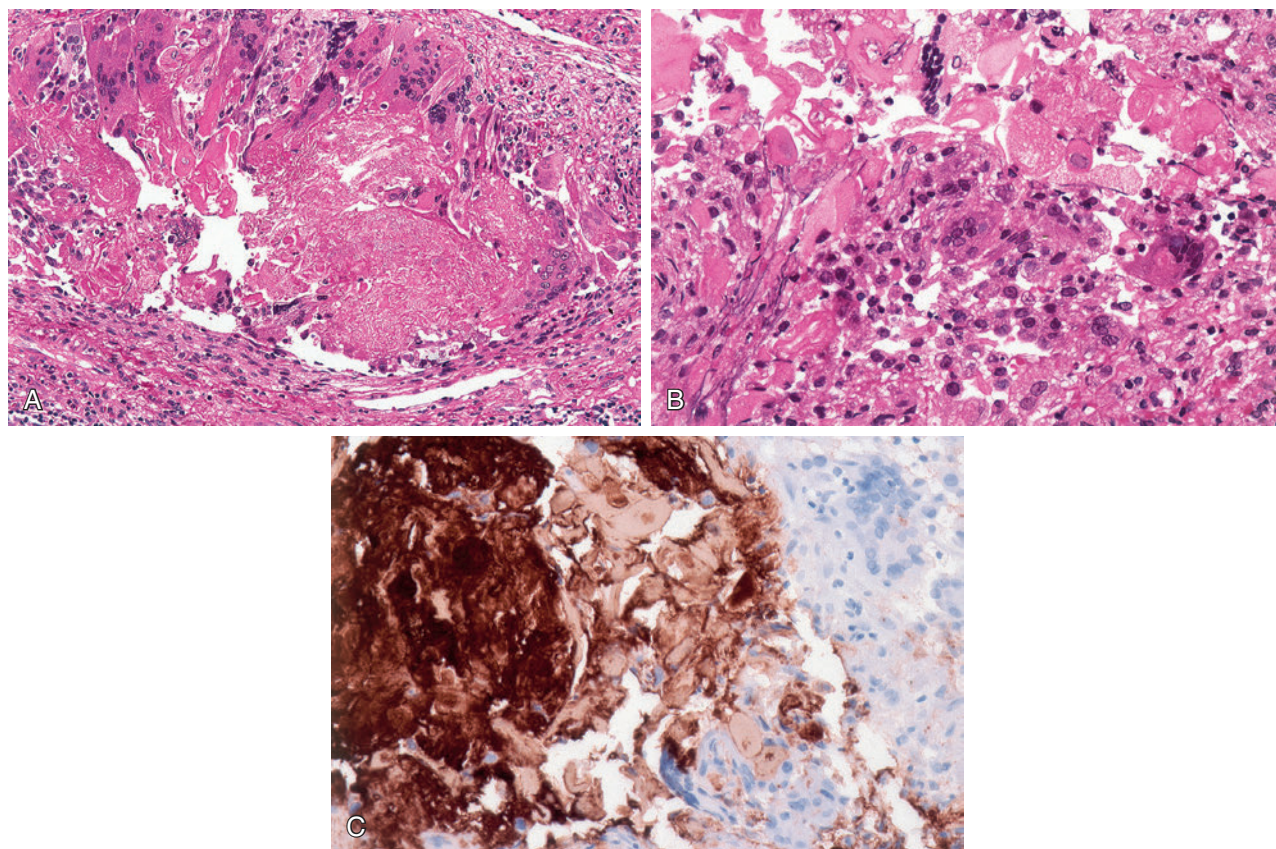


Fig. 16-26. Keratin granuloma.

Keratin granuloma formation is considered as presumptive evidence of invasive carcinoma. **A**, Granulomatous response including multinucleated giant cells rimming amorphous eosinophilic debris. **B**, Isolated keratinizing neoplastic cells are present in and around the granuloma but may not be as overtly identifiable in other cases. **C**, Cytokeratin immunoreactivity confirms the eosinophilic debris as keratin; note the absence of staining in the multinucleated giant cells (*upper right*), which would be reactive for CD68 (not shown).

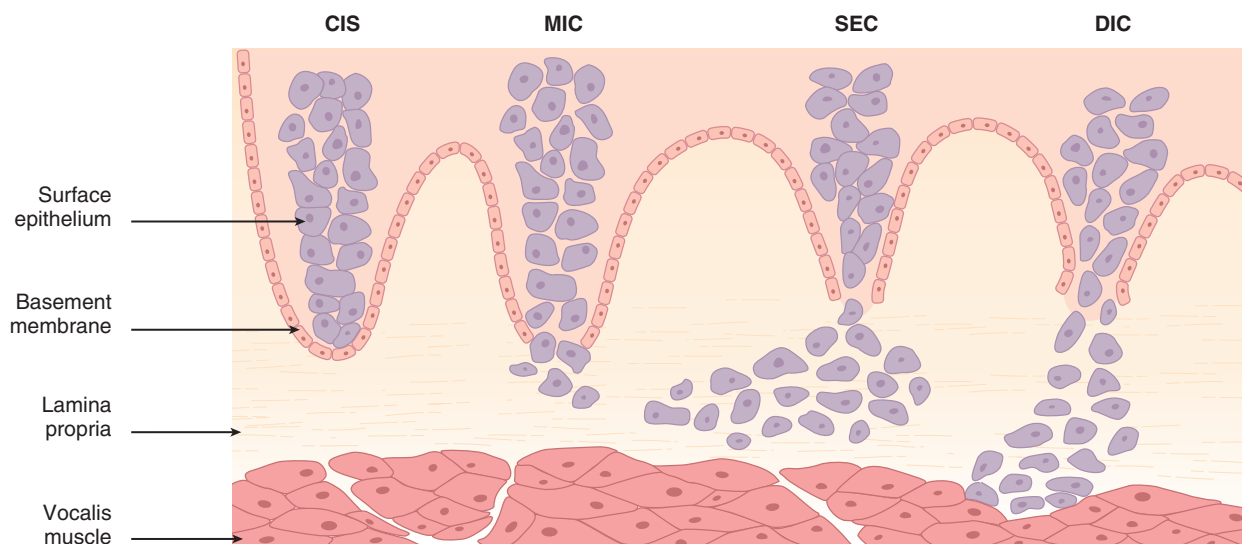


Fig. 16-27.

Diagrammatic depiction of superficial extending carcinoma (SEC) compared with carcinoma in situ (CIS), microinvasive carcinoma (MIC), and deeply invasive carcinoma (DIC). (Adapted from Barnes L: *Carcinoma in situ*. In Barnes L, editor: *Surgical pathology of the head and neck*, ed 2, New York, 2001, Marcel Dekker, pp 158-161.)

- Invasive nests are cytologically malignant, but invasive carcinomas may be extremely well-differentiated with minimal if any malignant cytologic features.
- Presence of invasive cancer generally results in a desmoplastic host response that includes edematous change immediately around the tumor nests with granulation tissue and fibrosis:
 - Identifying tumor-related desmoplasia from reactive stromal changes not straightforward:
 - There are no clear-cut criteria other than the presence of bona fide malignant cells (in nests or individual cells) to differentiate between tumor-related desmoplasia and reactive stromal changes to assist in a diagnosis of invasion.
 - In setting of well-differentiated squamous epithelium within the submucosa it can be very difficult if not impossible to determine neoplastic (malignant) epithelium from nonneoplastic squamous epithelium that is reactive and/or represents tangentially sectioned squamous epithelium:
 - No immunostains or molecular markers available to assist in such a differentiation
 - In such a scenario a diagnosis of carcinoma may not be possible and a designation of “well-differentiated squamous epithelial proliferation, not further specified” may be required with recommendation for:
 - Additional deeper biopsies
 - Conservative but complete excision of the lesion
 - Keratin granuloma formation in the submucosa represents supportive evidence of (at least) microinvasive carcinoma:
 - Represents a foreign body reaction to keratin in the submucosa
 - Appears as relatively well-formed granuloma formation, including the presence of histiocytes and multinucleated giant cells
 - Keratin material may or may not be identified by light microscopy.
 - May require cytokeratin immunohistochemical staining (e.g., AE1/AE3, CAM5.2, others) to confirm the presence of keratin-positive material
 - In the absence of cytokeratin-positive material, a diagnosis of keratin granuloma cannot be rendered.
 - Histiocytes and giant cells are CD68 (KP1) positive.

Differential Diagnosis

- Pseudoepitheliomatous hyperplasia
- Superficial extending carcinoma (see [Fig. 16-27](#)):
 - Early invasive carcinoma that does not extend beyond lamina propria
 - In contrast to microinvasive carcinoma, which is predominantly an in situ carcinoma with definite but limited invasion into the lamina propria, superficial extending carcinoma shows extensive invasion into (but not beyond) the lamina propria.
 - By definition there is no invasion into muscle or cartilage.
 - Associated carcinoma in situ is often present.
 - May be multifocal
 - Establishing this diagnosis may be problematic in limited biopsy sampling and may require surgical excision with thorough histologic evaluation.
 - Limited reports to date and the long-term prognosis remains uncertain
 - Presence of nodal metastasis in the setting of superficial extending carcinoma may exclude this entity as an “early” carcinoma.

Treatment and Prognosis

- No standardized approach to treatment:
 - Most authorities advocate conservative management with endoscopic removal of the lesion (mucosal stripping with or without laser ablation) and close clinical follow-up of the patient rather than surgical resection (e.g., some type of laryngectomy) or radiation.
 - Behavior is similar to that of carcinoma in situ, and if presence of a coexisting invasive squamous cell carcinoma can be excluded, then therapy is similar to carcinoma in situ.
- Conservative management supported by:
 - Studies have shown that in cases in which hemilaryngectomy was performed, no residual carcinoma was found in 20% of patients, indicating that the lesion was totally excised in original biopsy.
 - For microinvasive carcinoma of the laryngeal glottis, several studies have shown that the clinical significance is similar to CIS/severe dysplasia and that with appropriate therapy progression of disease from a microinvasive to a more invasive carcinoma does not occur.
 - This finding may be due to earlier clinical manifestations produced by glottic cancers, leading to an earlier diagnosis of cancer before it has invaded into deeper aspects of the larynx.
 - Glottic microinvasive cancers are generally not associated with metastatic disease due to the fact that glottic portion of the larynx has quantitatively less lymph-vascular spaces as compared with the supra- and subglottis.
- In contrast to laryngeal glottis, supraglottic microinvasive carcinomas are associated with metastatic disease in approximately 20% of patients.

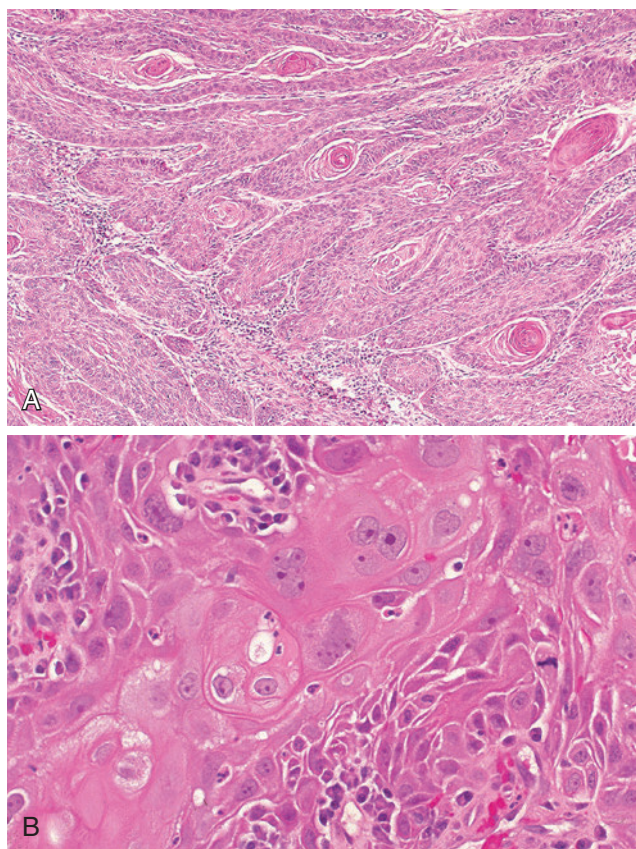


Fig. 16-28. Invasive well-differentiated squamous cell carcinoma.

A, Invasion includes cohesive nests and cords.
B, Keratinization and intercellular bridges are readily apparent.

LARYNGEAL INVASIVE SQUAMOUS CELL CARCINOMA

(Figs. 16-28 through 16-30)

General Considerations

- Laryngeal squamous cell carcinoma (SCC) accounts for approximately 0.8% of all cancers, 1.0% of all cancers in men, and approximately 0.3% of all cancers in women.
- Represents greater than 95% of all laryngeal carcinomas
- More common in men than in women; most commonly occurs in the fifth through seventh decades of life:
 - There has been an increase of laryngeal carcinoma in women over the past 20 years, likely linked to increase tobacco use in women over this time period.
 - Less than 1% occur in patients under 30 years of age.
- Rarely occurs in pediatric ages (first and second decades of life):
 - More common in girls than boys
 - Most occur in glottic region
 - Hoarseness most common complaint
 - No known risk factors but possible relationship to HPV and passive smoking exposure
- Cause:
 - Association with tobacco smoking:
 - Tobacco linked to glottic carcinoma:
 - Less than 5% of patients with laryngeal carcinoma are nonsmokers.
 - Alcohol linked to supraglottic carcinoma but less important risk factor as compared with tobacco use

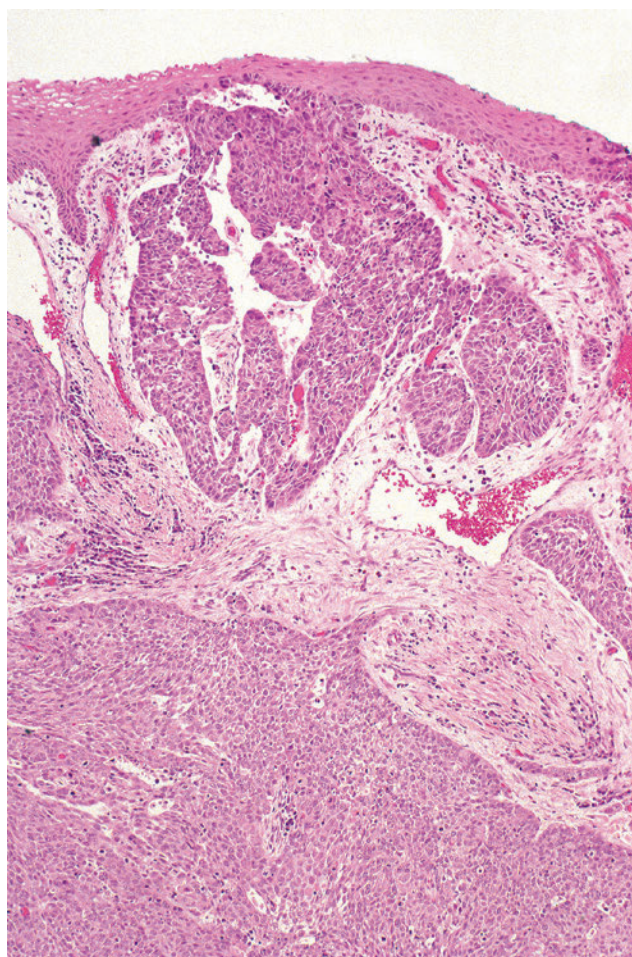


Fig. 16-29. "Drop off" invasive squamous cell carcinoma.

Example of a deeply invasive squamous cell carcinoma in which the carcinoma "drops off" from the basal zone of the surface epithelium, which otherwise shows bland cytomorphology and absence of full-thickness dysplasia.

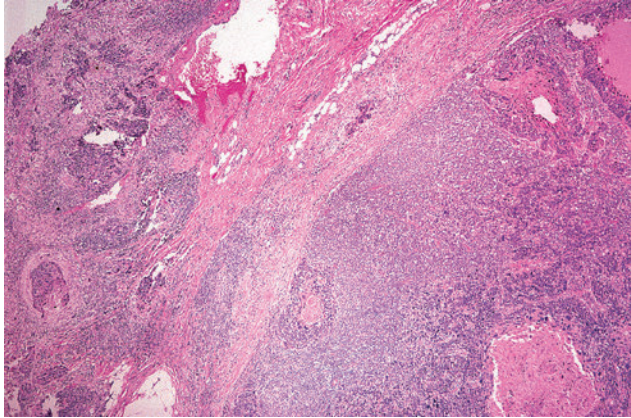


Fig. 16-30. Extranodal extension.

Laryngeal squamous cell carcinoma metastatic to cervical neck lymph node with extranodal extension, the latter characterized by the presence of carcinoma in perinodal soft tissues (upper left).

- Other potential contributing etiologic factors associated with but not definitively linked as a direct cause of squamous cell carcinoma include:
 - Genetic factors
 - Human papillomavirus infection
 - Dietary deficiencies (vitamin A, vitamin C, iron)
 - Previous irradiation to the neck
 - Environmental/occupational exposure (asbestos, nickel, wood, air pollution, isopropyl alcohol, mustard gas, others)
 - Chronic gastroesophageal reflux disease
- TNM staging of laryngeal carcinoma for all subsites detailed in [Box 16-3](#):
 - TNM staging for hypopharyngeal cancers is detailed in Section 3.
- See below for clinicopathologic features for site-specific laryngeal cancers.

Pathology

Gross

- Variable and includes ulcerated, flat, exophytic, verrucoid, or papillary growths

Histology

- Histologic appearance of invasive SCC may be as variable as gross appearance without specific correlation between gross appearance and the histopathologic findings.
- Invasive SCC includes keratinizing and nonkeratinizing carcinomas varying from well to poorly differentiated.
- Severe dysplasia/carcinoma in situ of the surface epithelium may be a common component found in

association with invasive SCC; this component need not be present.

- For all types of SCC, presence of invasion is diagnostic for malignancy:
 - Invasion can be as single cells or small irregular aggregates or can appear as large cords or cohesive aggregates.
 - Desmoplastic stromal response and foreign body reaction to keratin (keratin granuloma; see [Fig. 16-24](#)) in the stroma assist in identifying invasion.
 - Invasive cancer tends to efface normal histoanatomic architecture:
 - In contrast, lobular growth of seromucous glands is retained in association with sialometaplasia.
 - Invasion may be associated with lymph-vascular invasion, neurotropism, invasion into muscle, bone, and cartilage:
 - Invasion of cartilage often occurs in cartilage that has undergone ossification:
 - Ossification usually occurs in the third decade and not before the third decade of life.
 - Histology is similar to endochondral ossification.
 - Ossification of thyroid cartilage begins at posterior border near the root of the inferior cornu, spreads along inferior border and reaches midline, where there usually is a separate center of ossification.
 - Invasion of the laryngeal cartilage framework usually is in lower third of the thyroid cartilage.
 - Perichondrium appears to resist invasion and remains intact even when the cancer infiltrates and expands the cartilage.
 - Reasons cited for the presence of invasion in ossified cartilage include the absence of perichondrium in this areas.
 - Cartilaginous invasion usually is found in association with transglottic cancers.
 - Once cancer invades beyond a few millimeters or extends into muscle, cartilage, or other soft tissue components outside the anatomic structure from which it originates, then it is a higher clinical stage neoplasm with potential for a more aggressive behavior.
 - Immunohistochemical studies have shown that the presence or absence of basement membrane components around invasive cancer may correlate with pattern of tumor invasion:
 - Pattern of tumor invasion (single cell versus large cords) represents an inherent biologic parameter of tumor aggressiveness.

BOX 16-3 TNM Classification of Laryngeal Carcinoma**Primary Tumor**

- T = extent of the primary tumor
 - Includes the clinical (T) and pathologic (pT) categories
 - T designation varies according to the anatomic site involved
- TX = Primary tumor cannot be assessed.
- T0 = No evidence of primary tumor
- Tis = Carcinoma in situ

Supraglottis

- T1 = Tumor limited to one subsite with normal vocal cord mobility
- T2 = Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx
- T3 = Tumor limited to the larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space and/or minor thyroid cartilage erosion (e.g., inner cortex)
- T4a = Moderately advanced local disease
 - Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
- T4b = Very advanced local disease
 - Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Glottis

- T1 = Tumor limited to the vocal cord(s) (may involve anterior and posterior commissures) with normal cord mobility:
 - T1a = tumor limited to one vocal cord
 - T1b = tumor involves both vocal cords
- T2 = Tumor extends to the supraglottis and/or subglottis and/or with impaired vocal cord mobility
- T3 = Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space and/or minor thyroid cartilage erosion (e.g., inner cortex)
- T4a = Moderately advanced local disease
 - Tumor invades through the outer cortex of thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
- T4b = Very advanced local disease
 - Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

- T1 = Tumor limited to the subglottis
- T2 = Tumor extends to the vocal cord(s) with normal or impaired mobility
- T3 = Tumor limited to the larynx with vocal cord fixation

- T4a = Moderately advanced local disease
 - Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
- T4b = Very advanced local disease
 - Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Regional Lymph Nodes (N)

- N = Absence/presence and extent of regional lymph node metastasis; includes the clinical (N) and pathologic (pN) categories
- NX = Regional lymph nodes cannot be assessed.
- N0 = No regional lymph node metastasis
- N1 = Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 = Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
 - N2a = Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
 - N2b = Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
 - N2c = Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
 - N3 = Metastasis in a lymph node, more than 6 cm in greatest dimension
- Metastases at Level VII are considered regional lymph node metastasis

Distant Metastasis (M)

- M = Absence or presence of distant metastasis; includes both the clinical (M) and pathologic (pM) categories
- M0 = No distant metastasis
- M1 = Distant metastasis present

Clinical Stage

- Stage 0 = TisN0M0
- Stage I = T1N0M0
- Stage II = T2N0M0
- Stage III = T3N0M0
 - T1N1M0
 - T2N1M0
 - T3N1M0
- Stage IVA = T4aN0M0
 - T4aN1M0
 - T1N2M0
 - T2N2M0
 - T3N2M0
 - T4aN2M0
- Stage IVB = T4b Any N M0
 - Any T N3M0
- Stage IVC = Any T Any N M1

- Sampling represents a major issue in the evaluation of SCC:
 - In absence of adequate representative tissue including epithelial-to-stromal interface, one should be circumspect relative to rendering a diagnosis of invasive SCC.
 - Diagnostic pitfalls in diagnosis of laryngeal SCC include pseudoepitheliomatous hyperplasia, necrotizing sialometaplasia, and radiation atypia.
- Factors affecting prognosis:
 - Tumor location:

- Transglottic tumors have higher incidence of lymph node metastasis compared with supraglottic and subglottic carcinomas.
- Tumor size:
 - Larger tumors have greater chance of metastasis.
- Tumor histology:
 - Poorer differentiation (grade) more likely to disseminate
- Cervical lymph node metastasis:
 - Metastatic tumor to cervical lymph nodes decreases survival by 50%.
 - Tumor extending beyond the confines of the lymph node into perinodal soft tissues (extranodal extension; see Fig. 16-30) represents an important finding relating to:
 - Recurrent disease in neck
 - Increased risk for distant metastasis
 - Presence or absence of extranodal extension should be specifically commented on in pathology report.
- Multiple malignancies:
 - Up to 12% of patients with laryngeal carcinoma develop a secondary primary malignant tumor either in lung, another upper aerodigestive tract site, or, less commonly distant unrelated site.
- Surgical resection margins:
 - For laryngeal carcinomas, a margin of resection of 2 mm is considered adequate:
 - In larynx margins of 2 mm or greater have been shown to have a similar behavior to margins with greater clearance (e.g., 5 mm).
 - Other studies have reported that in laryngeal squamous cell carcinomas:
 - 18% develop local recurrence with positive surgical margins
 - 6% develop local recurrence with negative margins
 - As compared with extralaryngeal mucosal sites, patients with primary laryngeal squamous cell carcinoma with positive surgical margins have a significantly lower incidence of local recurrence:
 - Larynx perhaps is an outlier in regard to positive margins and local recurrence.
 - Above findings suggest that margin status and local recurrence are site dependent and assist in explaining why surgeons are more apt to accept nearer margins for laryngeal carcinoma (free margins up to 2 mm) but require wider margins (5 to 10 mm) for carcinomas of extralaryngeal mucosal sites.
 - Factors that may contribute to the lower incidence of local recurrences in laryngeal

squamous cell carcinoma with positive margins supporting organ sparing (conservative) laryngectomy may include:

- These patients have early-stage carcinoma associated with a more favorable prognosis.
- Submucosa of the glottic region has (quantitatively) fewer lymph-vascular spaces, thereby decreasing the incidence of spread and lowering the incidence of locoregional failure.

Supraglottic Squamous Cell Carcinoma (Fig. 16-31)

Definition: Squamous cell carcinoma that involves structures of supraglottic larynx, including the epiglottis (laryngeal and lingual surfaces), aryepiglottic folds, arytenoids, false vocal cords, and ventricles.

Clinical

- Accounts for 30% to 35% of all laryngeal carcinomas
- In descending order supraglottic carcinomas involve epiglottis (45% to 55%) > false vocal cords (12% to 33%) > aryepiglottic folds (8% to 21%) > ventricles (4% to 7%) and arytenoids (5% to 6%):
 - In combination with other sites epiglottis is involved in 70% to 90% of cases.
 - Marginal or epilaryngeal carcinomas represent carcinomas involving the suprahoid epiglottis and aryepiglottic folds and account for approximately 20% of cases.
- Symptoms include:
 - Dysphagia, changes in quality of voice, foreign body sensation in the throat, neck mass, hemoptysis, odynophagia, and dyspnea
 - Marginal (epilaryngeal) carcinomas tend to remain quiescent for longer periods and present with more advanced disease.

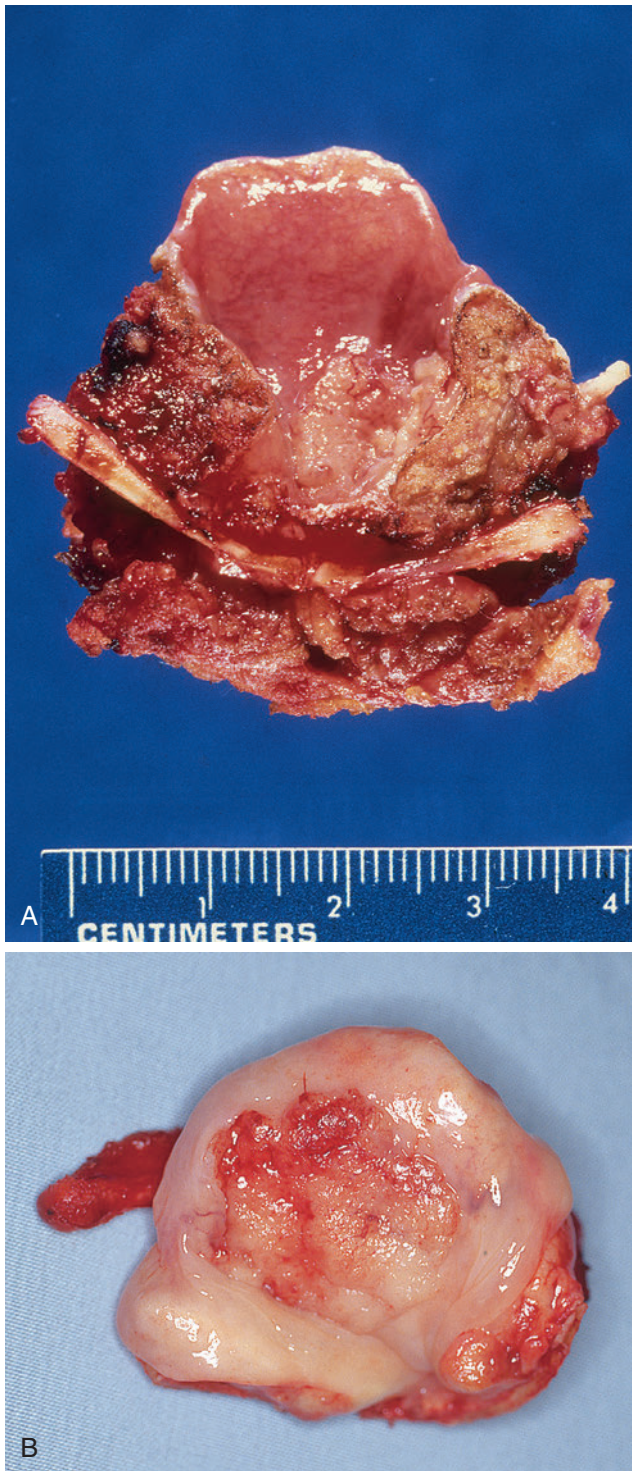
Pathology

Gross

- Vary in size and appearance:
 - Tend to be large
 - Ulcerated, flat, exophytic, or rarely papillary

Histology

- Tend to be moderately to poorly differentiated carcinomas
- An in situ component is common and may be extensive.
- Invasive pattern can be pushing or infiltrative.
- Mitoses and necrosis can be seen and their presence relates to the grade of the tumor (tend to be more common with poorer differentiated tumors).

**Fig. 16-31.**

A, B, Supraglottic laryngectomy specimens showing supraglottic-based (squamous cell) carcinoma.

Spread

- Tendency for supraglottic carcinomas to spread:
 - Upward toward the free margins of the epiglottis and aryepiglottic folds
 - Into piriform sinus

- Into vallecula (i.e., base of tongue)
- High incidence of invasion of the preepiglottic space:
 - Involvement of the preepiglottic space is associated with an increased incidence of nodal metastasis.
- Uncommon to spread posteriorly to arytenoids or to glottis or thyroid cartilage
- Marginal carcinomas tend to spread to:
 - Base of tongue
 - Less common to spread to the pre-epiglottic space

Treatment and Prognosis

- Treatment depends on stage:
 - Early stage lesions (T1N0 and T2N0):
 - Radiation therapy or supraglottic laryngectomy with or without adjuvant radiotherapy
 - Advanced-stage lesions (T3 and T4):
 - Combined modalities often including total laryngectomy and adjuvant radiotherapy:
- Decision to use radiation therapy or partial laryngeal therapy depends on several factors, including:
 - Anatomic extent of the tumor
 - Medical condition of the patient
 - Status of the surgical margins
 - Presence or absence of nodal metastasis with or without extracapsular spread
 - Philosophy of the treating physician
 - Inclination of the patient and family
- Potential for nodal metastasis even in early-stage lesions is substantial, and neck dissection is often performed in conjunction with laryngeal surgery:
 - Majority of supraglottic carcinomas are located in epiglottis and many of these tumors are midline, putting the patient at risk for contralateral neck metastases, thereby necessitating bilateral neck dissection.
 - Site of treatment failure in supraglottic carcinoma is neck, requiring neck management for supraglottic carcinomas.
 - For the N0 neck, selective neck dissection or elective radiation is indicated.
 - For clinically positive neck disease, neck dissection, therapeutic irradiation, or combination of both indicated
 - Supraglottic larynx is rich in lymphatic spaces, increasing the likelihood of cervical lymph node metastasis even in early-stage disease.
 - Increased rates of cervical lymph node metastasis correlated to:
 - Tumor size: larger tumors (>4 cm) have higher rate of metastasis
 - Location:
 - Tumors arising from marginal supraglottis have higher rate of metastasis
 - Anterior tumors or tumors that cross the midline may produce bilateral metastases

- Supraglottic lymphatic drainage is to upper and middle jugular chains.
- Distant metastasis (i.e., below the clavicle) from supraglottic cancers is uncommon (5% to 15%) and when it occurs more commonly involves the lung and mediastinal lymph nodes
- Overall 5-year survival rate for all stages of supraglottic carcinomas is 65% to 75%:
 - Prognosis depends on:
 - Extent and location of the primary lesion
 - Presence of cervical lymph node metastasis:
 - Appears to represent most important determinant of survival
 - Influenced by location of primary tumor (see above)
 - Occurs in 30% to 40% of cases
 - Most commonly involves upper and midjugular lymph nodes
 - Uncontrolled neck metastasis is a source of therapeutic failure.
 - Nature of the primary therapy

Glottic Squamous Cell Carcinoma

(Fig. 16-32)

Definition: Squamous cell carcinoma that involves structures of glottis, including the true vocal cords, and anterior and posterior commissures.

Clinical

- Represents from 60% to 65% of all laryngeal squamous cell carcinomas
- Majority arise from anterior portion of true vocal cord:
 - Involvement of anterior commissure alone is uncommon (less than 10% of cases)
 - Secondary involvement is more common, seen in up to 46% of cases.
 - Posterior portion of true vocal cord is uncommon site for carcinoma to develop.
 - Equally distributed between right and left true cord
- Most common presenting symptom is hoarseness.
- As a result of interference with vocal cord mobility symptoms develop early in the course of disease.
- Many glottic carcinomas are small, limited in size, tend to be localized and are amenable to conservative therapy.

Pathology

Gross

- Early lesions:
 - Irregular area of mucosal thickening of varying size
- Advanced lesions:
 - Exophytic, fungating, endophytic, or ulcerated mass, which can attain a large size

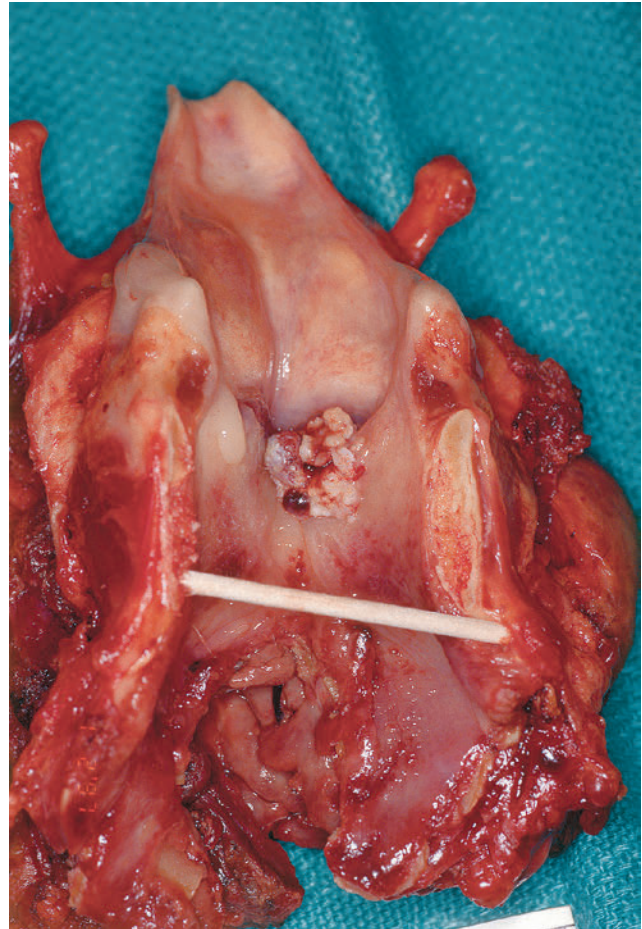


Fig. 16-32.

Laryngectomy specimen showing a glottic-based (squamous cell) carcinoma.

Histology

- Most often are well-differentiated to moderately differentiated squamous cell carcinomas
- High-grade intraepithelial dysplasia/CIS seen adjacent to invasive carcinoma
- Invasive pattern is predominantly infiltrative but can be pushing.

Spread

- Spread of glottic carcinomas include:
 - Across the anterior commissure to involve the opposite vocal cord
 - Anteriorly through the Broyle's ligament (anterior commissure tendon) with deep invasion and penetration of the thyroid cartilage in the midline with invasion of the soft tissues of the neck
 - Posteriorly to involve arytenoids
 - Extension to supraglottis with involvement of the ventricle, false vocal cords, and epiglottis:
 - Occurs in approximately 20% to 25% of cases

- Extension to subglottis:
 - Occurs in approximately 20% to 25% of cases
 - Greater access to lymphatic channels with potential for spread to paratracheal and mediastinal lymph nodes
 - Potential to invade cricothyroid membrane growing into soft tissues of the neck
 - Do not invade thyroid cartilage until more than 1 cm into subglottis
- Extension into Reinke space along the vocal cord ligament with infiltration into the vocalis muscle:
 - This pattern of invasion defines vocal cord fixation.
 - In presence of fixed cord incidence of nodal metastasis is approximately 25%.
 - If cord is not fixed, then invasion is superficial to conus elasticus.
 - Absent cord fixation incidence of nodal metastasis is less than 2%.
- Incidence of nodal metastasis in T1 lesions ranges from 0 to 6%.
- Incidence of nodal metastasis in T2 lesions ranges from 4% to 11%.
- Majority of cervical lymph node metastasis occurring in glottic carcinomas is seen in T3 and T4 lesions:
 - Incidence of nodal metastasis in T3 lesions ranges from 14% to 22%.
 - Incidence of nodal metastasis in T4 lesions ranges from 25% to 41%.
- Overall 5-year survival rates include:
 - T1: 82% to 96%
 - T2: 51% to 85%
 - T3: 48% to 59%
 - T4: 0 to 30%
- Risk factors associated with incidence of locoregional failure include:
 - Prior tracheotomy
 - Poor histologic differentiation
 - Subglottic extension >1 cm
 - Histologically positive lymph nodes
- Risk of distant metastases increased in association with presence of metastatic carcinoma to a lymph node with extranodal invasion into perinodal soft tissue (extranodal extension)

Treatment and Prognosis

- Treatment depends on staging:
 - For early glottic cancers (T1 and T2) excellent control can be achieved by radiation or partial laryngectomy or even endoscopic resection in some lesions.
 - Advantages of radiation include:
 - Better voice control than that achieved by hemilaryngectomy
 - Hemilaryngectomy (i.e., vertical hemilaryngectomy) can be used successfully for salvage in those patients in whom radiation has failed.
 - For advanced glottic cancers (T3 and T4) total laryngectomy with or without radiation therapy:
 - Not all advanced glottic cancers require total laryngectomy.
 - Certain T3 glottic cancers, including those with mobile arytenoids and less than 7 mm of subglottic extension, are potential candidates for subtotal laryngectomy.
- Neck dissection (radical neck dissection or modified radical neck dissection):
 - Performed in patients with clinically N+ neck disease
 - For advanced glottic carcinomas rates of occult metastasis in clinically N0 neck approach 20% and are higher for those carcinomas that cross the midline, so these patients may be considered for elective neck dissection for staging purposes when surgery is performed for primary disease.
 - Glottic lymphatic drainage is to upper and lower jugular chains.
- Glottic region has sparse lymphatic drainage; as such the overall incidence of lymph node metastasis is low:

Subglottic Squamous Cell Carcinoma (Fig. 16-33)

Definition: Squamous cell carcinoma that involves subglottis, which begins 1 cm below apex of ventricle to its inferior border represented by rim of cricoid cartilage.

Clinical

- Considered uncommon, accounting for less than 5% of all laryngeal carcinomas
- Tend to remain clinically quiescent, presenting with advanced disease
- Most common presenting symptoms relate to airway obstruction (dyspnea, stridor) and to vocal cord fixation (voice changes):
 - May necessitate emergency tracheotomy to maintain airway

Pathology

Gross

- Large exophytic, fungating, ulcerating, or endophytic mass

Histology

- Tend to be moderately to poorly differentiated squamous cell carcinoma
- Invasive pattern is predominantly infiltrative.

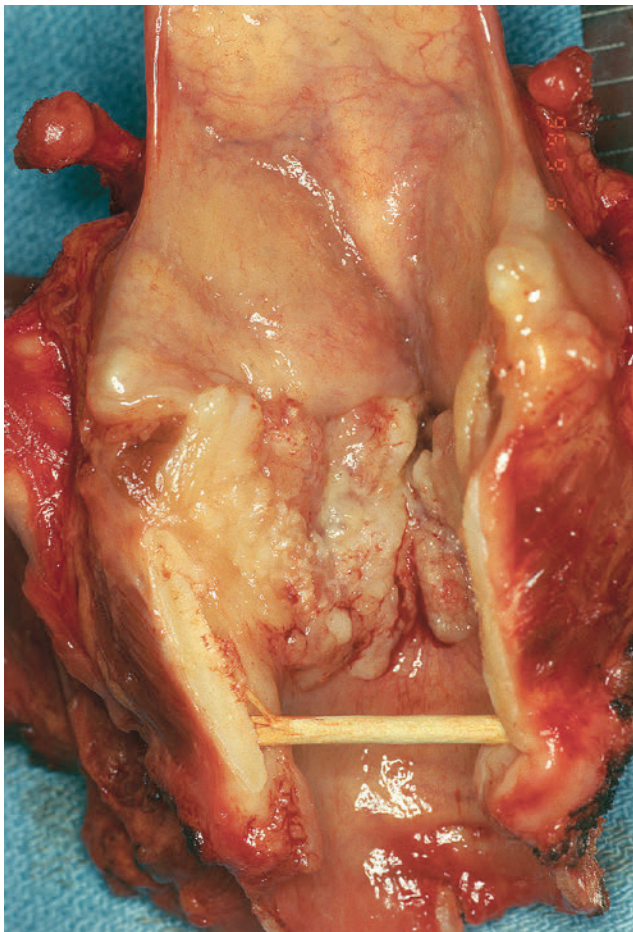


Fig. 16-33.

Laryngectomy specimen showing a subglottic-based (squamous cell) carcinoma.

Spread

- Tendency to spread circumferentially and anteriorly through the cricothyroid membrane with involvement of thyroid gland and paratracheal and prelaryngeal (Delphian) lymph nodes
- May spread:
 - Posteriorly below the thyroid cartilage with involvement of the cervical esophagus
 - Inferiorly with involvement of the trachea
 - Medially into the cricoarytenoid joint with involvement of the hypopharynx
 - Into the thyroarytenoid muscle to produce vocal cord fixation
 - Superiorly to involve the glottic and supraglottic regions
- Subglottic region of larynx has lymphatic drainage to:
 - Upper and lower jugular lymph node chains
 - Anteriorly to prelaryngeal (Delphian) lymph node, which in turn drains to the pretracheal and supraclavicular lymph nodes
- Posterolateral to the paratracheal lymph nodes, which are continuous with lymph nodes in the superior mediastinum

Treatment and Prognosis

- Treatment is dependent on staging:
 - For early-stage subglottic cancers (T1 and T2):
 - Radiotherapy alone or conservative surgery
 - For advanced-stage subglottic cancers (T3 and T4):
 - Radical surgical extirpation through wide field laryngectomy
 - In general, subglottic tumors present with advanced disease and because of proximity to cricothyroid space and the cricoid cartilage; surgical treatment usually necessitates a total laryngectomy.
 - Due to involvement of the thyroid gland in approximately 10% to 20% of cases, recommended that one or both thyroid lobes be removed
- Radical neck dissection is advocated in advanced subglottic carcinoma:
 - Approximately 15% to 25% of patients have cervical lymph node metastases but paratracheal lymph nodes that are clinically negative (N0) harbor metastatic tumor from subglottic primary carcinoma in up to 50% of cases, leading to recommendation of clearing the paratracheal as well as superior mediastinal lymph nodes.
- Overall 5-year survival rate is approximately 40%:
 - Death due to subglottic carcinoma often due to local or stomal recurrence:
 - Refers to diffuse infiltration of carcinoma at junction of amputated trachea and skin
 - Dreaded complication of total laryngectomy
 - Occurs in approximately 2% to 15% of patients who have had total laryngectomies
 - Most often occurs within 1 to 2 years after total laryngectomy
 - 70% of patients with stomal recurrence die within the first year after laryngectomy and 98% within 2 years.
 - Inadequate tumor resection at the inferior margin contributes to early stomal recurrence.
- Distant metastases occur in 15% to 20%:
 - Most often to lungs and bones

Transglottic Squamous Cell Carcinoma (Fig. 16-34)

Definition: Transglottic carcinoma represents a carcinoma that crosses ventricles in a vertical direction to involve supraglottis and glottis (and often subglottis):

- Most likely are glottic cancer with supraglottic extension

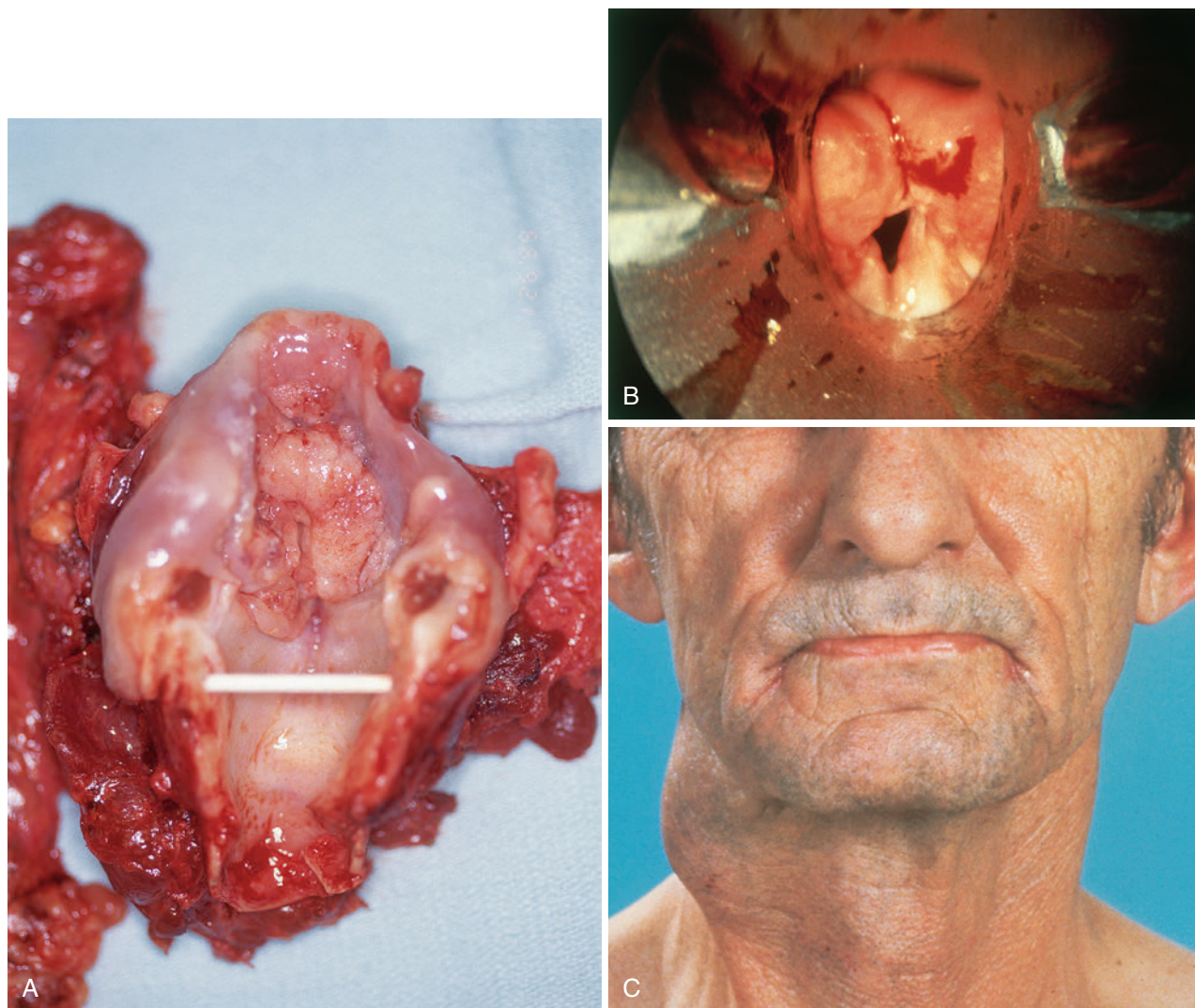


Fig. 16-34. Transglottic carcinoma.

A, Transglottic carcinoma characterized by carcinoma that crossed the ventricles in a vertical direction with involvement of the glottic and supraglottic larynx. **B,** Bilateral vocal cord paralysis in a patient with a transglottic carcinoma. **C,** Patients with transglottic carcinoma have a high incidence of nodal metastasis as seen in this patient with a right lateral neck mass histologically composed of a keratinizing squamous cell carcinoma.

Clinicopathologic Features

- Usually but not always represent advanced-stage tumors
- Majority are moderately differentiated with infiltrating margins.
- High incidence of nodal metastases and extralaryngeal spread:
 - Extralaryngeal spread present in approximately one third of patients
 - Spread to paraglottic space
 - Submucosal spread to piriform sinus
 - Extralaryngeal escape by growing through the cricothyroid or thyrohyoid membranes
- Should be suspected in patients with referred otalgia
- 26% with nodal metastasis at presentation and additional 19% subsequently develop positive lymph nodes during course of disease
- High incidence of vocal cord paralysis
- May be understaged as a result of undetectable cartilaginous invasion
- Treatment generally requires radical surgery and radiotherapy.
- In limited patients conservation techniques may be used.
- Overall 5-year survival is approximately 50%.

Tracheal Squamous Cell Carcinoma

Clinical

- Most common malignant neoplasm of the trachea
- More common in men than in women; most common in the fifth to seventh decades of life
- Clinical presentation includes stridor, cough, hemoptysis, hoarseness, weight loss; superior vena cava syndrome may occur in minority of cases:
 - Delay in diagnosis is common as symptoms may be attributed to asthma.
- Tracheal carcinoma at the level of the thyroid can be misinterpreted as invasive thyroid cancer.
- In order of frequency tracheal carcinomas occur:
 - Lower third (45%) > upper third (32%) > middle third (15%) > multiple sites (8%)
- Cause:
 - Most patients reported to be heavy tobacco smokers

Pathology

Gross

- Polypoid mass protruding into the tracheal lumen:
 - Most tend to be large, measuring 4 cm in greatest dimension.
- Uncommonly grows circumferentially or with an annular appearance

Histology

- Variable architectural features including exophytic and papillary
- Variable morphologic findings ranging from well to poorly differentiated

Spread

- Invasion through tracheal wall is common.
- Lymph node metastasis is common and includes spread to paratracheal, deep cervical, mediastinal, and peribronchial lymph nodes.

Treatment and Prognosis

- Surgical resection and primary reconstruction is best curative treatment modality available at present:
 - Many tracheal carcinomas are too large or extensive at presentation for surgical cure.
- In patients with advanced disease (i.e., inoperable tumors), radiotherapy can represent a management option:
 - Variable success in controlling disease
- Approximately 35% have nodal metastasis at presentation.
- Distant metastases commonly occur:
 - Primarily to lungs, liver, and bones
- Clinical course is rapid and prognosis is poor:
 - 5-year survival rates 5% to 15%
 - 10-year survival rates 6% to 7%

BOX 16-4 Variants of Squamous Cell Carcinoma

- Papillary squamous cell carcinoma
- Verrucous carcinoma
- Spindle cell squamous carcinoma
- Basaloid squamous cell carcinoma
- Adenosquamous carcinoma
- Lymphoepithelial-like carcinoma
- Giant cell carcinoma
- Others

- There is no current TNM classification for tracheal carcinomas.

VARIANTS OF SQUAMOUS CELL CARCINOMA (Box 16-4 and Table 16-3)

Papillary (Exophytic) Squamous Cell Carcinoma (PSCC)

(Figs. 16-35 through 16-37)

Definition: Invasive squamous cell carcinoma with a predominant papillary and/or exophytic component.

Clinical

- Uncommon but distinct subtype of head and neck SCC
- Demographics are similar to those of conventional SCC with the tendency to affect men more than women and occurring in adults with a mean age in the seventh decade of life.
- Predilect to the larynx, oral cavity, oropharynx, hypopharynx, and sinonasal tract:
 - Larynx is most common site of occurrence.
 - Within the larynx most of these carcinomas are located in the supraglottis followed by the glottis and rarely in the subglottis.
 - Less commonly, may occur in other mucosal sites of the upper aerodigestive tract including (but not limited to):
 - Oropharynx (tonsil and base of tongue), oral cavity, sinonasal tract, nasopharynx
- Symptoms vary according to the site of involvement:
 - Laryngeal involvement includes hoarseness and airway obstruction; less often, dysphagia and hemoptysis may occur.
- Development:
 - Majority arise de novo unassociated with pre- or coexisting papilloma
 - Minority develop in association
- Cause:
 - Etiologically associated with human papillomavirus (HPV) but histology and subsite localization may corroborate whether HPV may be involved:

TABLE 16-3 Clinicopathologic Features of Select Squamous Cell Carcinoma Variants

	PSCC	VC	SCSC	BSCC
Age/Gender	7th decade; M > F	6th-7th decades; M > F	6th-8th decades; M > F	6th-7th decades; M > F
Site*	Larynx > oropharynx, oral cavity, sinonasal tract nasopharynx	Oral cavity > larynx (glottis)	Larynx: true vocal cord > false vocal cord, supraglottis	Hypopharynx (piriform sinus), larynx (supraglottis), oropharynx (tonsil, base of tongue)
Symptoms	Hoarseness and airway obstruction	Oral: mass with or without pain Larynx: hoarseness	Hoarseness, airway obstruction, dysphagia	Hoarseness, dysphagia, pain, neck mass
RF	Tobacco and alcohol	Tobacco (chewing, smoking)	No known risk factors	Tobacco and alcohol
HPV-associated (transcriptionally active)	Transcriptionally active high-risk HPV may be identified	Not implicated	Transcriptionally active high-risk HPV may be identified; often site specific [†]	Transcriptionally active high-risk HPV may be identified; often site specific [†]
Histology	Filiform to papillary to broad-based bulbous to exophytic growth with fibrovascular cores; squamous epithelium is cytologically malignant; surface keratinization is generally limited and often absent; considered as being invasive even in the absence of definitive stromal invasion; usually arise de novo but may be associated with precursor papilloma or occurrence at site of prior papilloma	Epithelial proliferation with uniform squamous cells without dysplastic features or mitoses; marked surface keratinization ("church-spire" keratosis); broad or bulbous rete pegs with a pushing, not infiltrative, margin	Malignant undifferentiated spindle cell and pleomorphic cellular proliferation and the presence of a conventional squamous cell component (carcinoma in situ and/ or invasive SCC); may be entirely composed of malignant undifferentiated spindle cells (cellular or hypocellular collagenized) without differentiated epithelial component	Invasive neoplasm composed predominantly of pleomorphic basaloid cells with associated minor squamous cell component (epithelial dysplasia, abrupt keratinization, carcinoma in situ, invasive carcinoma); variety of growth patterns, including solid, lobular, cribriform; cords, trabeculae and gland-like or cystic growth; increased mitotic activity, comedonecrosis in center of neoplastic lobules; peripheral nuclear palisading and basement membrane- like material may be seen
IHC	Positive for cytokeratins (IHC typically not required for diagnosis); p16 typically negative	Positive for cytokeratins (IHC typically not required for diagnosis); p16 typically negative	Positive for cytokeratins in majority of cases (approximately 60%), but may be negative in approximately 40% of cases; variable reactivity for p63; may be positive for vimentin, desmin, actins; p16 typically negative but may be positive [†]	Consistently positive for cytokeratins; neuroendocrine markers are usually negative but occasional cases may be positive; variable expression for vimentin, NSE, S100 protein, and actins; site specific tumors may be p16+ [†]
Treatment	Surgery	Surgery	Surgery with or without adjunctive radiotherapy	Surgery, ND, radiation, and chemotherapy
Spread	Regional lymph nodes; distant metastasis is rare (lung)	Locally invasive; not metastatic	Metastasizes to regional lymph nodes and lung	Early dissemination to regional and distant lymph nodes, lung, bone, skin, brain

Continued

TABLE 16-3 Clinicopathologic Features of Select Squamous Cell Carcinoma Variants—cont'd

	PSCC	VC	SCSC	BSCC
Prognosis	Similar to conventional SCC of similar stage although may have an overall more favorable prognosis than comparable conventional SCC; HPV-related PSCCs not associated with statistically significant improved patient outcomes, although the HPV-positive tumors tend to have better survival compared with the HPV-negative tumors	Excellent	Dependent on stage but overall prognosis is poor Although number of HPV-positive cases are too small for any definitive conclusions, positive viral status does not appear to confer any prognostic benefit	For non-HPV-associated: poor, often resulting in death within a year from diagnosis For HPV-associated BSCC: share better outcomes similar to oropharyngeal nonkeratinizing (HPV-associated) carcinomas

BSCC, Basaloid squamous cell carcinoma; HPV, human papillomavirus; IHC, immunohistochemistry; ND, neck dissection; PSCC, papillary squamous cell carcinoma; RF, potential risk factors; SCSC, spindle cell squamous carcinoma; VC, verrucous carcinoma.

*Most common sites in the head and neck.

[†]Oropharyngeal BSCCs and SCSCs may harbor transcriptionally active HPV.

- Oropharyngeal PSCCs tend to be nonkeratinizing and associated with high-risk HPV.
- Laryngeal and oral PSCCs tend to be keratinizing and not associated with HPV.
- Smoking and alcohol linked to the development of PSCC

Pathology

Gross

- Most often seen as a solitary lesion with a polypoid, exophytic, or papillary growth
- Tumor size may range from 2 mm up to 4 cm.

Histology

- Filiform growth with finger-like projections and identifiable fibrovascular cores or a broad-based bulbous to exophytic growth with rounded projections resembling a cauliflower-like growth pattern in which fibrovascular cores can be seen but tend to be limited to absent.
- Squamous epithelium is cytologically malignant:
 - Malignant epithelium identifies these tumors as carcinomas as opposed to papillomas.
- Surface keratinization is generally limited and often absent.
- Two morphologic types may be identified:
 - Keratinizing type:
 - Epithelial cells show maturation with minimal surface parakeratin.
 - Tend to predilect to larynx, oral cavity
 - Tend to be p16 negative and p53 positive:
 - May be p16 positive

- Tend to lack transcriptionally active virus:
 - May be shown to harbor transcriptionally active virus
 - Oral cavity and to a lesser extent larynx more likely to be associated with transcriptionally active HPV than conventional SCC.
- Nonkeratinizing type:
 - Papillae completely covered by immature basaloid cells
 - Tend to predilect to oropharynx
 - Tend to be p16 positive and p53 negative
 - Tend to harbor transcriptionally active virus
- May be entirely in situ (irrespective of size) or show only superficial invasion:
 - Definitive invasion may be difficult to demonstrate in biopsy specimens.
 - Multiple biopsies may be required to establish the diagnosis.
 - Some authorities believe that, despite the presence of carcinomatous epithelium suggesting an in situ process rather than invasive carcinoma, the extent of growth with the formation of a clinically appreciable exophytic mass goes beyond the general concept of an in situ carcinoma and that these tumors should be considered as being at least superficially invasive even in the absence of definitive stromal invasion.
- Usually arise de novo without identification of coexisting benign lesion such as a papilloma although association with precursor papilloma or occurrence

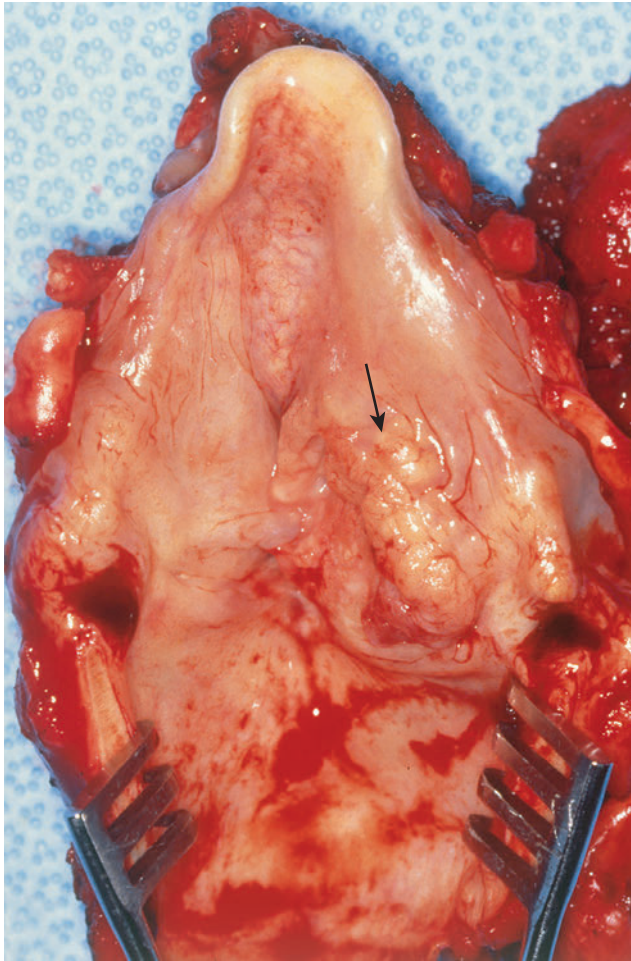


Fig. 16-35. Resected PSCC.

Laryngectomy specimen showing papillary squamous cell carcinoma appearing as a solitary papillary/exophytic lesion in the supraglottic larynx.

in patients with previous history of a papilloma at the site of the papillary SCC has been reported

- Immunohistochemistry and molecular genetics:
 - Transcriptionally active high-risk HPV may be identified:
 - Indirectly by p16 overexpression
 - Directly by mRNA in situ hybridization (ISH) for E6/E7 proteins
 - Tend to be located in oropharynx with non-keratinizing morphology
 - Oral cavity and less often laryngeal PSCC may be shown to harbor transcriptionally active HPV by p16 staining and E6/E7 mRNA ISH
 - p53 immunoreactivity reported:
 - Tend to occur in keratinizing type
 - Tend to be absent in nonkeratinizing type

Differential Diagnosis

See Table 16-3.

- Papilloma/papillomatosis:
 - Papillomas are distinguished by their bland epithelial proliferation.
 - Cytologic abnormalities may be seen in papillomas, but they tend to be focal when present but do not approach the level of dysplasia seen in papillary SCC.
- Conventional squamous cell carcinoma
- Verrucous carcinoma:
 - Characterized by a verrucous growth pattern with marked keratosis in layers or tiers, absent nuclear atypia, absent mitotic activity beyond the basal layer, and a pushing rather than infiltrative pattern of invasion:
 - Such features contrast with those seen in PSCC.

Treatment and Prognosis

- Surgery is preferred treatment.
- Adjunctive therapy (i.e., radiation) may be used.
- Majority of papillary SCCs are low clinical stage (T2)
- Overall behavior similar to conventional SCC of similar stage, although a better overall prognosis reported for PSCC than for conventional SCC when matched for T stage.
 - 2- and 5-year disease-free survival rates reported to be 68% and 46%, respectively
 - Overall survival rate reported to be 90% and 72% at 2 and 5 years, respectively
- Recurrence and metastasis (locoregional and distant) may occur:
 - Distant metastases are rare and may include the lung.
- HPV-related PSCCs:
 - Not associated with statistically significant improved patient outcomes, although the HPV-positive tumors tend to have better survival compared with the HPV-negative tumors
 - Even though PSCCs in larynx and oral cavity harbor transcriptionally active HPV, it has been not shown that they are biologically different from HPV-negative ones or that they should be treated differently
 - Based on current state of knowledge, HPV testing in routine practice advocated only for oropharyngeal PSCC with no known utility for HPV testing in PSCCs of larynx and oral cavity
- p53 staining reported to be associated with poor survival

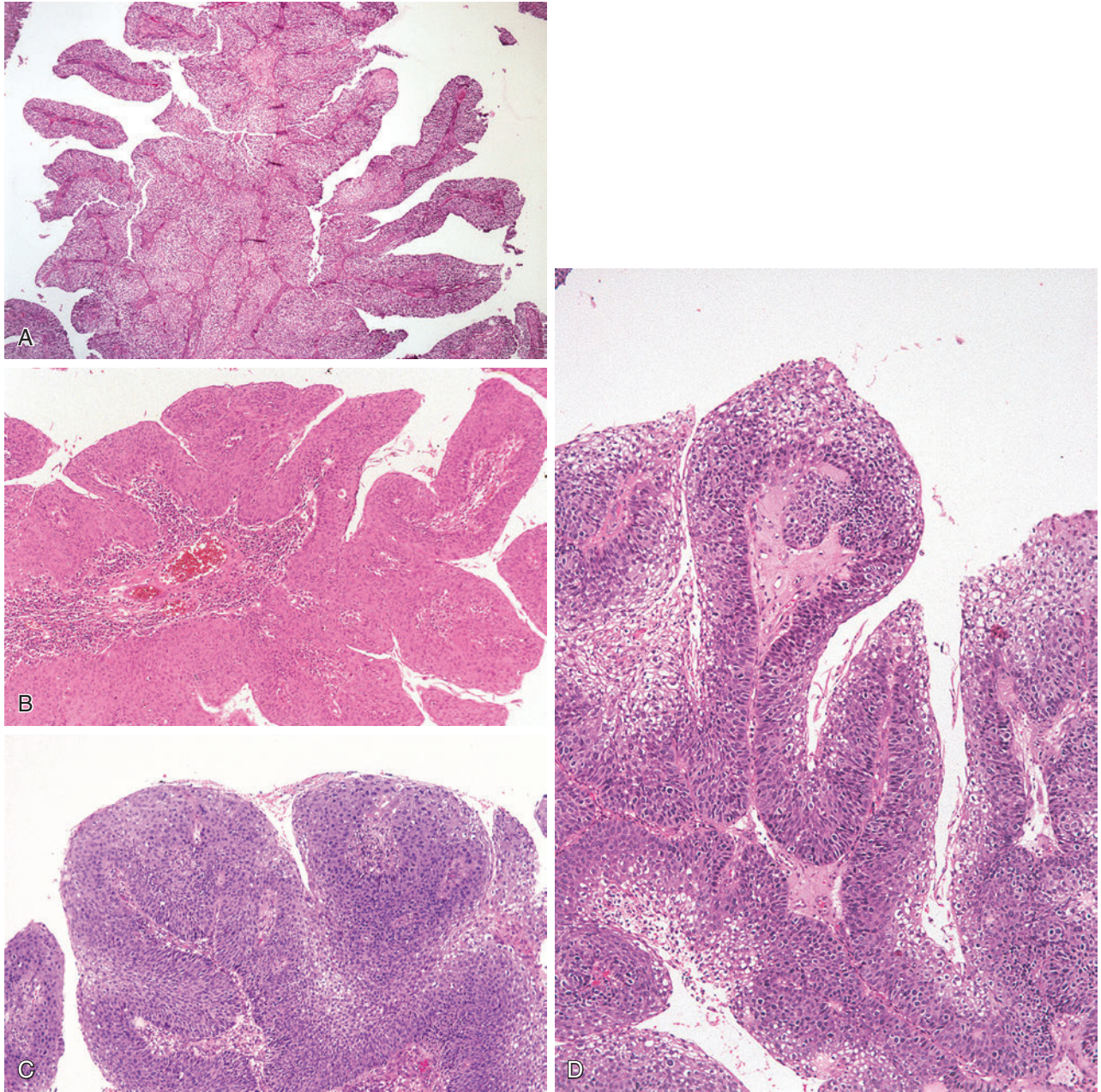


Fig. 16-36. Papillary squamous cell carcinoma.

Papillary/exophytic squamous cell carcinoma showing (A and B) papillary or filiform growth, (C and D) broad-based bulbous to rounded exophytic growth. Note the absence of surface keratosis.

Verrucous Carcinoma (VC)

(Figs. 16-38 through 16-40)

Definition: Highly differentiated variant of squamous cell carcinoma with locally destructive but not metastatic capabilities characterized by exophytic and/or warty appearance, absence of epithelial dysplasia, and presence of pushing margins.

Synonym: Ackerman tumor

Clinical

- Affects men more than women; generally occurs in the sixth and seventh decades of life
- Can occur anywhere in the upper aerodigestive tract, but most common sites of occurrence include:
 - Oral cavity:
 - Represents the most common site of occurrence in the head and neck, accounting for approximately 75% of all cases

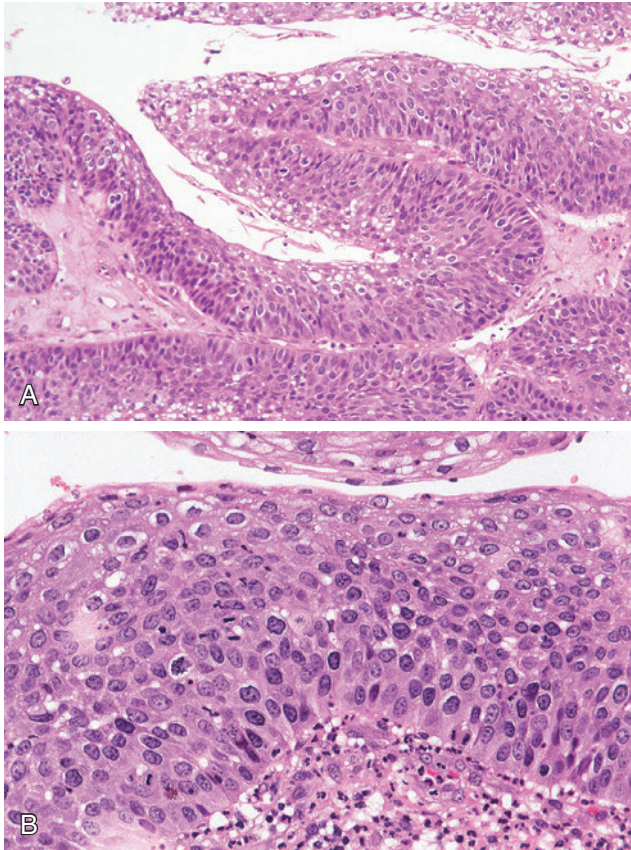


Fig. 16-37. PSCC.

The epithelium in papillary squamous cell carcinoma is cytologically malignant, which differentiates it from a papilloma; surface keratosis is absent.

- Most commonly arise on the buccal mucosa and gingiva
- Larynx:
 - Represents the second most frequent site of occurrence
 - Accounts for 15% to 35% of all VCs
 - Represents from 1% to 4% of all laryngeal carcinomas
 - Most common site of occurrence in the larynx is the glottic area (anterior true vocal cord); less common sites of occurrence include the supraglottis, hypopharynx and subglottis, and trachea.
- Nasal fossa
- Sinonasal tract and nasopharynx
- Middle ear (rare)
- Symptoms vary according to site:
 - Larynx: hoarseness is most common complaint, less frequent symptoms include airway obstruction, hemoptysis, dysphagia
 - Oral cavity: mass with or without pain
 - Sinonasal tract: airway obstruction
 - Nasopharynx: dysphagia



Fig. 16-38. Verrucous carcinoma.

Laryngeal verrucous carcinoma appearing as a large, tan-white, and warty to fungating mass.

- Cause of VC remains speculative and includes:
 - Tobacco smoking or chewing
 - Most recent data from the literature do not support etiologic link to HPV (high risk or low risk).
 - Active role of HPV is more likely as a promoter in the multistep process of carcinogenesis in squamous cells of the upper aerodigestive tract.
 - Two viral oncoproteins of high-risk HPVs, E6 and E7, promote tumor progression by inactivating the p53 and retinoblastoma tumor suppressor gene products, respectively, thereby disrupting cell-cycle regulatory pathways in the genetic progression to head and neck SCC.

Pathology

Gross

- Tan or white, warty, fungating or exophytic, firm to hard mass of varying size measuring up to 9 to 10 cm in diameter
- In general, the tumors are attached by a broad base.

Histology

- Histologic appearance is that of a benign-appearing squamous cell proliferation, requiring the following characteristics for diagnosis:
 - Marked surface keratinization (“church-spire” keratosis):
 - Filiform projections
 - Commonly in form of parakeratin
 - Orthokeratin with sparse keratohyaline granules may be present.
 - Uniform cells without dysplastic features or mitoses:
 - Cells arranged in orderly maturation pattern toward (markedly keratotic) surface
 - Mitotic figures can be seen along basal zone but should not be present in more superficial aspects of the epithelium.
- Advancing front of tumor characterized by broad or bulbous rete ridges with a pushing but not infiltrative margin with smooth stromal interface
 - Extends below level of identifiable intact subjacent normal epithelium
- Chronic inflammatory cell infiltrate composed of lymphocytes, plasma cells, and histiocytes may be prominent along the advancing front of the tumor.
- Immunohistochemistry and molecular genetics:
 - May be p16 (false) positive showing patchy staining lacking diffuse (greater than 75%) nuclear and cytoplasmic staining associated with true positive reactivity
 - Lack evidence of transcriptionally active high-risk HPV by DNA polymerase chain reaction (PCR) and E6/E7 mRNA reverse transcription PCR
 - p53 overexpression may be found.

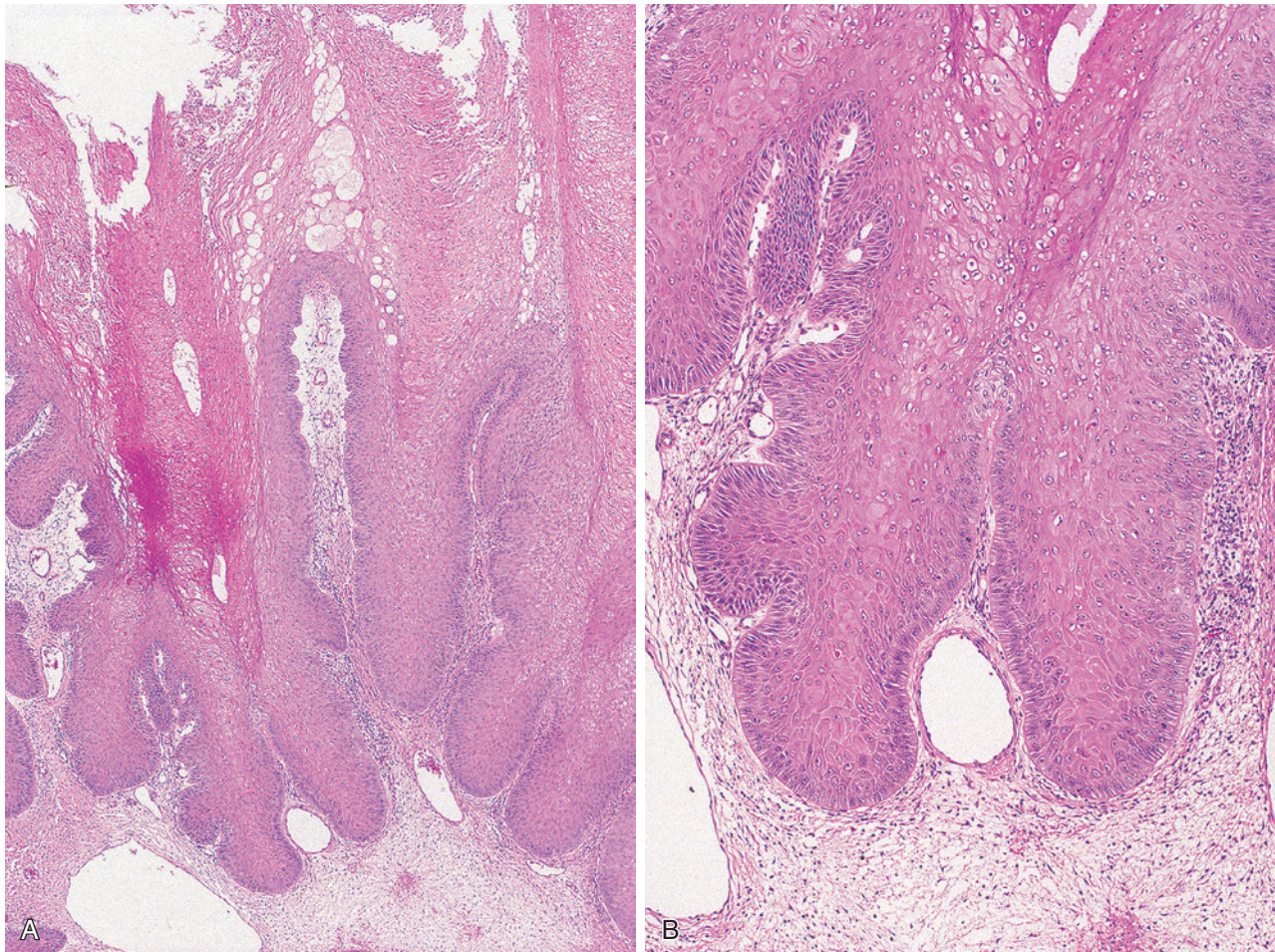


Fig. 16-39. Histology of verrucous carcinoma.

The histologic features of verrucous carcinoma include (**A, B**) marked surface keratinization (“church-spire” keratosis), bulbous rete pegs “pushing” into the underlying stroma;

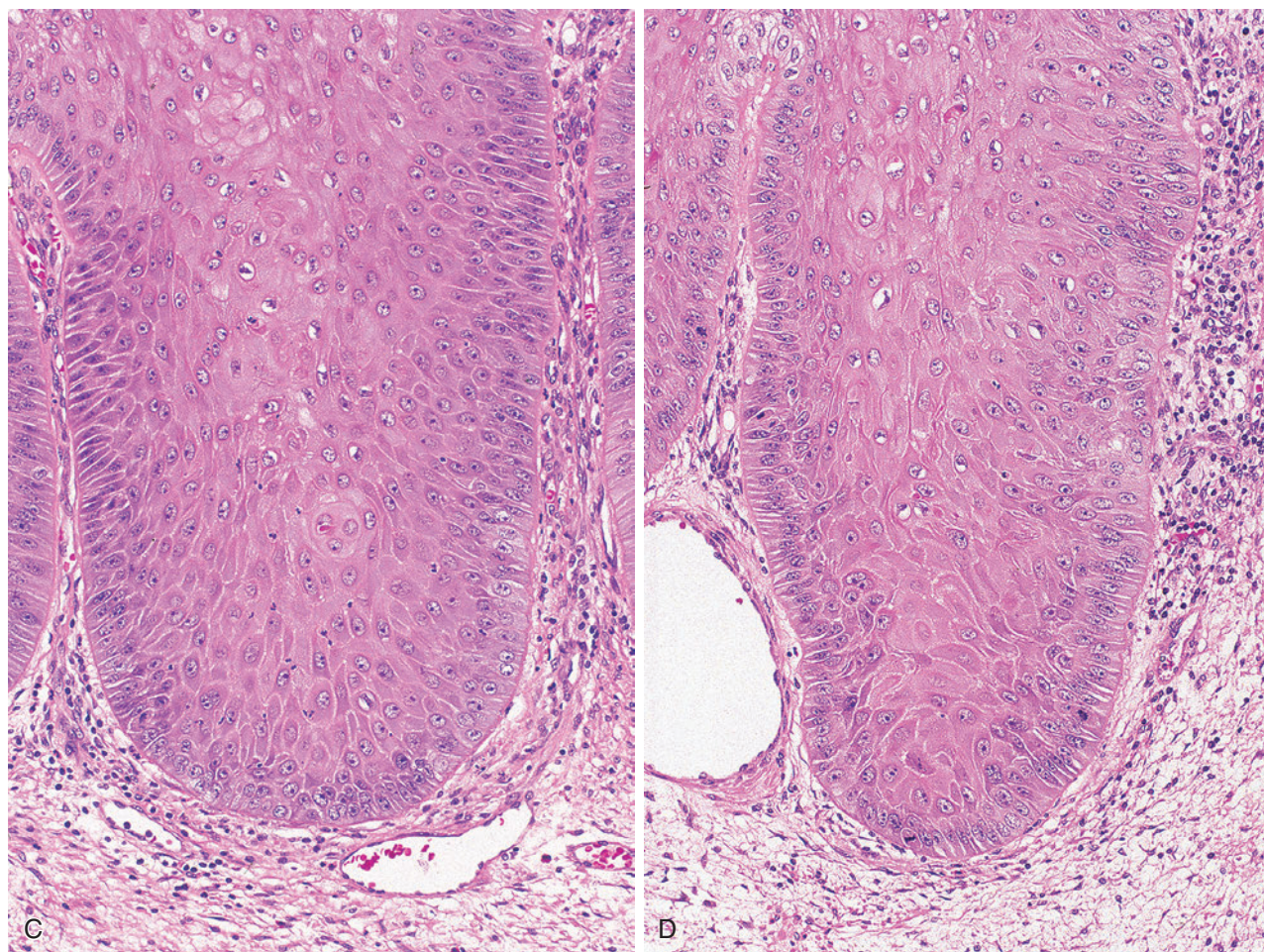


Fig. 16-39, cont'd

(C) rounded rete pegs with absence of cytologic atypia; (D) mitotic figures can be seen but are limited to the basal zone area. Note the rounded nests with smooth stromal interface.

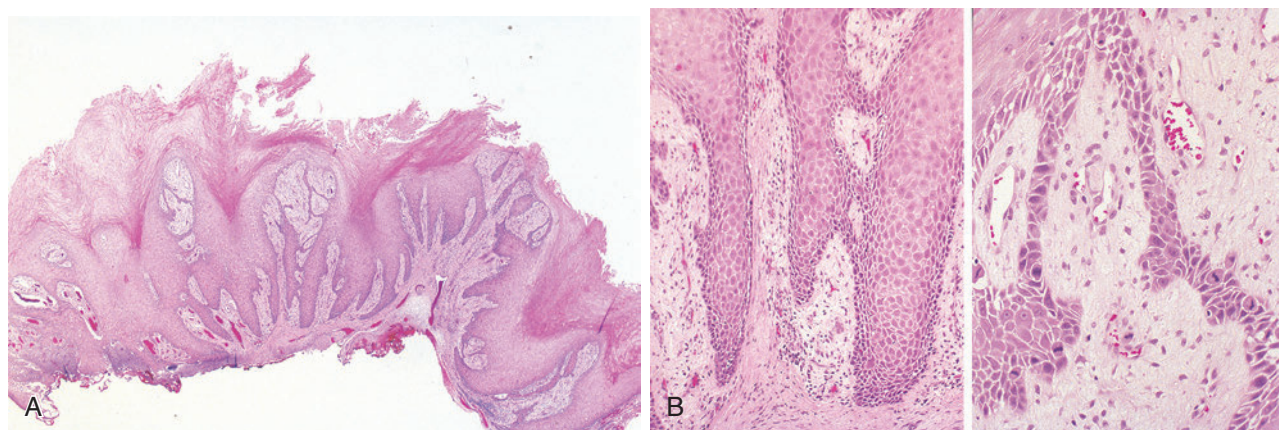


Fig. 16-40. Squamous cell carcinoma with verrucoid features.

A, The histologic features of laryngeal squamous cell carcinoma with verrucoid features at low magnification may suggest a possible diagnosis of verrucous carcinoma. **B**, At higher magnification despite cytologically bland-appearing elongated/angulated rete ridges (*left*) areas of marked dysplasia are present, conferring a diagnosis of a conventional squamous cell carcinoma differentiating it from verrucous carcinoma. The overall changes were not those of a hybrid carcinoma (i.e., admixture of verrucous carcinoma and conventional squamous cell carcinoma). Hybrid carcinomas may occur in the larynx but more often occur in oral cavity lesions.

Hybrid Carcinoma

- Tumor showing mixed histology, including foci of VC and foci of conventional squamous cell carcinoma:
 - Biologic risk is that of conventional SCC including potential for metastatic tumor.
 - May occur in larynx but more commonly seen in oral cavity lesions
 - Careful sampling and evaluation of the depth of the lesion are important to exclude a possible diagnosis of hybrid carcinoma.
 - Some authorities suggest that the SCC component be invasive >2 mm beyond verrucous component.

Biopsy Diagnosis of Verrucous Carcinoma

- Pathologic diagnosis of VC may be extremely difficult, requiring multiple biopsies over several years prior to identification of diagnostic features supporting appropriate interpretation:
 - Clinician and pathologists should be aware of this fact.
 - Adequate biopsy material is critical to interpretation and should include adequate epithelial-stromal interface.
 - Pathologist should not overinterpret a verrucoid lesion as a carcinoma without adequate tissue sampling including the presence of ample subjacent stroma.
 - Diagnosis of VC at initial presentation and biopsy is extremely challenging given overall bland cytomorphology and shared features with reactive verrucoid hyperplastic lesions
 - Recurrence of tumor at a future time may be the diagnostic clue to diagnosis of VC.

Differential Diagnosis

See [Table 16-3](#).

- “Conventional” squamous cell carcinoma:
 - Differentiation of VC from a “conventional” type of carcinoma is based on the presence or absence of cytologic abnormalities (i.e., dysplasia).
 - Any dysplastic epithelial changes should raise serious concern for the possible diagnosis of conventional SCC and exclude a diagnosis of VC although recent classification suggested a category of VC with epithelial dysplasia or invasion ≤ 2 mm in depth from nearest VC area (referred to as VC with dysplasia or minimal invasion).
 - Hybrid neoplasms composed of VC and coexisting conventional SCC occur (see above).
- Proliferative verrucoid leukoplakia (PVL):
 - PVL and verrucous hyperplasia represent interrelated and irreversible mucosal lesions of the oral cavity and upper aerodigestive tract with a

propensity to progress to either VC or conventional types of squamous cell carcinomas:

- Considered premalignant lesion
- Rare aggressive form of oral leukoplakia with a tendency to recur, often with multifocal oral involvement, and to undergo malignant transformation
- Most common in women (4:1), mean age in eighth decade of life, and long history (decades) of oral leukoplakia
- Most commonly begins on the buccal mucosa followed by the hard and soft palate, alveolar mucosa, tongue, floor of mouth, gingiva, and lip
- Cause:
 - No specific risk factors associated with development of PVL
 - History of tobacco use present in a high percentage of patients (greater than 50%) but a significant minority of patients have no history of tobacco use
 - No relationship to HPV or EBV
- Clinical and pathologic appearance in the early stages of PVL no different from any other type of leukoplakic lesion, making diagnosis of PVL in its early stages virtually impossible
- Clinically, lesion is flat, thickened keratosis with the histologic appearance of a nondysplastic keratosis; with progression of disease, the lesions become multiple, multifocal, and confluent with an exophytic and/or warty (verrucoid) appearance; it is in the latter clinical form that squamous cancer (verrucous carcinoma or conventional squamous cell carcinoma) is seen.
- Any given lesion may show a combination of verrucous hyperplasia, verrucous carcinoma, and conventional well-differentiated squamous cell carcinoma.
- Given the fact that PVL is associated with VC in a high percentage of cases, some authors believe that PVL should be considered as a premalignant condition or an early biologic form of VC:
 - This consideration would then obviate the confusion, clinically and pathologically, that surrounds the use of the term verrucous hyperplasia in describing these oral cavity lesions.
- Histology of PVL (see Section 2 for images) includes:
 - Composed of hyperplastic squamous epithelium with regularly spaced, verrucous epithelial projections and associated hyperkeratosis
 - Sharply defined lesion and in contrast to the downward growth into the underlying submucosal compartment by the bulbous rete pegs in VC, hyperplastic epithelium in PVL remains superficial (without submucosal invasion) and does not extend deeper than that of the

adjacent epithelium; this raises the issue of adequate sampling and the difficulties in differential diagnosis on incisional biopsy material.

- To exclude the presence of submucosal invasion, complete excision of the lesion allowing for histologic examination of the entire lesion is most appropriate.
- Treatment of PVL is by surgical excision.
- Disease-free survival rates after surgery are low due to recurrence and multifocal involvement.
- Radiotherapy has not been shown to be effective in controlling disease.
- Keratotic squamous papilloma
- Reactive keratosis and epithelial hyperplasia
- Pseudoepitheliomatous hyperplasia
- Verruca vulgaris
- Keratoacanthoma (when verrucous carcinoma affects cutaneous sites)

Treatment and Prognosis

- Surgery is the preferred therapeutic modality for VC of all sites:
 - In larynx extent of surgery depends on clinical stage:
 - T1: laser excision
 - T2: hemilaryngectomy
 - T3, T4: total laryngectomy
- Radiotherapy can be used in selected cases:
 - May be used in patients with advanced disease and/or in patients who are not good surgical candidates
 - Previous reason cited for not irradiating VC is purported induction of anaplastic transformation of VC after radiotherapy.
 - Reported VC treated by radiation that underwent anaplastic transformation more likely did not represent VC but represented hybrid carcinomas or pure conventional SCC misdiagnosed as VC.
- Prognosis is excellent after complete surgical removal.
- Local recurrence may occur if incompletely excised.
- Therapy and prognosis for VC with epithelial dysplasia or minimal invasion appears to be similar to (pure) VC than to hybrid carcinoma.
- Cervical adenopathy may be associated with VC, representing reactive changes and not metastatic disease:
 - Neck dissection generally not warranted in treatment
 - Hybrid carcinomas have potential to metastasize.
 - Hybrid carcinomas should be staged and managed as conventional squamous cell carcinomas.
- Distant metastases do not occur
- Death due to disease occurs in approximately 4% of cases:
 - Due to local uncontrollable disease

Spindle Cell (Squamous) Carcinoma (SCSC)

(Figs. 16-41 through 16-50)

Definition: Biphasic variant of squamous cell carcinoma composed of conventional squamous cell carcinoma (in situ or invasive carcinoma) associated with a malignant spindle-shaped and pleomorphic (epithelioid) component.

Synonyms: “Sarcomatoid” carcinoma, carcinosarcoma, pleomorphic carcinoma, metaplastic carcinoma, collision tumor, pseudosarcoma, Lane tumor

Clinical

- Considered uncommon
- Overwhelming majority occur in men (85%); most frequent in sixth through eighth decades of life
- Can occur anywhere in upper aerodigestive tract, but most common sites of occurrence include larynx and oral cavity:
 - Larynx:
 - True vocal cords > false vocal cords and supraglottis
 - Oral cavity:
 - Lips, tongue, gingiva, floor of mouth, buccal mucosa
 - Other sites include:
 - Oropharynx (tonsil, base of tongue), hypopharynx, sinonasal tract, nasopharynx
- Symptoms vary according to site:
 - Larynx: hoarseness, voice changes, airway obstruction, dysphagia
 - Oral cavity: mass or nonhealing sore with or without pain
 - Oropharynx, hypopharynx, sinonasal tract. and nasopharynx: airway obstruction, pain, epistaxis, discharge, facial deformity, unilateral otitis media, orbital symptoms
- Cause:
 - Associated with tobacco use (cigarette smoking)
 - May occur in areas of prior irradiation:
 - Radiation-induced carcinoma
 - Prior radiation used in treatment of other mucosal-based carcinomas
 - Not associated with transcriptionally active HPV:
 - Limited numbers of oropharyngeal cases shown to harbor transcriptionally active, high-risk HPV; HPV may be identified in both conventional and spindle cell components.
- Histogenesis of the spindle cells is controversial as evidenced by the array of names given to this tumor:
 - Epithelial derivation is supported by:
 - Intimate association with conventional squamous cell carcinoma

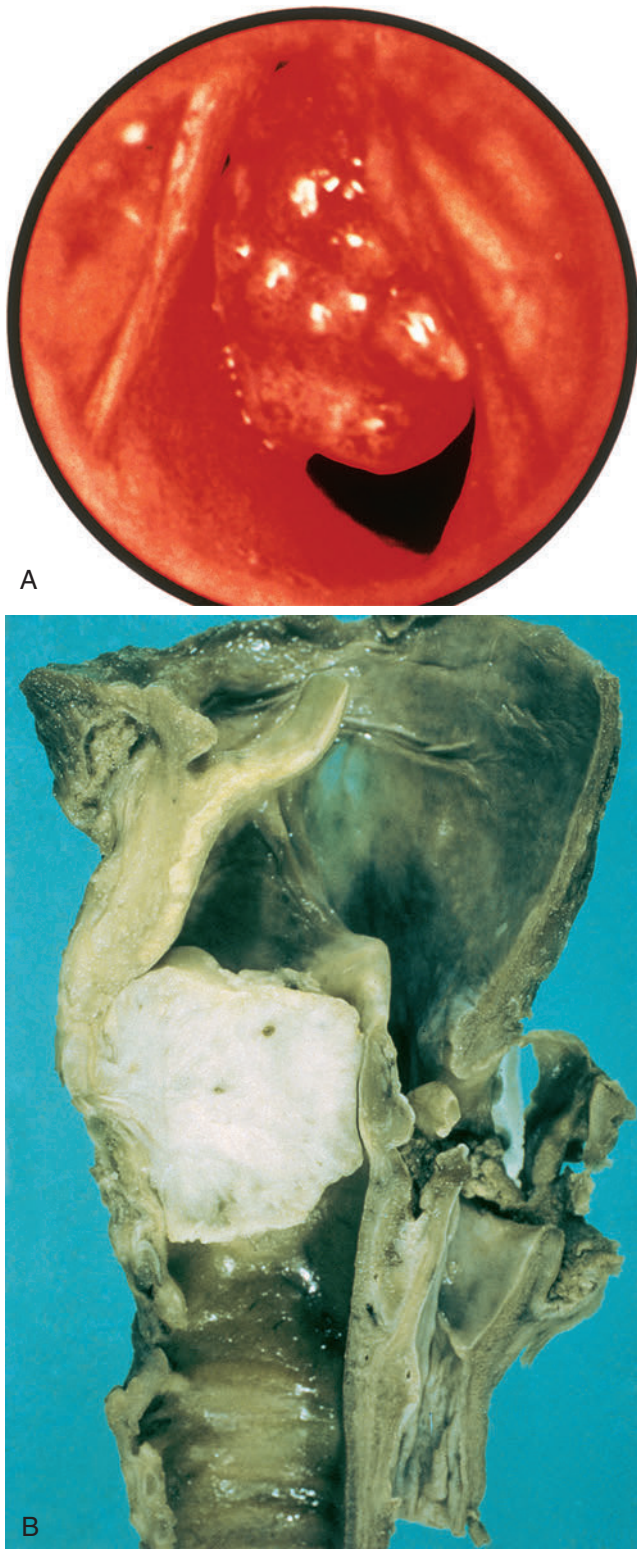


Fig. 16-41.

A, Laryngeal spindle cell squamous carcinoma endoscopically appearing as a polypoid mass protruding into and partially obstructing the laryngeal lumen.
B, Autopsy specimen of a large, solid laryngeal spindle cell carcinoma completing obstruction of the airway.

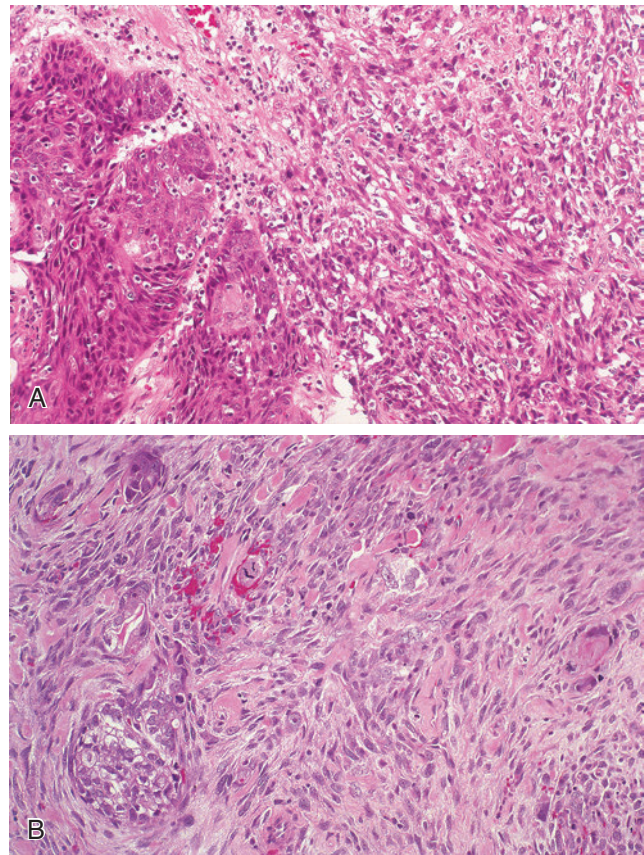


Fig. 16-42. Histology of SCSC.

A, B, The diagnostic histologic features of spindle cell squamous carcinoma include the presence of differentiated squamous cell carcinoma in the form of intraepithelial dysplasia/carcinoma in situ and/or invasive squamous cell carcinoma and associated undifferentiated malignant spindle-shaped and pleomorphic cell proliferation. Note the intimate association of the differentiated squamous cell carcinoma and the malignant spindle cell component.

- Presence of cytokeratin immunoreactivity in the majority of cases and absence of immunoreactivity with other antibodies
- Ultrastructural evidence of epithelial differentiation
- Tendency to metastasize to lymph nodes rather than viscera by hematogenous routes supports carcinomatous nature
- Epithelial tropism of HPV infection confirms the epithelial nature of the spindle cell component.

Pathology

Gross

- Polypoid or fungating mass commonly found in the larynx, hypopharynx, oral cavity, and sinonasal tract
- Variations in the gross appearance may correlate with the primary site of occurrence:

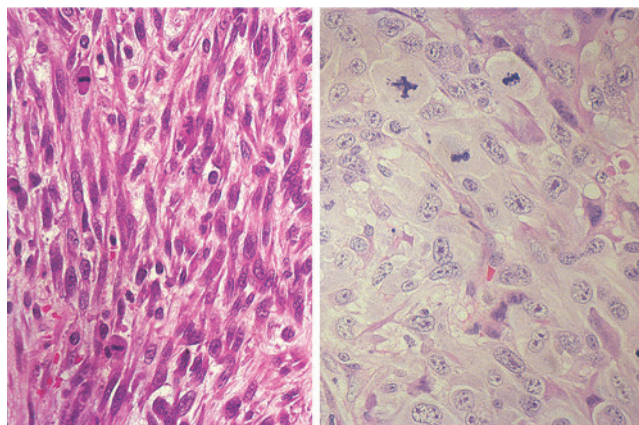


Fig. 16-43. Histology of SCSC.

In spindle cell squamous carcinoma the undifferentiated malignant cell component may include (*left*) spindle-shaped cells and/or (*right*) pleomorphic (epithelioid) cells. Mitotic figures including atypical mitoses can be identified.

- Larynx: polypoid or exophytic
- Other sites: fungating and/or ulcerative
- Firm, tan-white, gray, or pink mass varying in size from 1 to 6 cm

Histology

- Histologic features that define SCSC include the identification of a malignant undifferentiated spindle cell and pleomorphic cellular proliferation and the presence of a conventional squamous cell component.

Differentiated Squamous Cell Component

- Includes either intraepithelial dysplasia and/or frankly invasive squamous carcinoma (typically keratinizing and of varying differentiation)
- Squamous cell component may be limited, requiring multiple sectioning for identification or it may be absent in a given lesion:
 - Surface ulceration with associated fibrinoid necrosis, granulation tissue, and mixed acute and chronic inflammation may be present.
 - Reactive (nonneoplastic) myofibroblastic cell component as part of the inflammatory cell response may be present.

Spindle Cell Component

- Spindle-shaped and/or pleomorphic (epithelioid) cellular components generally represent dominant cell type.
- Growth pattern varies including fascicular, storiform, or palisading and may include an associated collagenized to myxoid-appearing stroma.
- Generally is hypercellular and pleomorphic with large, hyperchromatic nuclei, prominent nucleoli,

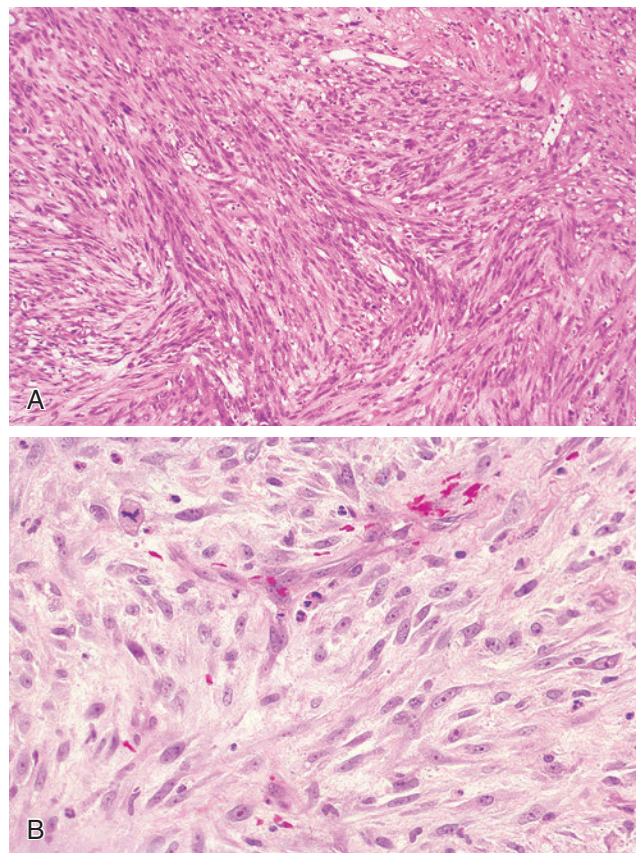


Fig. 16-44. Histology of SCSC.

Some examples of spindle cell squamous carcinoma lack a differentiated epithelial component and are entirely composed of an undifferentiated spindle-shaped cellular proliferation with a storiform and/or fascicular growth. These histologic findings coupled with absence of immunoreactivity for epithelial markers and possible presence of immunoreactivity for mesenchymal markers may suggest a diagnosis of a sarcoma. In spite of these findings, the presence of a polypoid (superficial) mucosal-based mass is a feature of carcinomas, including spindle cell squamous carcinoma and not typically one associated with a mucosal-related sarcoma.

many mitoses, including typical and atypical forms:

- Multinucleated giant cells may be present.
- Necrosis is not uncommon.
- Hypocellular collagenized variant:
 - Spindle cell proliferation may be sparsely cellular (hypocellular) with marked stromal collagenization.
 - Even in presence of limited cellularity there is still nuclear pleomorphism and mitotic figures, including atypical mitoses.
- Heterologous elements can be seen including bone and cartilage and may include:
 - Benign bone (osteoid) and/or cartilage

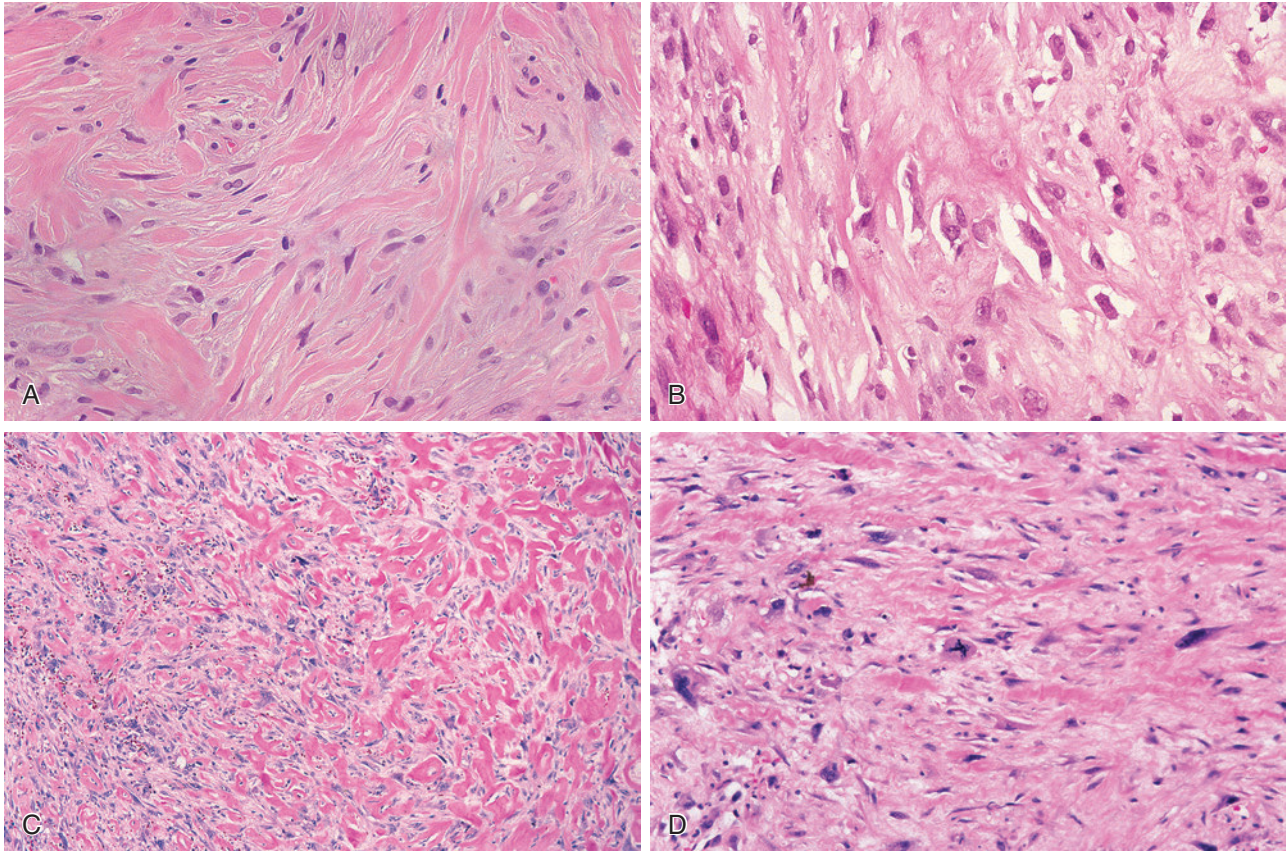


Fig. 16-45. Collagenized or hypocellular SCSC.

Collagenized and hypocellular variant of spindle cell squamous carcinoma shows a prominent collagenized stroma with varying but less cellularity as compared with more usual type of spindle cell squamous carcinoma. Despite the relative hypocellularity, the cells are markedly pleomorphic and atypical mitotic figures are identified.

- May include malignant bone (osteosarcomatous) and/or malignant cartilage (chondrosarcomatous) foci
- Rhabdomyosarcomatous elements may rarely be present:
 - Rhabdomyoblasts identified
 - Myogenic markers including desmin, myogenin, and myoglobin are positive.
- Histochemical stains:
 - Essentially noncontributory to the diagnosis
- Immunohistochemistry:
 - Spindle cells are cytokeratin immunoreactive in the majority of cases but may be absent in up to 40% of cases.
 - Broad spectrum of cytokeratin staining should be used, including:
 - Pancytokeratin (AE1/AE3), CAM5.2, CK5/6, OSCAR, CK18, CK903
 - May vary from focal to diffuse
 - Absence of cytokeratin staining does not preclude a diagnosis of spindle cell squamous carcinoma.
 - p63 (nuclear) immunoreactivity often mirrors cytokeratin reactivity but may be positive in cases lacking cytokeratin staining:
 - Transcription factor consistently expressed in normal squamous epithelium and in squamous cell carcinoma
 - Recognizes DNp63 and TAp63 isoforms of the p63 molecule
 - May be positive in soft tissue tumors and reactive stromal proliferations
 - p40 (nuclear) immunoreactivity may be present:
 - Recognizes only squamous-specific isoform DNp63
 - Less consistently positive than p63
 - Less likely to be positive in soft tissue tumors and reactive stromal proliferations

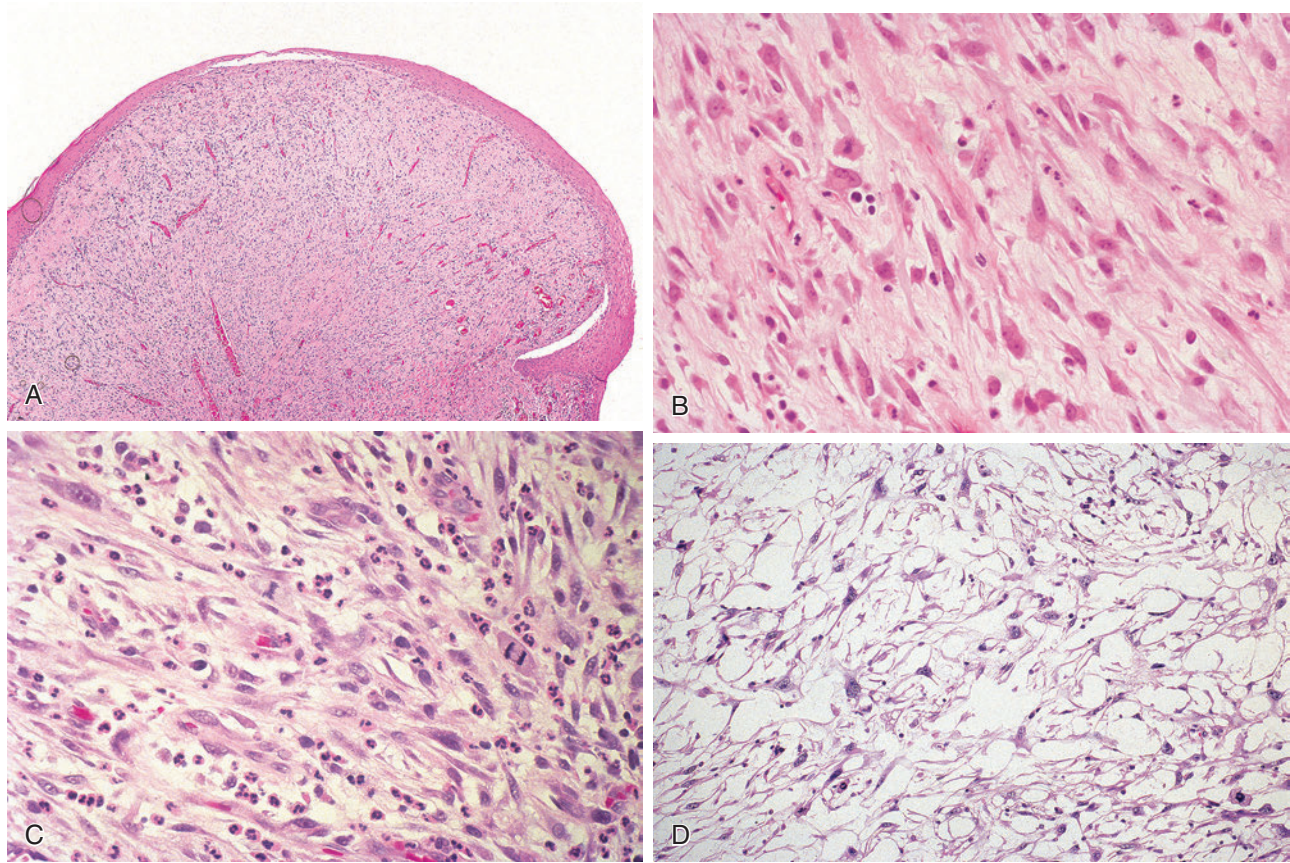


Fig. 16-46. SCSC with features suggesting inflammatory myofibroblastic tumor (IMT).

SCSCs may coexist with a reactive myofibroblastic proliferation or may have features suggesting a myofibroblastic dominant lesion (e.g., IMT), including **(A)** polypoid mass with a granulation tissue-like appearance; **(B through D)** cells with basophilic to eosinophilic fibrillar-appearing cytoplasm, some with axonal extensions, with or without an associated inflammatory cell infiltrate. Although myofibroblastic dominant lesions may have increased mitotic activity, the presence of atypical mitoses (not shown) would be a feature associated with malignancy.

- Vimentin reactivity consistently identified in all cases:
 - Diffuse and strongly reactive
- Various myogenic markers, including desmin and actins, may be present:
 - Coexpression of mesenchymal markers and epithelial markers (i.e., cytokeratin) may occur.
 - Expression of myogenic markers could correlate to presence of myofibroblastic cells as a reactive proliferation as part of wound healing secondary to ulceration.
 - In the absence of rhabdomyoblastic differentiation, other myogenic markers including myogenin and myoglobin typically are not present.
- S100 protein and melanoma-related markers (HMB-45, melan-A, tyrosinase, MITF1, Sox10) are negative.
- p16 positivity may be present in a minority of cases:
 - Positive cases tend to be located in oropharynx.
 - Rare in nonoropharyngeal locations
- Electron microscopy:
 - Majority of cases show evidence of epithelial derivation, including desmosomes, tonofilaments, macula adherens.
 - Considered less sensitive in comparison to immunohistochemistry in identifying epithelial differentiation
- Cytogenetics and molecular genetics:
 - Identical (immunohistochemical) p53 expression patterns in the epithelial and spindle cell components support concept that these phenotypically divergent cell populations share similar developmental pathways and divest concept that SCSC represents a reactive process or a collision tumor between epithelial and mesenchymal components

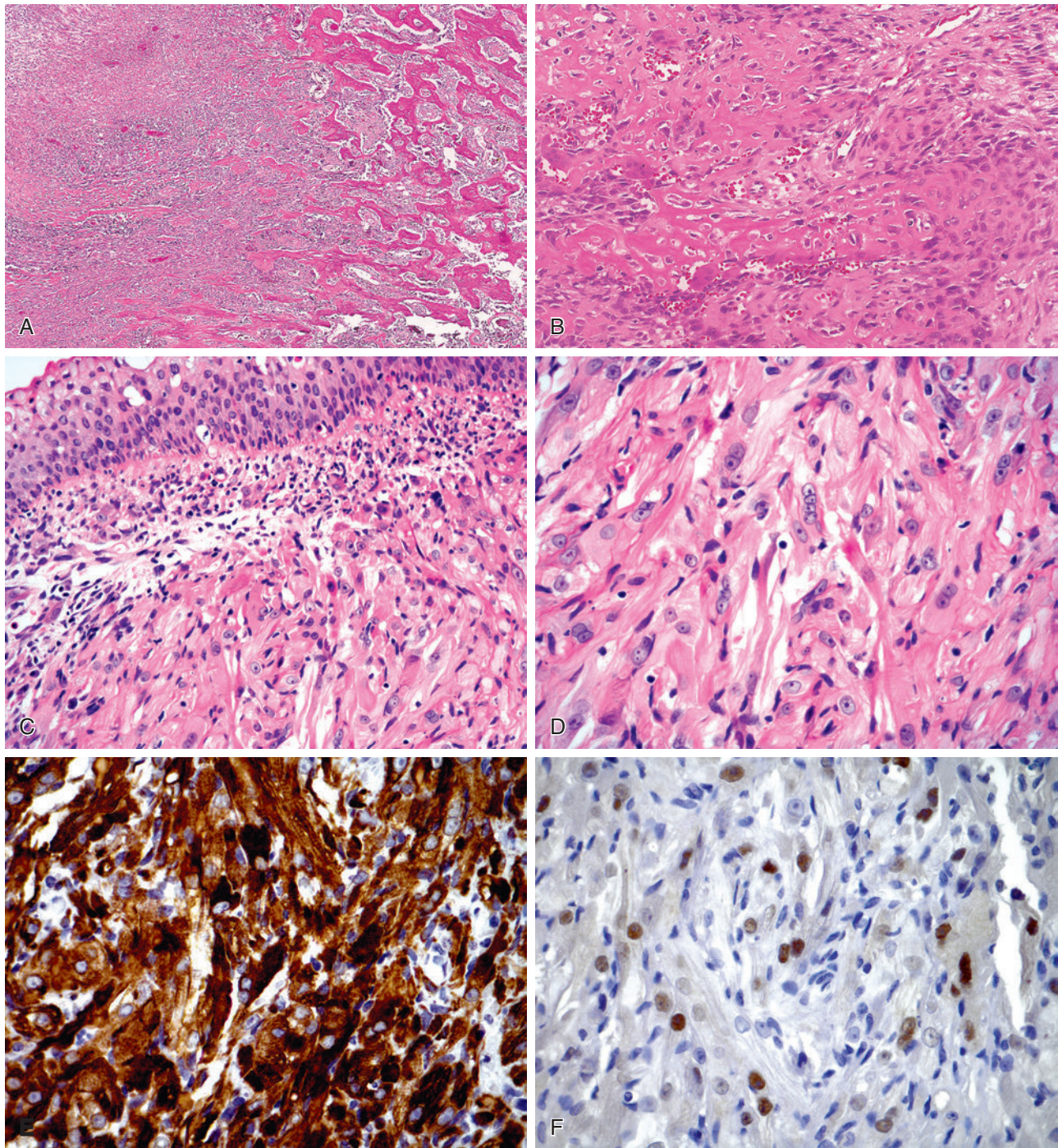


Fig. 16-47. Heterologous elements in SCSC.

Heterologous elements that may be found in spindle cell squamous carcinoma include **(A)** osteoid and **(B)** osteosarcomatous foci. Additional heterologous components that can be found in spindle cell squamous carcinoma include chondroid and chondrosarcomatous foci (not shown). **C** and **D**, Rhabdomyosarcomatous differentiation can on rare occasions be seen in association with SCSC manifested in the form of spindle-shaped strap cells lying just below the surface squamous epithelium confirmed by **(E)** desmin and **(F)** myogenin (nuclear) immunoreactivity.

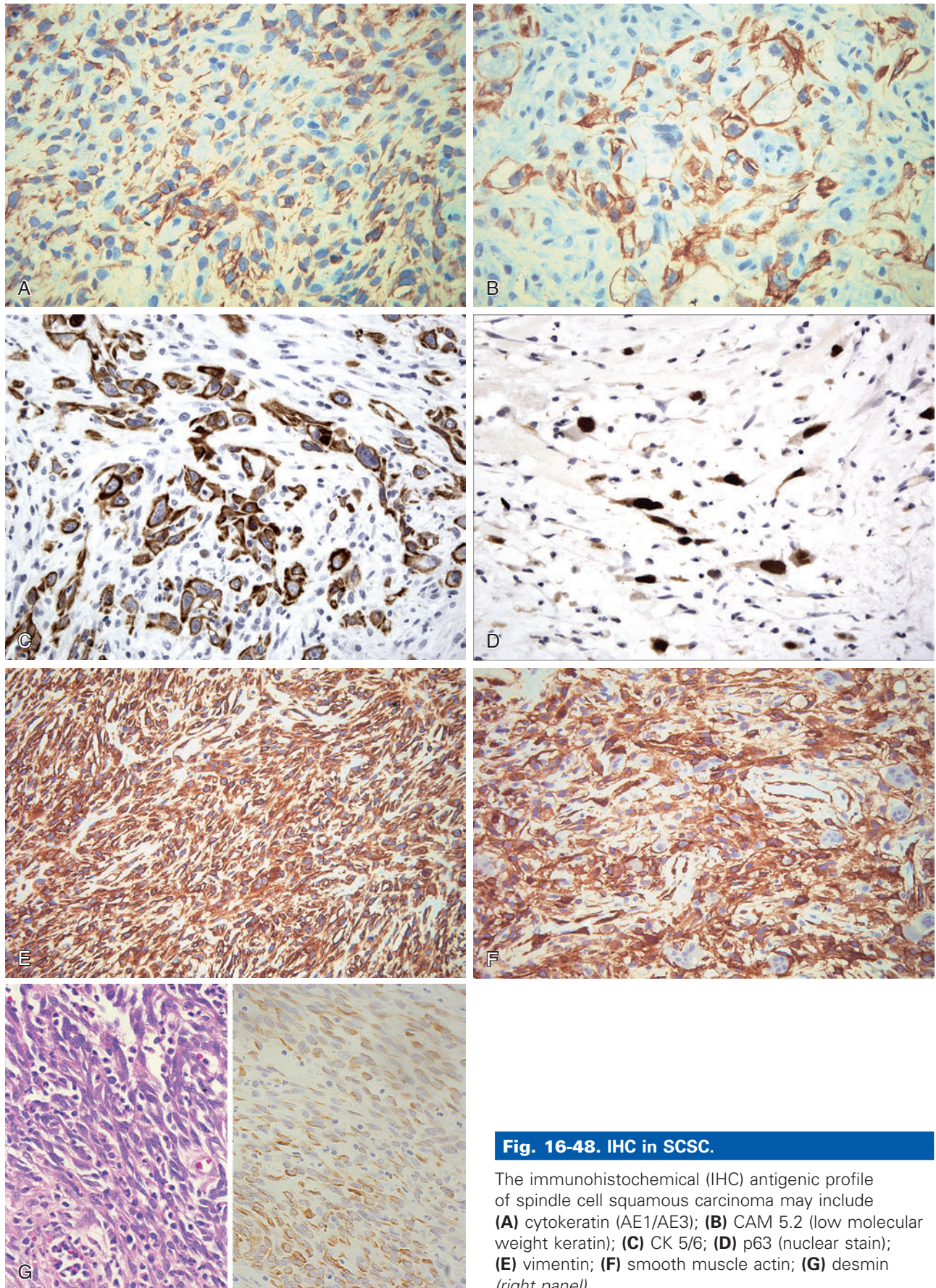


Fig. 16-48. IHC in SCSC.

The immunohistochemical (IHC) antigenic profile of spindle cell squamous carcinoma may include **(A)** cytokeratin (AE1/AE3); **(B)** CAM 5.2 (low molecular weight keratin); **(C)** CK 5/6; **(D)** p63 (nuclear stain); **(E)** vimentin; **(F)** smooth muscle actin; **(G)** desmin (right panel).

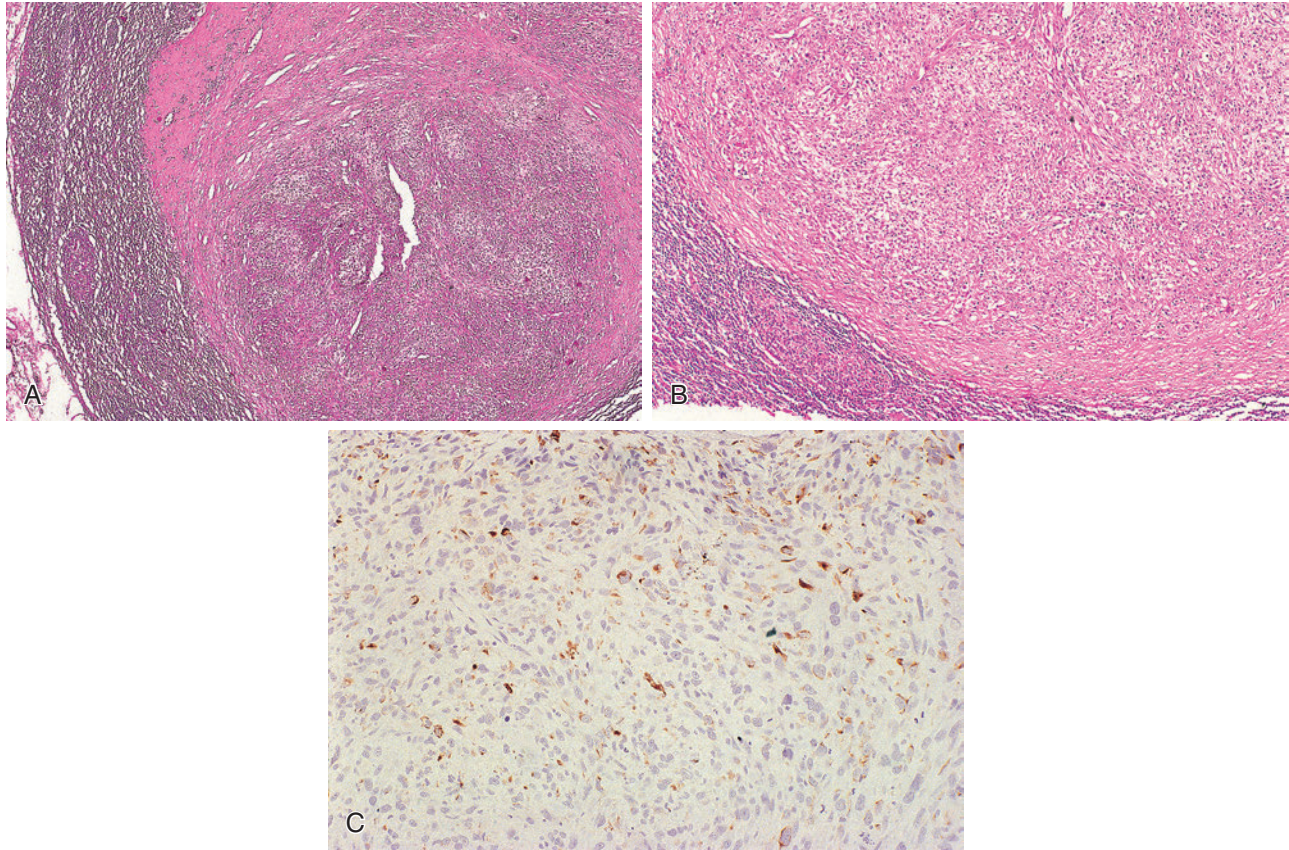


Fig. 16-49. Metastatic SCSC.

Nodal metastasis in spindle cell squamous carcinoma may include the differentiated epithelial component only, the spindle cell component only, or both. (**A** and **B**) This cervical neck nodal metastasis that occurred in a patient with a laryngeal spindle cell squamous carcinoma was entirely composed of a malignant spindle cell component. **C**, The neoplastic cells were focally cytokeratin (AE1/AE3) positive.

- Varying findings reported on the presence of high-risk HPV in SCSC:
 - Majority of SCSC of head and neck, including those arising in the oropharynx, are not related to transcriptionally active HPV
 - A few p16-positive oropharyngeal SCSCs shown to harbor HPV16 by DNA in situ hybridization but HPV not detected in p16-positive nonoropharyngeal lesions:
 - In HPV-positive tumors, HPV identified in both conventional and spindle cell components
- Significant downregulation of miR-200 family and miR-205, loss of desmosomal cadherins, and altered expression of classic cadherins in SCSC reported in comparison with conventional squamous cell carcinoma:
 - Downregulation of miR-200 family and miR-205 strongly supports the postulated role of epithelial-mesenchymal transition in spindle cell squamous carcinoma.
- Altered expression of cadherin-catenin complex associated with morphologic transition from epithelial to spindle cell phenotype:
 - Reminiscent of epithelial-mesenchymal transition (EMT)
 - Supports role of EMT in pathogenesis of SCSC, which is further supported by presence of Snail-1 expression, a potent inducer of EMT, in cases of SCSC
- Studies on mouse model developed in SCSC showed:
 - Marked downregulation of epithelial differentiation markers and cell adhesion genes
 - Inhibition in expression of growth factors and receptors important for epithelial proliferation with increase in expression of growth factors and receptors that regulate fibroblast and mesenchymal cell proliferation
 - Largest class of upregulated genes in SCSC was chemokine receptors and ligands involved in tumor cell invasion and metastasis.

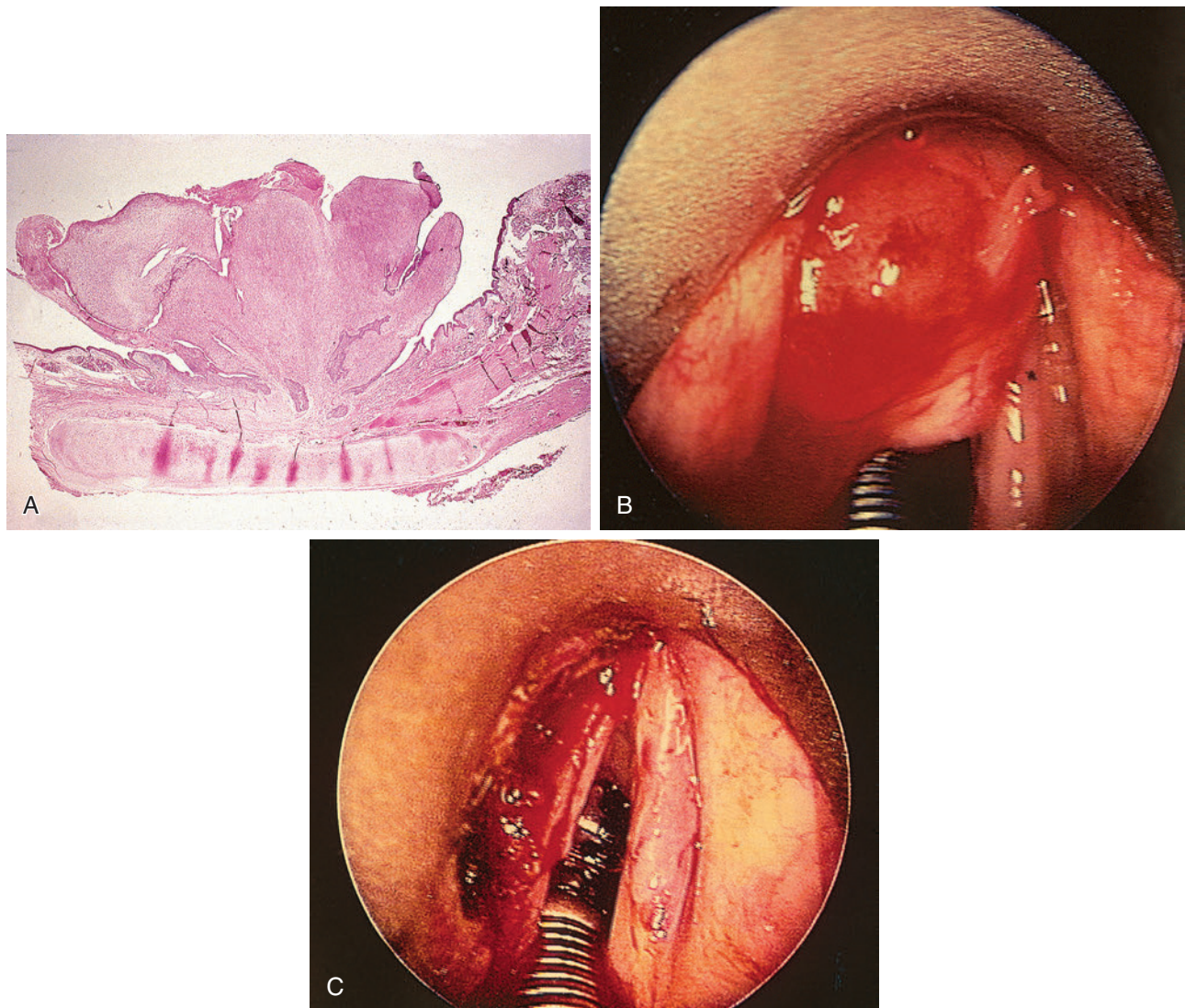


Fig. 16-50. Laser resection of polypoid SCSC.

A, Polypoid spindle cell squamous carcinoma; such a tumor with polypoid growth and limited invasive component could potentially be treated by conservative surgery to include polypectomy with tumor free margins. **B**, Example of a patient with a vocal cord polypoid spindle cell squamous carcinoma treated by laser excision (polypectomy); intraoperative consultation (frozen section) identified the absence of carcinoma at the deep surgical margins (not shown). **C**, Postlaser removal. On long-term follow-up (>5 years), this patient has been free of tumor (recurrence or progression).

- Above changes in gene expression show loss of epithelial characteristics, acquisition of mesenchymal phenotypes, and increased propensity for invasion and metastasis by SCSC.

Differential Diagnosis

See [Table 16-3](#).

- Reactive lesions (e.g., contact ulcers), reactive myofibroblastic lesions (e.g., nodular fasciitis), and inflammatory myofibroblastic tumor (IMT):

- These lesions are moderately cellular with a proliferation of spindle-shaped cells but do not display a striking degree of nuclear pleomorphism.
- Mitotic figures may be encountered but atypical mitoses are not seen; the findings of atypical mitoses should prompt consideration of a true malignancy.
- Although these lesions are not encapsulated, they do not exhibit the insidious pattern of infiltration of adjacent tissues, which is characteristic of more aggressive lesions, such as SCSC.

- May fill the submucosal region, abutting the basement membrane on which the mucosal epithelial cells are resting; however, the spindle cell proliferation does not infiltrate into the mucosal epithelial cells; nevertheless, the overlying mucosa may appear atrophic in areas.
- Typically are cytokeratin, p63, and p40 negative:
 - Cytokeratin or p63 reported in IMT and granulation tissue
- Myofibroblastic cells may be muscle-specific actin (HHF35), smooth muscle actin, and vimentin positive.
- Cells of IMT may be ALK1 positive, a feature not identified in SCSC.
- Postradiation changes:
 - Radiation (myo)fibroblasts may raise concern for presence of malignant spindle cells.
 - Radiation (myofibroblasts) may be cytokeratin and p63 positive.
 - Tend to occur in association with other radiation-associated histologic changes
- Subglottic stenosis
- Sarcomas:
 - Sarcomas of the mucosal surfaces of the head and neck in general and the larynx in specific (except for chondrosarcoma), including undifferentiated pleomorphic sarcoma, fibrosarcoma, malignant peripheral nerve sheath neoplasm, synovial sarcoma, and others, are rare.
 - In general, mucosal-based sarcomas of the upper aerodigestive tract are deeply seated in any given location and do not usually result in a polypoid mass protruding from a mucosal surface.
 - As a rule, in the absence of any other confirmatory studies, a malignant spindle cell neoplasm of a mucosal surface of the upper aerodigestive tract presenting as a polypoid lesion or identified in more superficial locations of the submucosa should be considered as an SCSC; the latter is true even in the absence of a squamous carcinomatous component, the presence of heterologous matrix-producing elements, absence of cytokeratin immunoreactivity and presence of mesenchymal type markers.
- Mucosal malignant melanoma
- Radiotherapy may be used as an adjunct to surgery but neither radiotherapy nor chemotherapy has merit as sole therapeutic modality:
 - Reports of patients with early-stage SCSC of the glottis (i.e., T1 and T2 lesions) treated with radiation in a similar manner as early-stage conventional squamous cell carcinoma:
 - Histologic diagnosis of SCSC by itself should not influence the decision to treat a patient with early-stage glottic disease with irradiation.
 - Results show that patients with early-stage glottic SCSC treated by radiation alone had similar control rates to irradiated patients with similar volume disease with the more typical squamous cell carcinoma
- Overall 5-year survival of patients with laryngeal SCSC reported to be 59%
- Prognosis dependent on the clinical stage but, in general, is considered poor:
 - Depth of invasion important prognostic parameter:
 - Minimally invasive tumors better prognosis than tumors with any significant degree of invasion
 - Polypoid lesions with limited presence of limited invasion behave less aggressively than flat, ulcerative, and more deeply invasive tumors:
 - 90% overall 3-year survival reported for patients with glottic polypoid SCSC
 - 44% overall 3-year survival reported for patients with sessile glottic SCSC
 - Polypoid configuration alone does not confer better prognosis but depends on extent of invasion within the polypoid lesion.
 - Size of tumor does not correlate with survival.
- Prognosis also linked to location of lesion:
 - Vocal cord lesions, in particular glottic SCSC, tend to manifest symptoms early in the disease course and have better prognosis than SCSC arising in other sites (supraglottis, hypo-, oro-, and nasopharynx, oral cavity, and sinonasal tract) in which symptoms tend to occur only after the tumor has become large and extensively infiltrative.
- Although number of HPV-positive cases are too small for any definitive conclusions, positive viral status does not appear to confer any prognostic benefit.
- Metastatic disease primarily occurs to cervical lymph nodes and lung and may include:
 - Conventional squamous cell carcinoma alone
 - Spindle cell carcinoma alone
 - Both conventional and spindle cell squamous carcinoma

Treatment and Prognosis

- Surgery is the preferred mode of therapy:
 - Often necessitates radical extirpation
 - Conservative (limited) surgery such as polypectomy can be performed in limited settings such as the occurrence in an at-risk or poor surgical candidate who has a polypoid lesion and tumor-free margins can be achieved.

Basaloid Squamous Cell Carcinoma (BSCC) (Figs. 16-51 through 16-56)

Definition: High-grade variant of squamous cell carcinoma histologically characterized by an invasive neoplasm predominantly composed of basaloid-appearing cells intimately associated with dysplastic squamous epithelium, in situ squamous cell carcinoma, and/or invasive squamous cell carcinoma.

Synonyms: Basaloid carcinoma; adenoid-cystic-like carcinoma

Clinical

- Occurs more commonly in men than in women; predominantly occurs in the sixth to seventh decades of life
- May occur in any mucosal site of upper aerodigestive tract but tends to predilect to:
 - Hypopharynx (piriform sinus)
 - Larynx (supraglottis)
 - Oropharynx (palatine tonsil, base of tongue)
- Symptoms depend on the site of occurrence and relative to laryngeal tumors include:
 - Hoarseness, dysphagia, pain, or a neck mass
- Cause:
 - Strong association with tobacco and alcohol use:
 - Generally linked to hypopharyngeal and laryngeal lesions
 - Association with human papillomavirus (HPV):
 - Linked with oropharyngeal lesions
 - Referred to as HPV-associated basaloid squamous cell carcinoma of the oropharynx—see Section 3
 - Many but not all of oropharyngeal BSCCs associated with HPV 16

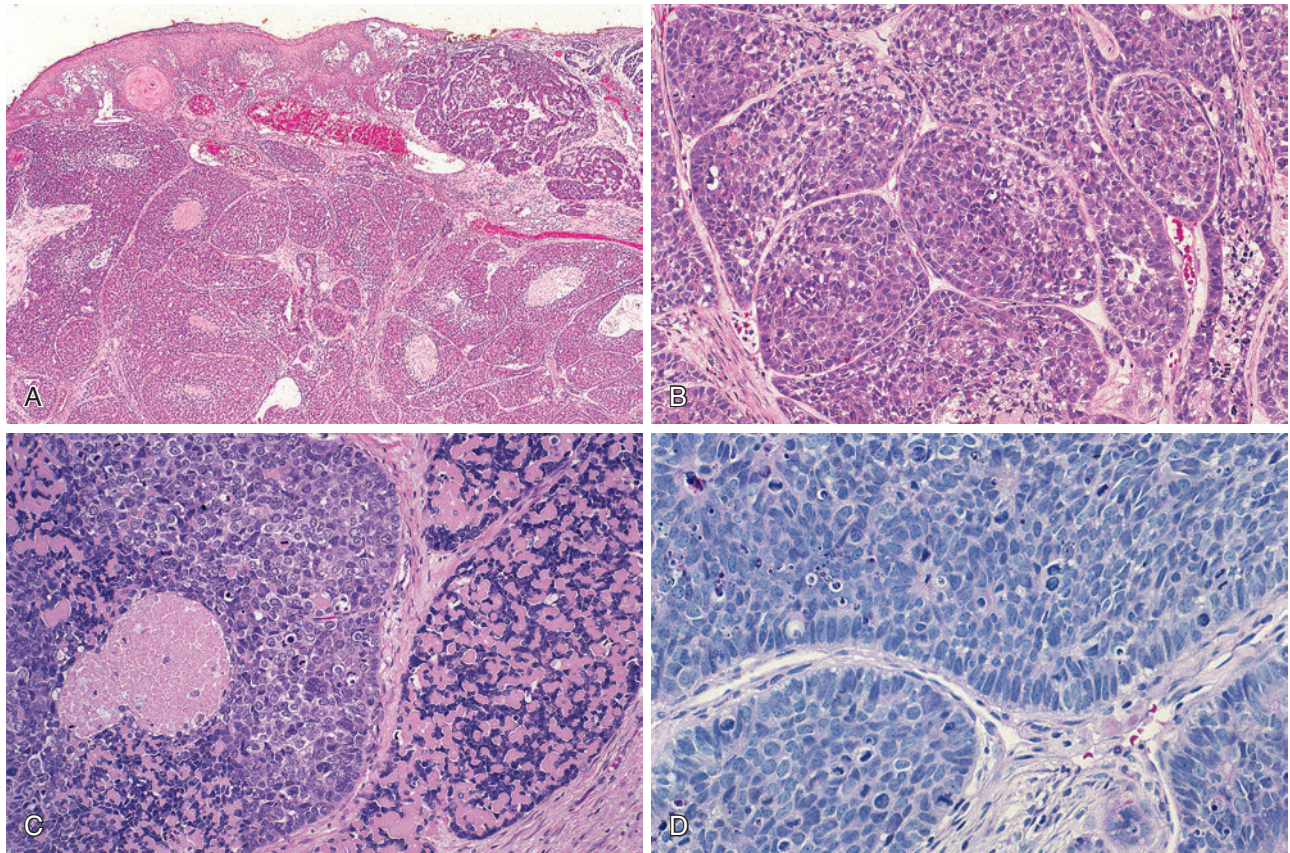


Fig. 16-51. Basaloid squamous cell carcinoma.

Histologic features of basaloid squamous cell carcinoma include **(A)** infiltrating cellular neoplasm with varied growth patterns including lobular, trabecular, and solid; comedonecrosis can be seen in the center of neoplastic lobules; **(B)** “jigsaw” puzzle-like configuration of the neoplastic lobules; **(C)** higher magnification showing juxtaposition of a lobule with comedotype necrosis (left) and adjacent area in which reduplicated basement membrane-like material (right) reminiscent of salivary gland tumors is present; **(D)** a predominant basaloid cell proliferation characterized by nuclear hyperchromasia, marked nuclear pleomorphism, increased mitotic activity, and individual cell necrosis; peripheral nuclear palisading is present, usually focally, but without retraction artifact of adjacent stroma as occurs in cutaneous basal cell carcinomas.

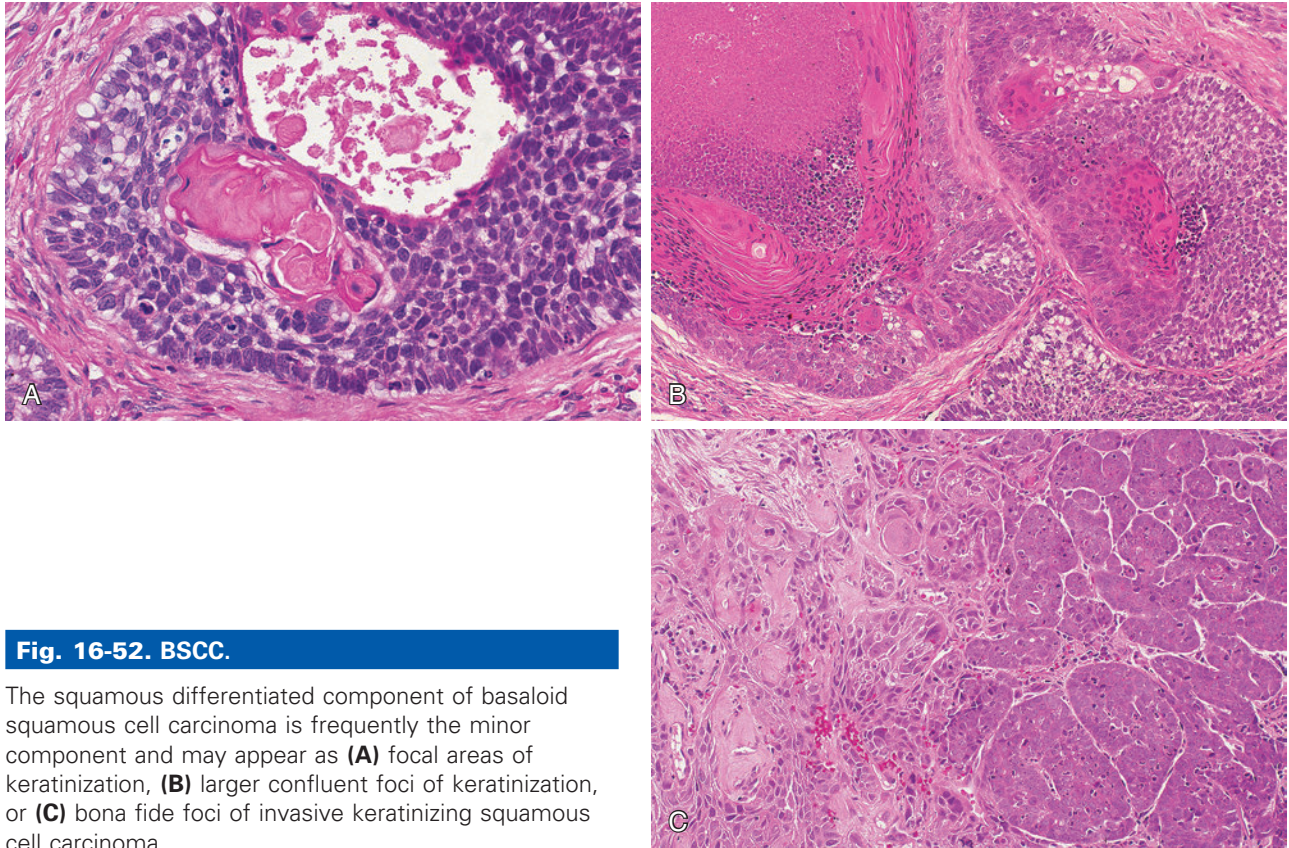


Fig. 16-52. BSCC.

The squamous differentiated component of basaloid squamous cell carcinoma is frequently the minor component and may appear as **(A)** focal areas of keratinization, **(B)** larger confluent foci of keratinization, or **(C)** bona fide foci of invasive keratinizing squamous cell carcinoma.

- HPV-associated basaloid squamous cell carcinoma of the oropharynx:
 - Predilect to base of tongue > tonsil
 - More common in men than women
 - p16 positive and presence of transcriptionally active HPV
 - Confers a better prognosis than non-HPV-associated BSCC
- Increasing evidence identifying the presence of HPV in association with BSCC of the head and neck (see later under Genetics and Cytogenetics)
- Cell of origin has not definitively been identified but in all probability is a single totipotent cell capable of divergent differentiation and located either in the basal cell layer of the surface epithelium or within seromucous glands.

Pathology

Gross

- Firm to hard, tan-white mass often with associated central necrosis measuring up to 6.0 cm in greatest dimension
- Infrequently, may be exophytic in appearance.

Histology

- Invasive neoplasm composed of basaloid cells with an associated squamous component demonstrating

variety of growth patterns, including solid, lobular, cribriform, cords, trabeculae, and gland-like or cystic growth.

Basaloid Cell Component

- Predominant cell type consists of cells with pleomorphic, hyperchromatic nuclei, scanty cytoplasm, and increased mitotic activity:
 - Peripheral nuclear palisading may be present.
- Comedonecrosis may be seen in the center of neoplastic lobules.
- Direct continuity with surface epithelium may be present:
 - Surface epithelium in direct continuity with invasive basaloid component may or may not show intraepithelial dysplasia.
- Interstitial deposition of a hyalin or mucohyalin material can be seen:
 - Similar appearance to reduplicated basement membrane material seen in some salivary gland tumors
 - May impart cribriform-type growth pattern
- Gland-like spaces may be present:
 - May contain mucinous or hyalinized material
- Cells with clear-appearing cytoplasm may be seen either focally or more extensively.

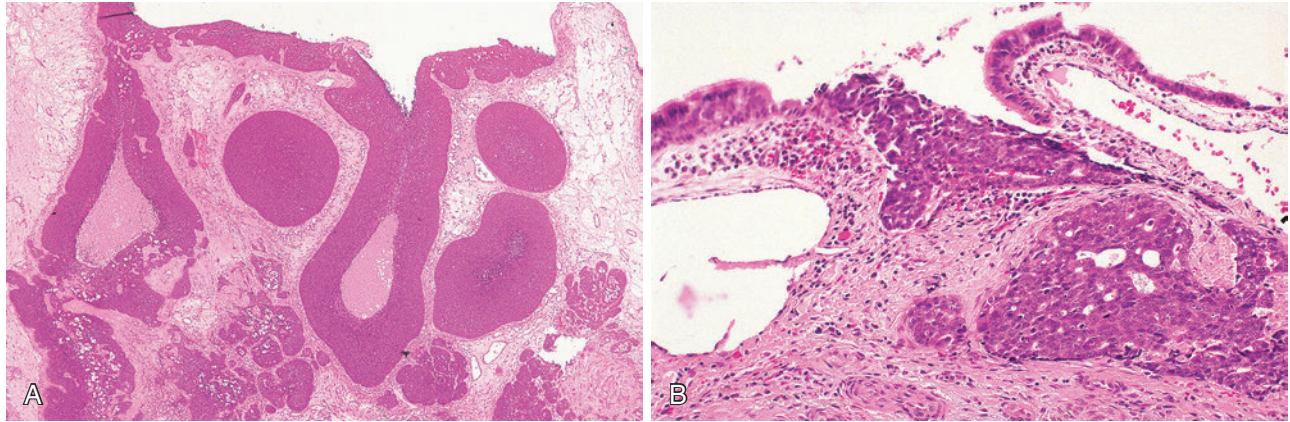


Fig. 16-53. BSCC with high-grade intraepithelial dysplasia/CIS.

A, B, High-grade intraepithelial dysplasia/CIS is a frequent feature seen in association with basaloid squamous cell carcinoma.

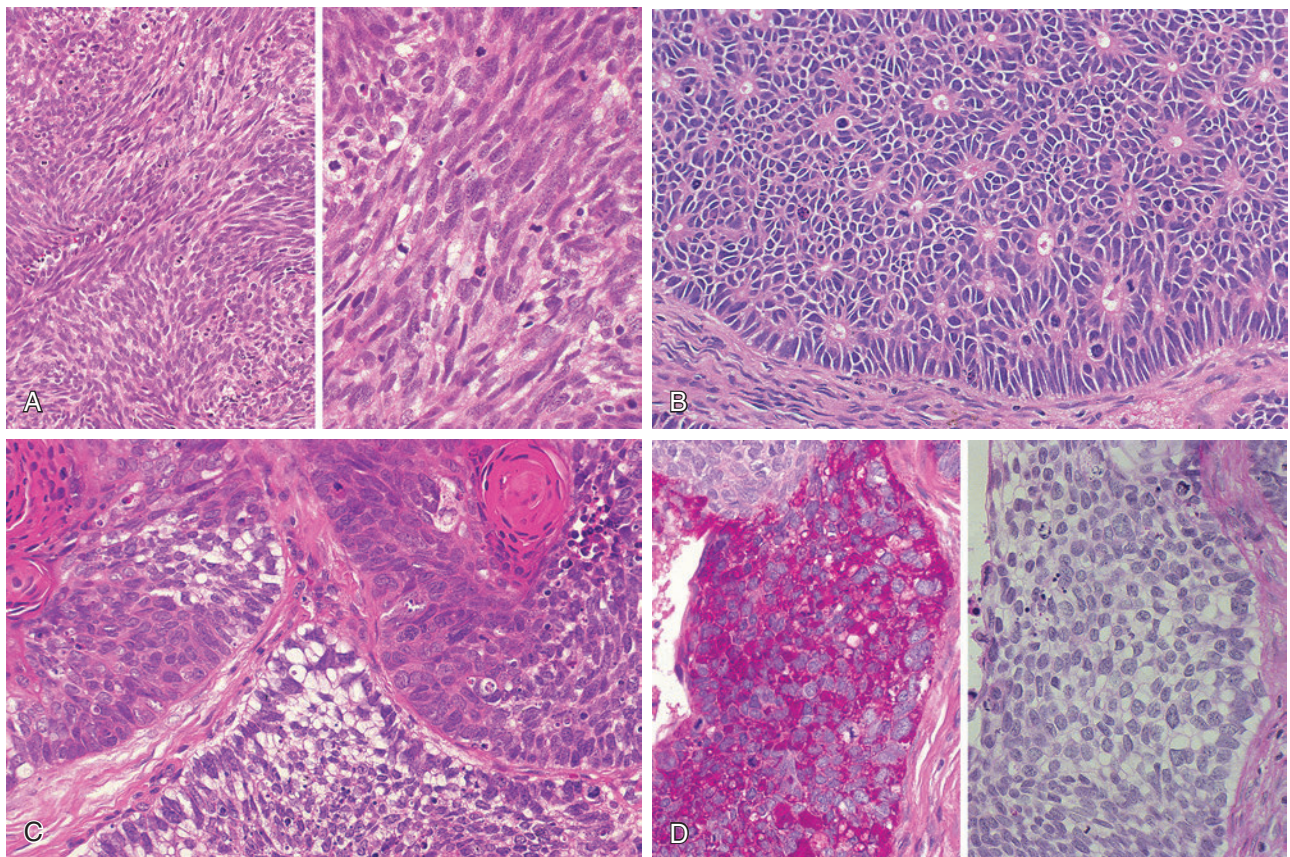


Fig. 16-54. Other findings in BSCC.

Morphologic variations that can be seen in association with basaloid squamous cell carcinoma include **(A)** spindle-shaped cells with storiform growth; **(B)** rosettes; **(C)** clear cells; **(D)** clear cells contain glycogen as evidenced by the presence of *(left)* periodic acid Schiff–positive intracytoplasmic material that is cleared by *(right)* diastase digestion.

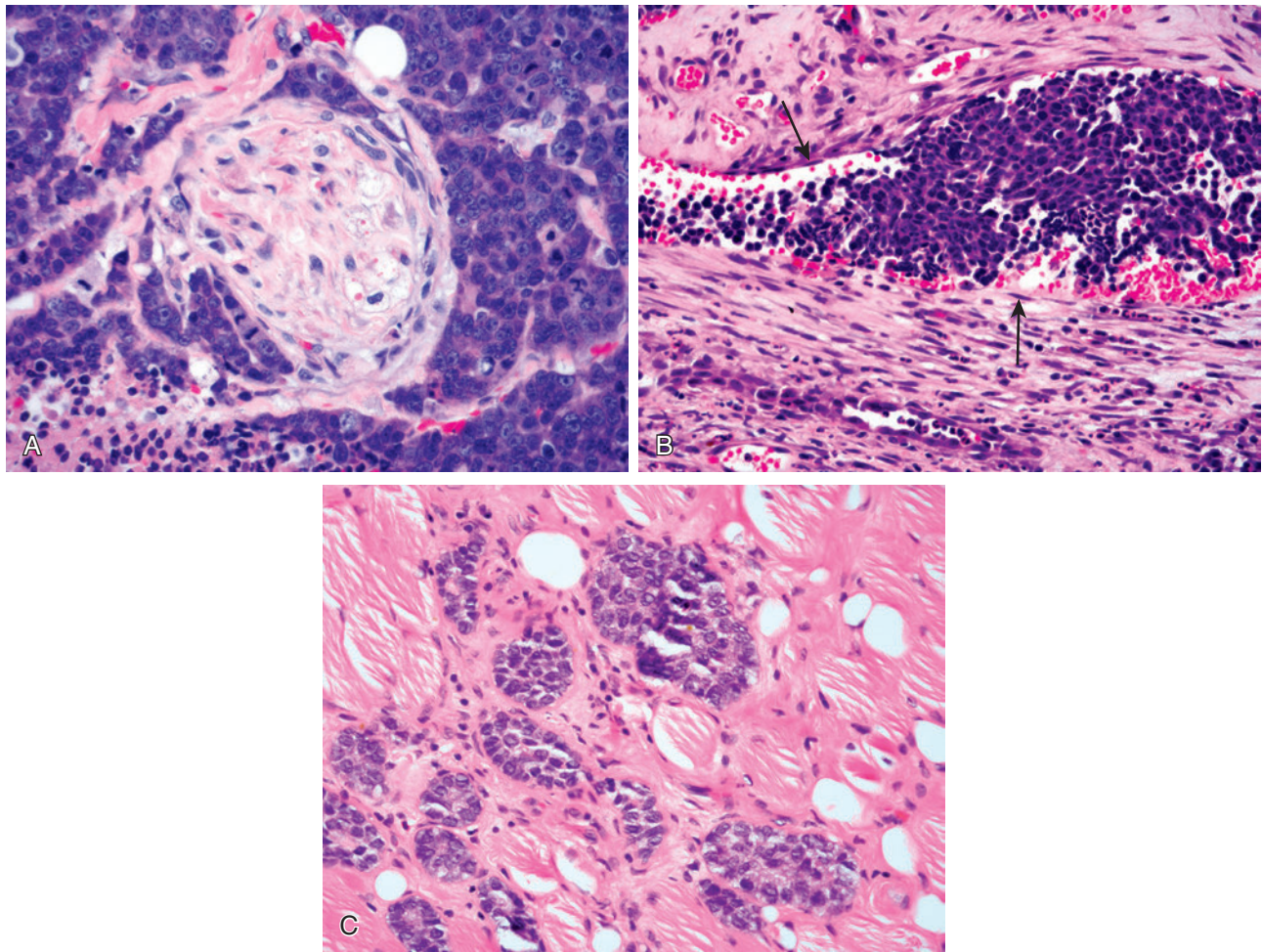


Fig. 16-55. Infiltrative growth in BSCC.

Basaloid squamous cell carcinomas often are extensively infiltrative, including the presence of **(A)** neurotropism and **(B)** endothelial-lined (arrows) lymph-vascular space invasion and **(C)** deep invasion into skeletal muscle.

- Additional findings may include:
 - Spindle cell component may be identified:
 - Usually very limited in extent and does not predominate
 - Rare examples in which the spindle cell component may predominate
 - Features diagnostic for BSCC still present
 - Infrequently, true neural-type rosettes may be present.
 - Extracellular calcifications may be present.

Squamous Cell Component

- Typically, represents minor component and may be focally present:
 - In biopsies squamous cell component may be absent.
- Squamous cell component may variably include:
 - Dysplastic squamous epithelium and/or carcinoma in situ (CIS)
 - Invasive differentiated squamous cell carcinoma characterized by presence of intercellular bridges, keratin pearl formation, and/or individual cell keratinization (cells with abundant eosinophilic cytoplasm)
 - Foci of abrupt keratinization
- Histologic features (growth patterns and cell types) are same whether associated with or not associated with HPV:
 - Presence or absence of HPV represents key feature in distinguishing these tumor types.
- Histochemistry:
 - Diastase-sensitive, periodic acid Schiff–positive intracytoplasmic material indicative of glycogen

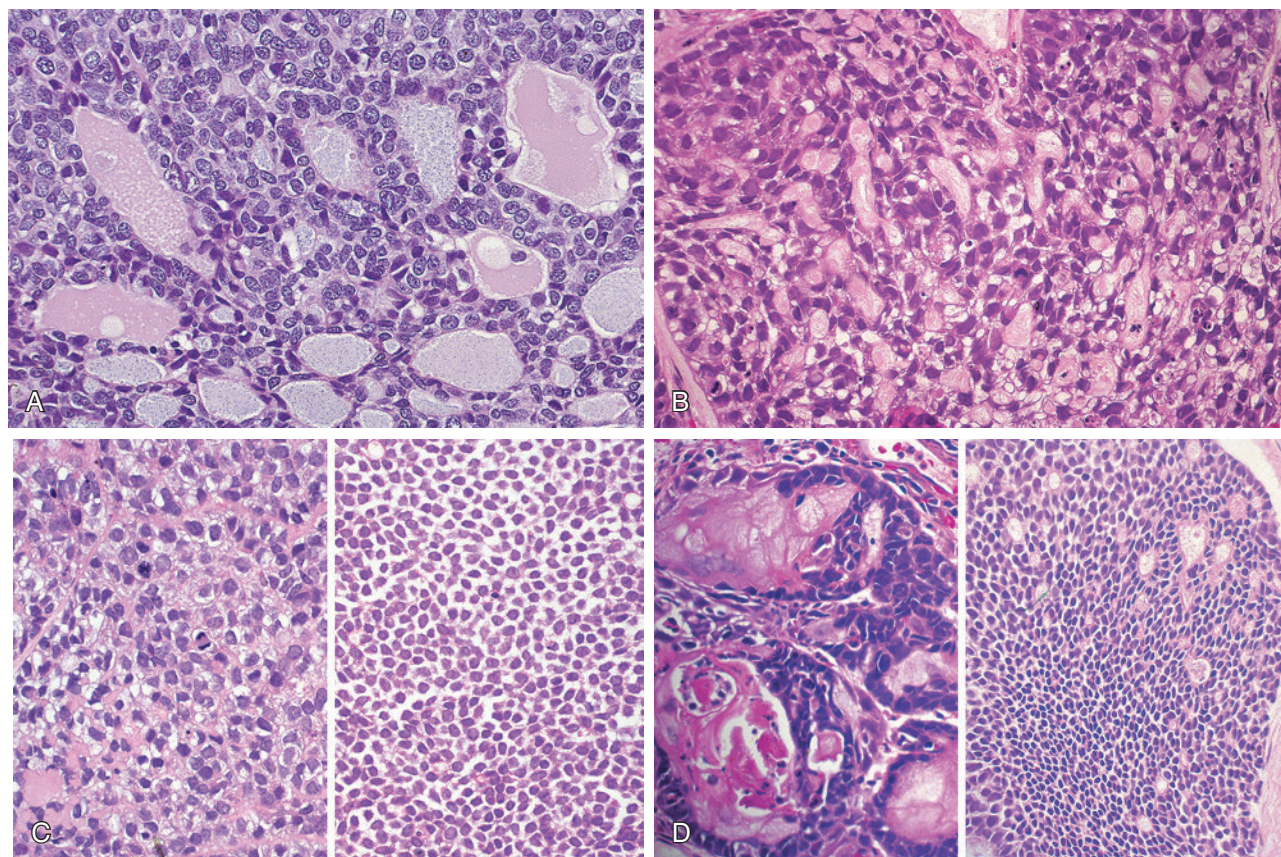


Fig. 16-56. BSCC: differential diagnosis.

The differential diagnosis of basaloid squamous cell carcinoma, especially in biopsy material, includes adenoid cystic carcinoma and small cell neuroendocrine carcinoma. The presence of a basaloid cell proliferation with **(A)** pseudocystic spaces and **(B)** reduplicated basement membrane material in these examples of basaloid squamous cell carcinoma can suggest a diagnosis of adenoid cystic carcinoma. **C**, However, the presence of *(left panel)* marked nuclear pleomorphism with increased mitotic activity seen in basaloid squamous cell carcinoma contrasts with the *(right panel)* isomorphic, small angulated basaloid cells lacking pleomorphism and mitotic activity as seen in usual types of adenoid cystic carcinomas. **D**, Further, the presence of *(left panel)* squamous differentiation in basaloid squamous cell carcinoma is a finding not identified in *(right panel)* adenoid cystic carcinoma. In addition, adenoid cystic carcinomas show the presence of true glandular differentiation, a feature not seen in basaloid squamous cell carcinoma (not shown). The absence of staining for neuroendocrine markers assists in differentiating basaloid squamous cell carcinoma from small cell neuroendocrine carcinoma.

- may be present, especially in cells with clear cytoplasm.
 - Alcian blue–positive material may be present within the cystic spaces.
- Immunohistochemistry:
 - Consistently reactive for cytokeratins (AE1/AE3, CAM5.2, CK5/6, CK903, OSCAR):
 - Do not show punctate paranuclear reactivity seen in small cell neuroendocrine carcinoma
 - p63 diffusely and strongly reactive
 - EMA positive in majority of cases
 - CEA may be positive and tend to be limited to squamous component.
 - CD56 reactive:
 - Not sensitive or specific marker for neuroendocrine differentiation
 - Neuroendocrine markers (i.e., chromogranin and synaptophysin) usually negative but occasional cases may be (focally) synaptophysin positive
 - Variable expression for vimentin, NSE, S100 protein, and smooth muscle actin:
 - Numerous S100 protein dendritic cells can be seen.
 - CD117 negative
 - Melanoma markers (e.g., HMB-45, melan-A, tyrosinase, MITF1, Sox10) negative

- May be p16 positive:
 - Typically seen in association with oropharyngeal tumors
- Electron microscopy:
 - Features of squamous cell carcinoma are present, including cell groups with numerous and prominent tonofilament bundles, increased desmosomes, and epithelial pearls and loose stellate granules or replicated basal lamina within the cystic spaces and absence of glandular differentiation.
- Cytogenetics and molecular genetics:
 - Increasing evidence identifying HPV in association with oropharyngeal BSCC:
 - High-risk HPV identified by in situ hybridization or PCR
 - MYB-NFIB gene fusion:
 - Absent in BSCC
 - Present in adenoid cystic carcinoma

Differential Diagnosis (Tables 16-3 and 16-4)

- Shallow biopsies may belie the depth and extent of invasion and may not be representative of the lesion, leading to erroneous classification.
- Adenoid cystic carcinoma
- Adenosquamous carcinoma
- Small cell undifferentiated neuroendocrine carcinoma
- Olfactory neuroblastoma (for sinonasal tract BSCC)

Treatment and Prognosis

- Preferred treatment includes radical surgical excision, neck dissection, and combined radiation and chemotherapy:
 - As result of early regional lymph node and distant visceral metastases, radical neck dissection and supplemental radio- and chemotherapy may be included in the initial management protocol.
- Aggressive, high-grade tumor with increased tendency to be multifocal, deeply invasive, and metastatic:
 - Metastases occur via lymphatics and blood vessels with sites of predilection including regional and distant lymph nodes, lung, bone, skin, and brain.
 - Metastases include basaloid and squamous cell components.
- Associated with increased incidence of second primary malignancy in upper aerodigestive tract
- Initially considered to be rapidly fatal neoplasm associated with high mortality rates within the first year after diagnosis and believed to be more aggressive than conventional SCC when matched stage for stage
 - Likely correlated to tendency to present with advanced clinical stage disease

- More recent data suggest stage for stage, prognosis similar to that for conventional SCC:
 - Compared with SCC, BSCC not shown to be an independent adverse prognostic factor for patients with head and neck cancer
 - BSCC histology does not have independent adverse prognostic effect on overall survival.
- HPV-positive BSCCs as compared with HPV-negative BSCCs:
 - Have improved overall survival
 - May be due to increased radiosensitivity of HPV-positive tumors
 - Explains lower hazard ratio for death in patients with oropharynx BSCC

Adenosquamous Carcinoma (ASC) (Figs. 16-57 through 16-59)

Definition: Malignant high-grade surface epithelial-derived neoplasm with histologic features of a squamous cell carcinoma and adenocarcinoma.

Clinical

- Rare neoplasm
- More common in men than in women; occur over a wide age range but are most frequently seen in the sixth to seventh decades of life
- May occur in virtually all upper aerodigestive tract sites but is identified most frequently in the larynx, hypopharynx, and less often in the oral cavity (tongue, floor of mouth, palate), oropharynx (tonsil, base of tongue) and sinonasal cavity
- Symptoms vary according to the site of occurrence:
 - Larynx: dysphagia, hoarseness, a mass with or without pain

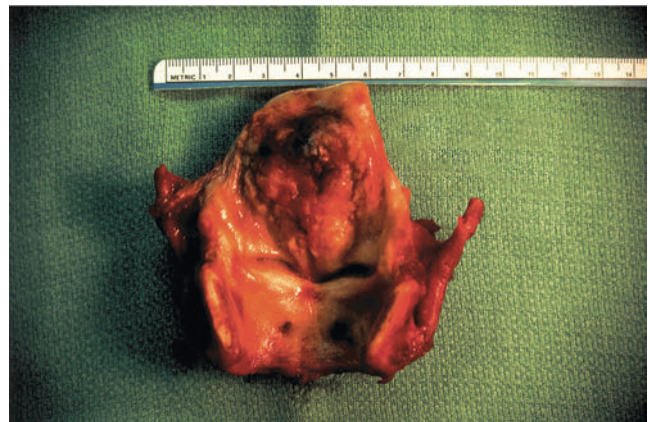


Fig. 16-57. Adenosquamous carcinoma.

Supraglottic exophytic and ulcerated neoplasm that proved to be an adenosquamous carcinoma.

TABLE 16-4 Basaloid Squamous Cell Carcinoma: Differential Diagnosis

	BSCC	AdCC	SCUNC
Age/Gender	6th-7th decades; M > F	5th-7th decades; no gender predilection except for submandibular tumors, which predilect to women	6th-7th decades; M > F
Location	Predilects to hypopharynx (piriform sinus), larynx (supraglottis), and oropharynx (tonsils, base of tongue)	Major salivary glands and minor (intraoral) minor salivary glands; may occur in other mucosal sites including sinonasal tract; rare in the larynx and hypopharynx	Uncommon in H&N: larynx (supraglottis) is the most common site; other H&N sites rare and may include sinonasal tract and parotid gland
Histology: 1. Growth 2. Cytomorphology	1. Invasive lobules with comedotype necrosis, solid, cords, trabeculae gland-like; cribriform pattern may be seen but tends to be limited; intercellular basement- membrane-type material may be present 2. Composed predominantly of pleomorphic, hyperchromatic basaloid cells with numerous mitoses; squamous cell component (dysplasia, CIS, invasive SCC) is the minor component; neural-type rosettes rarely may be present	1. Invasive with cribriform growth (representing the most frequent pattern), tubular/glandular, solid; pseudocysts present 2. Composed predominantly of abluminal (myoepithelial) cells composed of isomorphic cells with hyperchromatic (basaloid) angular to oval nuclei, absent to small nucleoli, eosinophilic to clear- appearing cytoplasm lacking nuclear pleomorphism and mitotic activity; in addition, luminal (duct) epithelial cells present lining true glandular spaces characterized by the cells with round nuclei and eosinophilic-appearing cytoplasm	1. Submucosal invasive tumor with solid nests, sheets or ribbons and absence of a fibrovascular stroma 2. Hypercellular tumor with hyperchromatic, pleomorphic, oval to spindle-shaped nuclei, increased nuclear-to- cytoplasmic ratio, nondescript cytoplasm, and indistinct cell borders; nuclear chromatin described as “salt and pepper” in appearance with absence of nucleoli; “crush” artifact is frequently present; confluent foci of necrosis and individual cell necrosis seen; abundant mitoses, including atypical forms; nuclear molding may be identified; neural-type rosettes may be present
Surface involvement	Present in the form of dysplasia or CIS	Absent	Absent but surface may be ulcerated
Squamous differentiation	Present but is the minor component and may only focally be found	Absent	Present but when found is typically limited in extent
Neurotropism	Yes	Yes	Yes
IHC	Diffuse and strong reactivity for cytokeratins and p63; neuroendocrine markers (e.g., synaptophysin, others) usually negative but occasionally may be positive; p16 typically negative in nonoropharyngeal sites and may be positive in oropharyngeal tumors	Abluminal cells: positive for cytokeratins, p63, S100 protein, calponin, SMA, SMMS, vimentin Duct cells: positive for cytokeratins, EMA, CEA, CD117 All cell types negative for neuroendocrine markers (chromogranin and synaptophysin)	Positive for cytokeratins often with punctate paranuclear pattern; CK5/6 usually negative; p63 may be positive but usually not as consistently positive as seen in BSCC and AdCC; neuroendocrine markers (e.g., synaptophysin, others) positive; calcitonin rarely positive
HPV association (transcriptionally active)	Possible*	No	Possible*
Gene fusion	Absent	MYB-NFIB present	Absent
Treatment	Surgery, radiotherapy, chemotherapy	Surgery and radiotherapy	Systemic chemotherapy and therapeutic irradiation

Continued

TABLE 16-4 Basaloid Squamous Cell Carcinoma: Differential Diagnosis—cont’d			
	BSCC	AdCC	SCUNC
Spread	Metastasis frequent often at presentation to cervical lymph nodes and lung	Metastasis (local or distant) uncommon: distant metastasis occurs late in disease course to lungs, bone, brain, and liver	Metastasis frequent (even at presentation) to regional lymph nodes and to liver, lung, bone, and brain
Prognosis	Dependent on clinical stage but overall considered to be poor; HPV-associated share better outcomes similar to oropharyngeal nonkeratinizing (HPV-associated) carcinomas	Short-term prognosis is good but long-term prognosis is poor; survival rates include: 5-year 71% to 89% 10-year 29% to 71% 15-year 29% to 55%	Poor: 16% 2-year survival; 5% 5-year survival Presence of transcriptionally active HPV does not alter poor prognosis

AdCC, Adenoid cystic carcinoma; BSCC, basaloid squamous cell carcinoma; CIS, carcinoma in situ; HPV, human papillomavirus; IHC, immunohistochemistry; SCUNC, small cell undifferentiated neuroendocrine carcinoma.

*BSCC and SCUNC may harbor transcriptionally active HPV especially when of oropharyngeal origin.

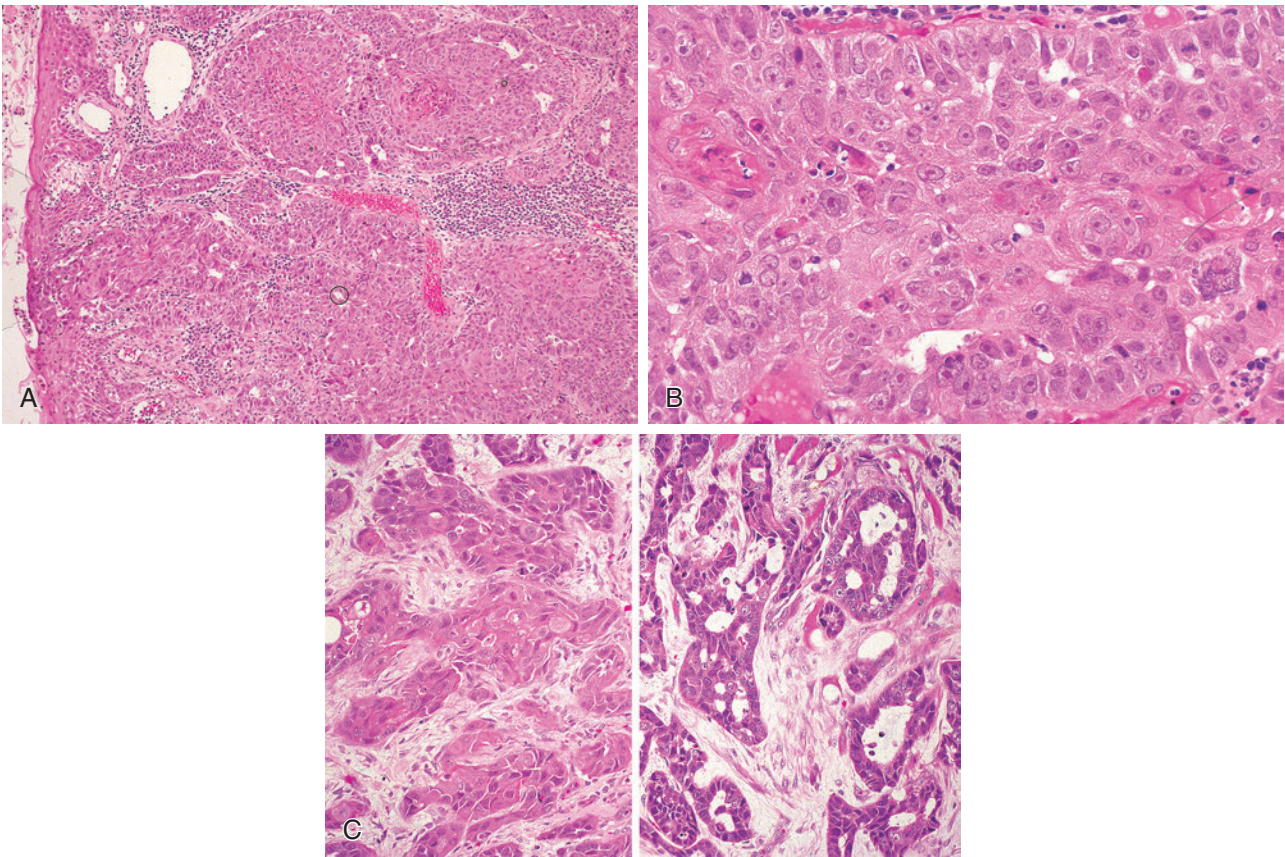


Fig. 16-58. Adenosquamous carcinoma.

A, Invasive carcinoma originating from the surface epithelium (*left*) consisting of an admixture of glandular and squamous differentiation. **B**, The glands and squamous foci may be intimately admixed or **(C)** lie adjacent to one another (*left panel* squamous differentiation and *right panel* glandular differentiation). These tumors are high-grade malignancies composed of pleomorphic cells with prominent eosinophilic nucleoli and increased mitotic activity.

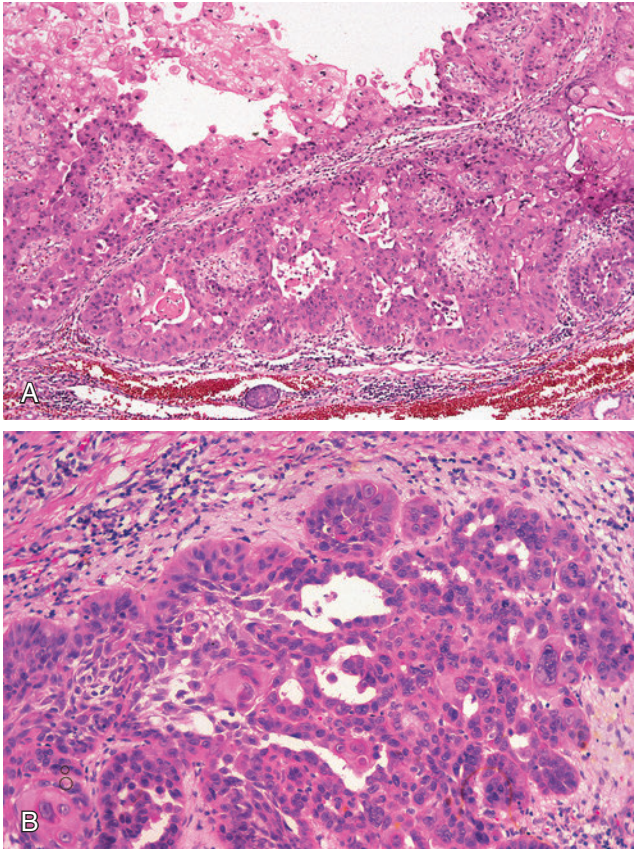


Fig. 16-59. Adenoid squamous cell carcinoma.

Adenoid squamous cell carcinoma is characterized by pseudolumen formation due to acantholysis, creating the appearance of gland formation that may suggest a diagnosis of adenosquamous carcinoma.

- Cause:
 - No clearly defined cause
 - May be related to alcohol and/or tobacco use
- Cell of origin not definitively identified but in all probability is a single totipotent cell capable of divergent differentiation and located either in the basal cell layer of the surface epithelium or within mucoserous glands; in the latter, the cell arises from excretory or interlobular salivary gland ducts

Pathology

Gross

- Exophytic or submucosal, friable, edematous, or granular mass with or without surface ulceration measuring from 0.6 to 5.0 cm.

Histology

- Infiltrating cytologically high-grade neoplasm composed of solid nests and glandular growth
- Necrosis and perineural invasion commonly identified

Squamous Cell Component

- Includes invasive SCC and/or high-grade intraepithelial dysplasia/CIS:
 - Squamous cell differentiation evident by the presence of individual cell keratinization, intercellular bridges, keratin pearl formation, and/or dyskeratosis
 - Varies from well to poorly differentiated
 - Often high-grade intraepithelial dysplasia/CIS of surface epithelium is present
 - May extend to seromucous glands
 - Often identified in direct continuity to surface epithelium
- May be admixed with or distinct from adenocarcinomatous component

Adenocarcinoma Component

- Characterized by gland formation with or without complex (gland in gland) growth
- Characterized by presence of moderate to marked nuclear pleomorphism and increased mitotic activity
- Necrosis may be present.
- Typically identified in the submucosa:
 - Usually seen in deeper aspects of the tumor
 - Mucous cell differentiation usually not seen and not a prerequisite for diagnosis
- May be admixed with or distinct from squamous cell carcinomatous component
- Histochemistry:
 - Intracellular and intraluminal mucicarmine and diastase-resistant, PAS-positive material is seen associated with the glandular component.
 - Intracytoplasmic mucin-positive material not typically present
- Immunohistochemistry (both components):
 - Cytokeratin positive, including AE1/AE3, CAM5.2, 34βE12 (CK903) in squamous and glandular components
 - p63 positive in squamous cell component
 - CEA, CK7 positive in glandular component
 - CK20 absent in glandular component
 - High proliferation rates as seen by Ki67 (MIB1) staining
 - Overexpression of p53
- Electron microscopy:
 - Squamous cell carcinoma component:
 - Bundles of tonofilaments, increased desmosomes, and epithelial pearls
 - Adenocarcinoma component:
 - Acini and luminal microvilli
- Cytogenetics and molecular genetics:
 - Absence of *MECT1-MAML2* gene translocation
 - High prevalence of aneuploidy

- Rare examples of ASC with intestinal phenotype reported:
 - Located in hypopharynx
 - Composed of superficial squamous cell carcinoma and adenocarcinoma with intestinal phenotype, the latter showing tubuloglandular and cribriform architecture and immunoreactivity for CK7, CK20, CDX2, CEA, and villin
- HPV-associated ASC:
 - Small minority may be associated with HPV.
 - Locations include oropharynx and sinonasal tract.
 - Histology similar to non-HPV-associated ASCs
 - Overexpression of p16
 - Show active viral transcription with detectable high-risk HPV E6 and E7
 - Appear to be associated with better clinical outcome than non-HPV-associated ASCs

Differential Diagnosis (Table 16-5)

- Mucoepidermoid carcinoma (MEC):
 - Rarely if ever a surface epithelial-derived neoplasm
 - Lacks squamous carcinoma in situ that is typically present in adenosquamous carcinoma
 - Typically lacks evidence of intercellular bridges or keratinization
 - In low-grade and intermediate-grade tumors shows combination of three cell types including mucocytes, epidermoid cells, and intermediate cells
 - Presence of *MECT1-MAML2* gene translocation:
 - Consistently present in low- and intermediate-grade MECs
 - High-grade tumors considered to be MEC but lacking *MECT1-MAML2* gene translocation likely not MECs and may be ASCs
- Adenoid squamous cell carcinoma (see Fig. 16-57):
 - Also referred to as acantholytic squamous cell carcinoma
 - Not a distinct clinical subtype but is a histomorphologic subtype of squamous cell carcinoma
 - Most common in sun-exposed areas of the head and neck; rare tumor of mucosal sites
 - Surface-derived squamous cell carcinoma that is histologically characterized by the presence of pseudolumen formation due to acantholysis, creating the appearance of gland formation; there is no evidence of glandular differentiation either in the form of mucocytes or glands
 - Histochemical stains for epithelial mucin are negative.
 - Cytokeratin, EMA, and p63 strongly positive
 - Absence of endothelial cell-related markers (e.g., CD31, CD34, factor VIII-related antigen, others)
- Prognosis similar to that of squamous cell carcinoma

Treatment and Prognosis

- Radical surgical excision is preferred treatment. As a result of the propensity for this neoplasm to demonstrate early regional lymph node metastasis, radical neck dissection may be necessary as part of the initial management; radiotherapy is of questionable benefit.
- Prognosis is poor as this neoplasm is aggressive and high grade with increased tendency to be multifocal, deeply invasive, and metastatic:
 - These neoplasms behave very aggressively regardless of the size of the neoplasm.
- Metastases occur via lymphatics and blood vessels with sites of predilection, including regional lymph nodes, lung, and liver:
 - Metastatic disease histologically is similar to the primary neoplasm and includes both malignant histologic components.
 - Nodal metastases reported in up to 75% of cases
 - Distant metastases reported in up to 25% of cases
- 5-year survival rates are approximately 15% to 25%.
- 3-year and median overall survival, disease-free survival (DFS), and locoregional control reported to be 52%, 32%, and 47%, respectively.
 - DFS negatively influenced by presence of extracapsular extension and advanced stage
 - Overall prognosis of locoregionally advanced ASC remains poor.
 - Early-stage ASC patients managed with combined modality treatment may have prolonged DFS.
- HPV-associated (oropharyngeal) ASC may have more favorable outcome as compared with non-HPV-associated ASC with longer survival rates:
 - Too few reported cases to clearly determine if these are distinct variant that can be classified according to HPV status.

OTHER UNCOMMON CARCINOMA VARIANTS

Lymphoepithelial-Like Carcinoma (Fig. 16-60)

Definition: Undifferentiated carcinoma with prominent associated benign lymphocytic cell infiltrate that is histologically identical to the more common nasopharyngeal undifferentiated carcinoma.

- See Section 3, Pharynx, for a more complete discussion.
- Rare tumor type of the larynx and trachea

TABLE 16-5 Adenosquamous Carcinoma: Differential Diagnosis

	ASC	MEC, Low- and Intermediate Grade	NS	SCC, Adenoid, or Acantholytic
Architecture/growth	Haphazard, infiltrative growth	Haphazard, infiltrative growth	Retention of lobular architecture	Haphazard, infiltrative growth
Cellular components	Invasive squamous cell carcinoma and adenocarcinoma: 2 components may be intermixed or more often are distinct and separate; adenocarcinoma is gland-forming but without mucocytes	Admixture of mucous, epidermoid, and intermediate; bland cytology; irregular cell nests	Smooth round to oval nests of metaplastic squamous epithelium with bland cytology; may show residual ductal lumina with mucous cells	Nests and cords of squamous cells with irregular outlines and variable amount of cytologic atypia; may entrap residual glands but the tumor itself contains no mucocytes
Cyst formation	Absent	Present: prominent component in low-grade and frequent component in intermediate-grade	Absent	Absent
Keratinization and intercellular bridges	Present	Absent	May be present	Present
Surface epithelium	HGSIL/CIS usually present; direct continuity with the carcinoma; surface may be ulcerated	Submucosal in location when occurs in mucosal sites without involvement (direct continuity) to surface epithelium; ulceration may be present	May show PEH; usually not connected with NS	Often dysplastic and/or in direct continuity with the carcinoma; may be ulcerated
Mucin production	Intraluminal; intracytoplasmic uncommon but may be present	Intracytoplasmic and intraluminal	Retained in residual mucocytes of seromucous glands	Absent
Extravasated mucin	Absent	Present	May be present	Absent
Necrosis	May show tumor necrosis	Absent	Lobular infarction of salivary gland acini	May show tumor necrosis
TALP inflammation	Typically absent although nonspecific chronic inflammation may be present in association with desmoplasia	Often present	Nonspecific chronic inflammation may be present	Typically absent although nonspecific chronic inflammation may be present in association with desmoplasia
Gene fusion	Absent	<i>MECT1-MAML2</i> present	Absent	Absent

ASC, Adenosquamous carcinoma; CIS, carcinoma in situ; HGSIL, high-grade squamous intraepithelial lesion; MEC, mucoepidermoid carcinoma; NS, necrotizing sialometaplasia; PEH, pseudoepitheliomatous hyperplasia; SCC, squamous cell carcinoma; TALP, tumor-associated lymphoid proliferation.

- More common in men than in women; most frequent in the seventh decade of life
- More common in Caucasian populations than in Asian populations
- Tendency to occur in the supraglottic larynx
- Most common symptoms include hoarseness and a neck mass:
 - Less often, sore throat, dysphagia, hemoptysis, and otalgia
- Histology identical to its more common nasopharyngeal counterpart, including:
 - Aggregates or syncytia of neoplastic cells characterized by enlarged vesicular nuclei and prominent nucleoli
 - Foci of squamous cell differentiation including abrupt keratinization of conventional foci of squamous cell carcinoma can be seen.
- Prominent benign lymphocytic cell infiltrate is present; a variable amount of plasma cell may be present.
- Carcinoma in situ of the overlying surface epithelium may be present.

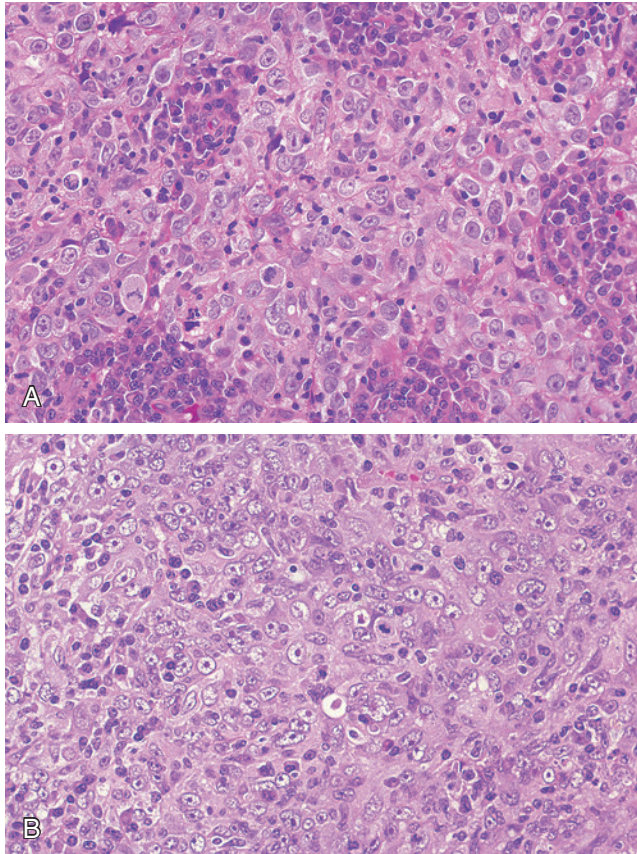


Fig. 16-60. Lymphoepithelial-like carcinoma.

Rare example of laryngeal lymphoepithelial-like carcinoma showing histomorphologic features similar to those of its more common nasopharyngeal counterpart, including neoplastic cells characterized by enlarged vesicular nuclei and prominent nucleoli with variable amount of associated benign lymphoplasmacytic cell infiltrate. In situ hybridization for Epstein-Barr–encoded RNA was negative (not shown).

- Neoplastic cells are immunoreactive for cytokeratins.
- Rarely associated with Epstein-Barr virus
- Risk factors for the development of this carcinoma may include excessive use of tobacco and alcohol.
- Treatment varies and has included limited to radical surgery with adjuvant therapy (radiation and chemotherapy).
- Cervical nodal metastases occurs in a nearly 75% of patients; distant metastases including to the lung, liver, bone, skin occur in approximately 25% of patients.
- Nearly one third of patients reported dead of disease at a 21-month median follow-up.

Giant Cell Carcinoma (Fig. 16-61)

Definition: Undifferentiated carcinoma with many bizarre multinucleated giant cells with or without light

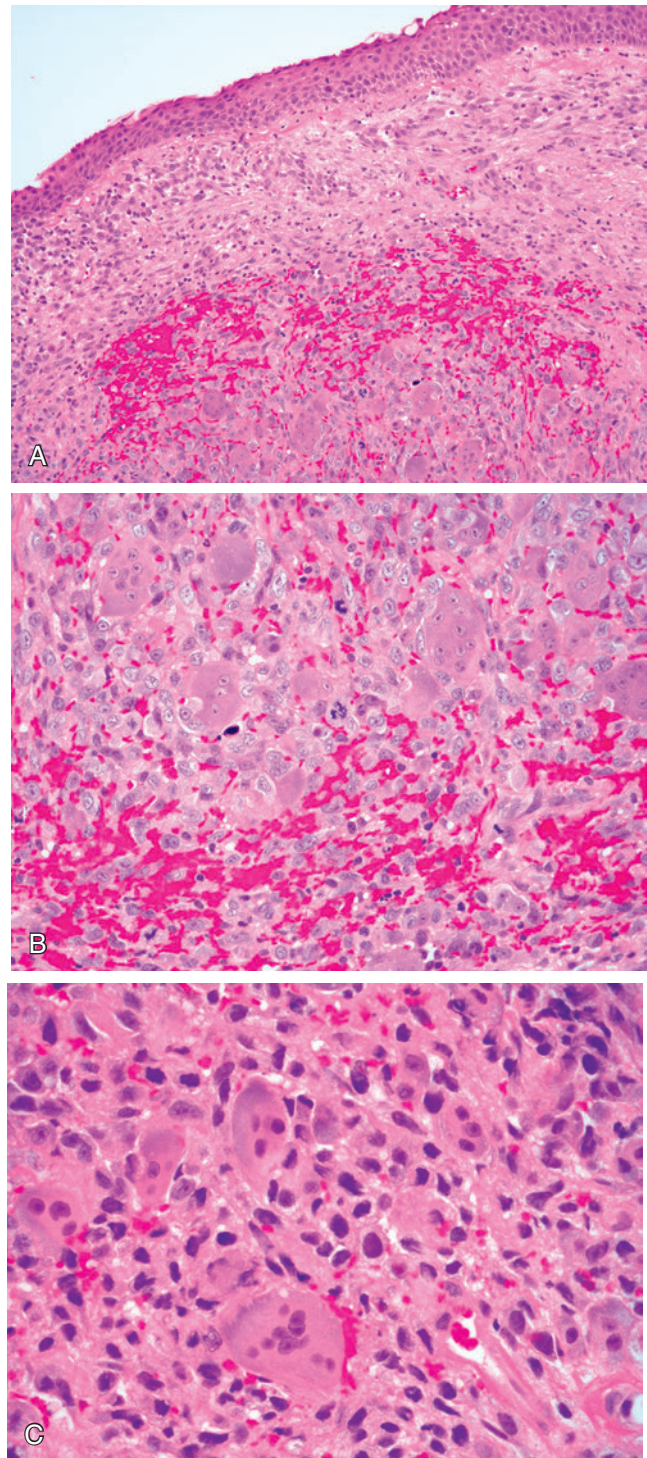


Fig. 16-61. Giant cell carcinoma.

A, B, Upper tracheal malignant neoplasm showing a submucosal proliferation composed of numerous noncohesive multinucleated (osteoclast-like) giant cells with abundant eosinophilic cytoplasm. **C,** Associated smaller malignant cells with increased mitotic activity including atypical mitoses are present. Immunoreactivity for cytokeratins was positive (not shown). Whether this neoplasm represents a distinct entity (i.e., giant cell carcinoma) or a part of another malignant neoplasm remains uncertain.

microscopic evidence of squamous or glandular differentiation, and with intracytoplasmic polymorphonuclear leukocytes or cellular debris.

Synonyms: Large cell carcinoma; pleomorphic carcinoma; anaplastic carcinoma

- By some criteria presence of squamous or glandular differentiation excludes a diagnosis of giant cell carcinoma.
- Diagnosis may be predicated on the quantity of giant cells in a given carcinoma, although various reports cite various percentages of giant cells as qualifying as a giant cell carcinoma.
- Given the fact that when giant cells are seen in squamous cell carcinoma or adenocarcinoma they represent a minor component focally present and are not diffusely present, a carcinoma with a diffuse giant cell population and/or a giant cell component seen in significant quantities should allow classification as a giant cell carcinoma.
- Presence of intracytoplasmic polymorphonuclear leukocytes or cellular debris would further buttress this diagnosis.

Clinical

- Extremely rare
- More common in men than in women; most frequent in the sixth to seventh decades of life
- Occurs in any site of the larynx without predilection to any one location
- Most common symptoms include dyspnea and dysphagia.
- May be linked to cigarette smoking and alcohol use

Pathology

Histology

- Histologically similar to giant cell carcinoma of the lung
- Light microscopy is characterized by:
 - Presence of numerous, noncohesive bizarre-appearing multinucleated giant cells with abundant eosinophilic cytoplasm that may be vacuolated
 - Often contain polymorphonuclear leukocytes or cellular debris
- A background cellular infiltrate that includes smaller anaplastic cells is present.
- Increased mitotic activity including atypical mitoses is present.
- Immunoreactivity for cytokeratin is present.
- May occur in a mixed form in association with squamous cell carcinoma, adenocarcinoma, or spindle cell squamous carcinoma:
 - May be referred to as pleomorphic carcinoma
 - Raises question whether giant cell carcinoma is a specific entity

Differential Diagnosis

- Spindle cell squamous carcinoma
- Sarcomas

Treatment and Prognosis

- Surgery (i.e., partial or total laryngectomy) plus adjuvant therapy (radiation and chemotherapy) is the recommended treatment.
- Increased incidence of cervical nodal metastasis necessitates neck dissection
- Very few reported cases but overall prognosis is poor

LARYNGEAL SALIVARY GLAND MALIGNANT NEOPLASMS

- Malignant salivary gland tumors of the larynx and trachea are rare.
- Although any type of malignant salivary gland tumor may occur in these locations, the most common tumor types are adenoid cystic carcinoma and mucoepidermoid carcinoma.

Adenoid Cystic Carcinoma of the Larynx and Trachea

- Equal gender predilection; occurs over a wide age range but most common in the sixth to eighth decades
- Majority are subglottic followed by the supraglottis
- Symptoms include airway obstruction, dysphagia, hoarseness, sore throat, and pain.
- Histology is similar to adenoid cystic carcinoma of more common locations.
- Differential diagnosis includes basaloid squamous cell carcinoma and small cell undifferentiated neuroendocrine carcinoma (see [Table 16-4](#))
- Surgery is the preferred treatment with postoperative radiotherapy:
 - Given the propensity to occur in the subglottic larynx, a total laryngectomy is often required.
 - Supraglottic tumors may be treated by partial laryngectomy.
- Unless there is clinical evidence of neck disease, a neck dissection would not appear to be warranted.
- Prognosis is similar to adenoid cystic carcinomas of more usual sites.

Mucoepidermoid Carcinoma of the Larynx and Trachea

- More common in men than in women; occurs over a wide age range but most common in the sixth decade:
 - Tracheal tumors may occur in pediatric ages.

- Majority are supraglottic.
- Symptoms include hoarseness, dyspnea, dysphagia, foreign body sensation, and a neck mass.
- Histology is similar to mucoepidermoid carcinomas of more common locations.
- Differential diagnosis includes adenosquamous carcinoma and necrotizing sialometaplasia (Table 16-5):
 - Likely many tumors reported as laryngeal high-grade mucoepidermoid carcinoma with poor prognosis represent adenosquamous carcinoma.
- Surgery is the preferred treatment:
 - Supraglottic tumors may be treated by partial laryngectomy.
- Unless there is clinical evidence of neck disease, a neck dissection for low- and intermediate-grade mucoepidermoid carcinoma is not warranted.
 - Neck dissection is warranted for a diagnosis of high-grade mucoepidermoid carcinoma.
- Prognosis is similar to mucoepidermoid carcinomas of more usual sites:
 - Overall survival rates for all grades of laryngeal MEC are 75% to 80%.
 - For low-grade MEC the 5-year survival rate is 90% to 100%.
 - For high-grade MEC the overall 5-year survival rate is 50% to 55%:
 - As previously noted it is likely that tumors reported as laryngeal high-grade mucoepidermoid carcinoma with poor prognosis represent adenosquamous carcinoma.

LARYNGEAL NEUROENDOCRINE CARCINOMAS

Definition: Heterogeneous group of malignant neoplasms characterized by the presence of neuroendocrine differentiation with prognosis dependent on tumor type.

- In general, an uncommon class of neoplasms in the head and neck.
- May be identified in virtually all sites of the head and neck:
 - Most common: larynx \gg sinonasal tract
 - Less common: salivary glands, pharynx (nasopharynx and oropharynx), oral cavity
- Histologic and immunohistochemical findings similar irrespective of site of origin
- Classification of laryngeal neuroendocrine carcinomas includes (Box 16-5):
 - Carcinoid tumor or well-differentiated neuroendocrine carcinoma (WDNEC)
 - Atypical carcinoid or moderately differentiated neuroendocrine carcinoma (MDNEC)
 - Small cell carcinoma or poorly differentiated neuroendocrine carcinoma (PDNEC) or small

BOX 16-5 Classification of Laryngeal Neuroendocrine Tumors

Benign

- Laryngeal paraganglioma

Malignant

- Carcinoid tumor (well-differentiated neuroendocrine carcinoma)
- Atypical carcinoid (moderately differentiated neuroendocrine carcinoma)
- Small cell undifferentiated neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)
- Large cell undifferentiated neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)

- cell undifferentiated neuroendocrine carcinoma (SCUNC)
- Large cell neuroendocrine carcinoma (LCNEC) subsumed within the broader category of PDNEC
- Order of frequency of occurrence of laryngeal neuroendocrine carcinomas is:
 - Atypical carcinoid (MDNEC) > small cell carcinoma (PDNEC) > carcinoid tumor (WDNEC)

Clinical (as a Group)

- There is much overlap in demographics and clinical features for all subtypes of laryngeal neuroendocrine carcinomas:
 - Histology and prognosis vary per subtype
 - See Tables 16-6 and 16-7 for clinical and pathologic features of laryngeal neuroendocrine carcinomas.
- More common in men than in women; generally occurs in the sixth to seventh decades of life
- Supraglottic larynx is overwhelmingly the most common site of occurrence:
 - May occur less often in the glottis and subglottis
- Hoarseness is most common complaint; other symptoms may include dysphagia.
- History of cigarette smoking linked with atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma but does not appear to be linked with development of carcinoid tumor

Carcinoid Tumor (Fig. 16-62)

Synonyms: Well-differentiated neuroendocrine carcinoma (WDNEC); typical carcinoid

Clinical

- Least common of the laryngeal neuroendocrine carcinomas
- Generally not associated with smoking history

TABLE 16-6 Clinical Features of Laryngeal Neuroendocrine Tumors

Feature	LP	CT	ACT	SCUNC	LCNEC
Frequency	Rare	Least common	Most common	2nd most common	Uncommon
Age/gender	5th decade; F > M	7th decade (on avg.); M > F	7th decade (on avg.); M > F	6th-7th decades; M > F	Occurs over a wide age range; average age of 59 years M > F
RF	None known	None known	Smoking	Smoking	Smoking
HPV-associated	None known	None known	None known	Possible*	None known
Site	Supraglottis: AE fold and FVC	Supraglottis: AE fold, arytenoid, FVC	Supraglottis: AE fold, arytenoids, FVC	Supraglottis, but may occur elsewhere in the larynx	Supraglottis
Symptoms	Hoarseness; dysphagia, dyspnea, stridor	Hoarseness	Hoarseness	Hoarseness	Hoarseness, dysphagia, otalgia, weight loss; heartburn, cervical adenopathy
Paraneoplastic syndrome	Exceptional; may be multicentric with other H&N paragangliomas	May occur but rare	Rare	Occasional	Unknown
Treatment	Surgery is curative	Surgery	Surgery; adjuvant radiotherapy and chemotherapy	Systemic chemotherapy and therapeutic irradiation	Chemoradiotherapy
Spread	None	Approximately 33% have distant metastases (liver and bone)	Metastasis common to cervical lymph nodes, lung, bone, liver, skin	Metastasis frequent (even at presentation) to regional lymph nodes and to liver, lung, bone, and brain	Commonly present with advanced stage (stages III and IV)
Prognosis	Excellent	Indolent biology with excellent behavior	Fully malignant neoplasm; tumor confined to larynx: 62% median 3.9-yr survival; 48% 5-yr survival; 30% 10-year survival	Poor: 16% 2-year survival; 5% 5-year survival; 5-year disease- specific survival (DSS) of 19%; presence of transcriptionally active HPV does not alter poor prognosis	5-year disease- specific survival (DSS) of 15% to 21%

ACT, Atypical carcinoid tumor; AE fold, aryepiglottic fold; CT, carcinoid tumor; FVC, false vocal cord; LCNEC, large cell neuroendocrine carcinoma; LP, laryngeal paraganglioma; RF, risk factor(s); SCUNC, small cell undifferentiated neuroendocrine carcinoma.

*May harbor transcriptionally active HPV especially when of oropharyngeal origin.

TABLE 16-7 Pathologic Features of Laryngeal Neuroendocrine Tumors

Feature	LP	CT	ACT	SCUNC	LCNEC
Histology	Cell nest or “Zellballen” pattern characteristic of paragangliomas of all sites; cell nests separated by prominent fibrovascular tissue; chief cells (predominant cell) are round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm; sustentacular cells lie at the periphery of the cell nests as spindle-shaped, basophilic-appearing cells but are difficult, if not impossible, to identify by light microscopy	Submucosal tumor with organoid or trabecular growth pattern and fibrovascular stroma; neoplastic cells are uniform with centrally located round nuclei, vesicular chromatin, and eosinophilic cytoplasm; low nuclear-to-cytoplasmic ratio; nuclear chromatin described as “salt and pepper” in appearance with absence of nucleoli; absence of pleomorphism, mitoses, necrosis	Submucosal tumor with organoid, trabecular, cribriform, or solid growth and fibrovascular stroma; neoplastic cells show mild to marked cellular pleomorphism with round to oval nuclei, vesicular to hyperchromatic chromatin, and eosinophilic cytoplasm; nuclei can be centrally or eccentrically located; nucleoli may be prominent; nuclear chromatin described as “salt and pepper” in appearance with absence of nucleoli; mitotic activity present but uncommon; necrosis uncommon	Submucosal tumor with solid nests, sheets, or ribbons and absence of a fibrovascular stroma; hyperchromatic, pleomorphic, oval to spindle-shaped nuclei, increased nuclear-to-cytoplasmic ratio, nondescript cytoplasm and indistinct cell borders; nuclear chromatin described as “salt and pepper” in appearance with absence of nucleoli; “crush” artifact is frequently present; confluent foci of necrosis and individual cell necrosis seen; abundant mitoses, including atypical forms; nuclear molding may be identified; neural-type rosettes rarely may be present	Presence of tumor cells with moderate to abundant cytoplasm, presence of features of neuroendocrine differentiation including organoid nesting, trabecular growth, rosettes, and peripheral palisading; increase mitotic activity (greater than 10 mitoses per 10 high-power fields [2 mm ²])
Infiltration	Absent	Absent	Present including neurotropism	Present including neurotropism	Present including neurotropism; may invade pre-epiglottic space
Angioinvasion	Absent	Absent	Present	Common	Common
IHC	Chief cells positive for neuroendocrine markers (synaptophysin, others) and GATA3; sustentacular cells: S100 protein positive; p63 negative	Positive for cytokeratins and neuroendocrine markers (e.g., synaptophysin, others); may be positive for calcitonin, serotonin, somatostatin, and bombesin; p63 negative; GATA3 negative	Positive for cytokeratin (96%); chromogranin (94%), synaptophysin (100%), calcitonin (80%); also positive for NSE, Leu-7, NFP, EMA, CEA; p63 variably positive and when present tends to be weak; GATA3 negative	Positive for cytokeratins (AE1/AE3) but CK5/6 and 34βE12 typically negative; CK7 and CK20 may be positive for neuroendocrine markers (e.g., synaptophysin, others) NSE, Leu-7, NFP, EMA, CEA, TTF-1; calcitonin rarely positive; GATA3 negative	Neuroendocrine markers positive (e.g., synaptophysin, others); positive for cytokeratin (AE1/AE3) but CK5/6 and 34βE12 typically negative; calcitonin and TTF1 negative
HPV association (transcriptionally active)	No known association	No known association	No known association but identified in a single reported case	Possible*	Not known

ACT, Atypical carcinoid tumor; CEA, carcinoembryonic antigen; CT, carcinoid tumor; EMA, epithelial membrane antigen; LCNEC, large cell neuroendocrine carcinoma; LP, laryngeal paraganglioma; NFP, neurofilament protein; NSE, neuron specific enolase; SCUNC, small cell undifferentiated neuroendocrine carcinoma; TTF-1, thyroid transcription factor 1.

*May harbor transcriptionally active HPV, especially when of oropharyngeal origin with one reported positive case originating in the larynx.

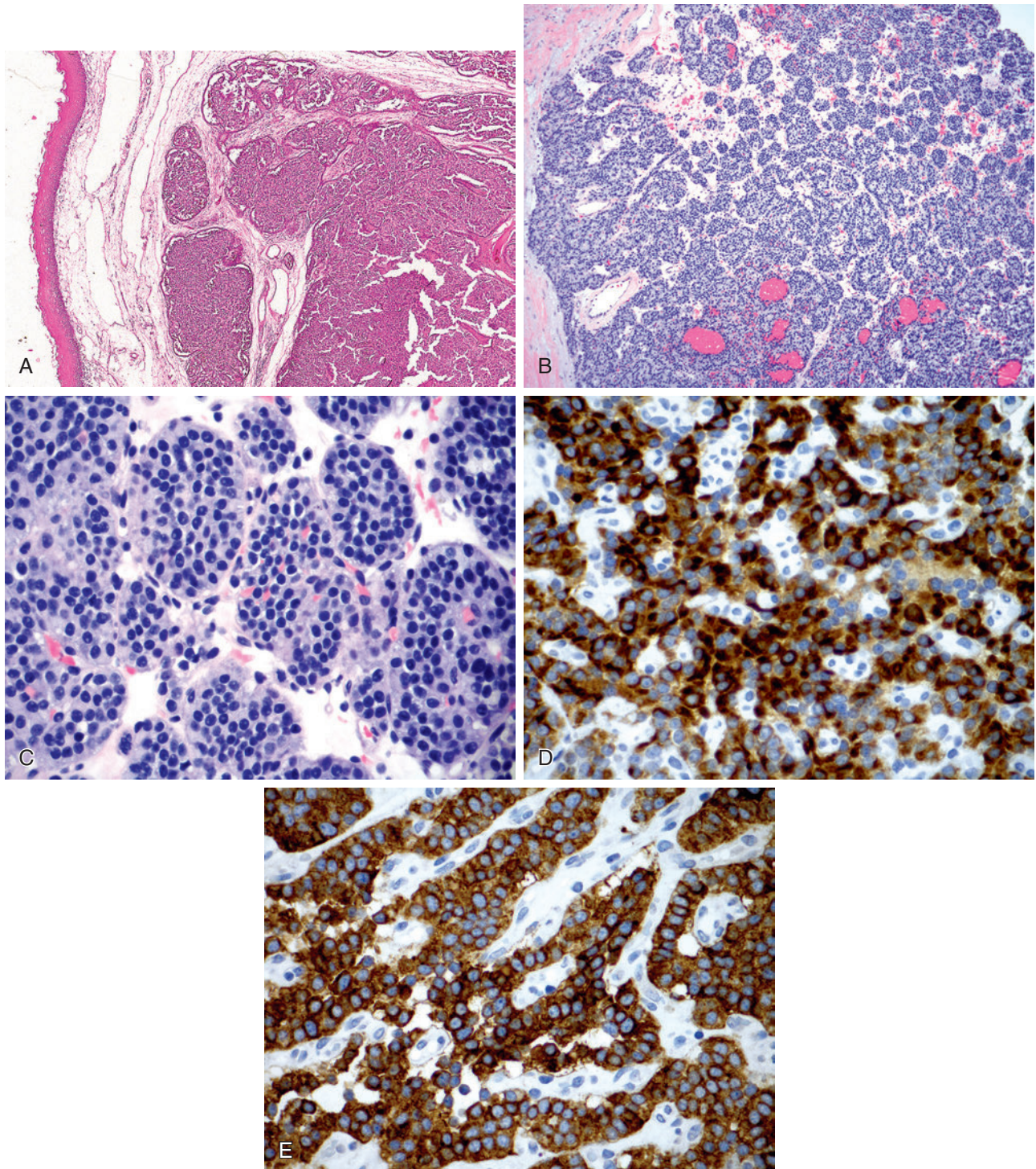


Fig. 16-62. Laryngeal carcinoid tumor.

A, Submucosal cellular tumor. **B** and **C**, Organoid and solid areas composed of uniform cells with centrally located round nuclei, dispersed nuclear chromatin-lacking pleomorphism, mitoses, or necrosis. Immunoreactivity is present for **(D)** cytokeratin (CAM5.2) with paranuclear dot-like staining and **(E)** synaptophysin.

- Carcinoid syndrome may rarely occur in association with carcinoid tumor:
 - Occurs when carcinoid tumor secretes certain chemicals into bloodstream, causing a variety of signs and symptoms
 - Most common in association with carcinoid tumors of the gastrointestinal tract or lungs
 - Typically occurs in patients who have advanced disease
 - Most common signs and symptoms of carcinoid syndrome include:
 - Skin flushing
 - Diarrhea:
 - Frequent watery stools sometimes accompanied by abdominal cramps
 - Rapid heartbeat
 - Difficulty breathing:
 - Asthma-like signs and symptoms (e.g., wheezing and shortness of breath) may occur at same time of skin flushing
 - Facial skin lesions:
 - Purplish spider-like veins may appear on nose and upper lip.
 - Treatment usually involves treating the cancer, but as most carcinoid tumors do not cause carcinoid syndrome until an advanced stage of disease a cure may not be possible:
 - In such cases, medications may relieve symptoms.
 - Medications used are able to block cancer cells from secreting chemicals:
 - Injections of medications octreotide (Sandostatin) and lanreotide (Somatuline Depot) may reduce the signs and symptoms of carcinoid syndrome, including skin flushing and diarrhea.
 - Octreotide may also slow growth of carcinoid tumors.
 - Side effects of octreotide and lanreotide include diarrhea, abdominal pain, and bloating, which may subside over time.

Pathology

Gross

- Submucosal nodular or polypoid mass with a tan-white appearance varying in size from a few millimeters up to 3 cm in diameter
- Surface ulceration is generally absent.

Histology

- Submucosal tumor arranged in organoid or trabecular growth pattern with fibrovascular stroma
- Uniform cells with centrally located round nuclei, vesicular chromatin and eosinophilic cytoplasm; low nuclear-to-cytoplasmic ratio; nuclear chromatin

described as “salt and pepper” in appearance with absence of nucleoli

- Absence of pleomorphism, mitoses, necrosis
- Glands and/or squamous differentiation can be seen.
- Surface ulceration uncommon
- Vascular, lymphatic, and perineural invasion absent
- Histochemistry:
 - Argyrophilic staining (e.g., Churukian-Schenk) positive characterized by presence of intracytoplasmic granular material typically appearing black
 - Extent and degree of staining inversely parallels tumor grade with decreasing staining with less differentiation
 - Argentaffin staining (e.g., Fontana-Masson) may be positive characterized by presence of intracytoplasmic black material.
 - In presence of glandular differentiation, intraluminal mucicarmine and diastase-resistant, PAS-positive material can be seen.
- Immunohistochemistry:
 - Cytokeratins positive:
 - AE1/AE3, CAM5.2 consistently strongly positive
 - CK7, CK20 may be positive
 - EMA, CEA positive
 - Synaptophysin, chromogranin, neuron-specific enolase, CD56, Leu-7 (CD57) positive
 - Serotonin and somatostatin may be positive.
 - Calcitonin, TTF1, S100 protein negative
 - p63 usually negative
- Electron microscopy:
 - Abundant neurosecretory granules (90 to 230 nm); cellular junctional complexes, intercellular, and intracellular lumina are present.

Differential Diagnosis

- Laryngeal paraganglioma:
 - Absent staining with epithelial markers:
 - Rare examples may be cytokeratin positive.
 - Presence of S100 protein (and GFAP) in peripheral situated sustentacular cells:
 - Feature not identified in neuroendocrine carcinomas
 - GATA3 immunoreactivity seen in paragangliomas but absent in (laryngeal) neuroendocrine carcinomas
- Atypical carcinoid (see below)

Treatment and Prognosis

- Conservative but complete surgical excision is preferred treatment.
- Neck dissection not indicated
- Indolent biologic behavior:
 - Generally carries an excellent prognosis after excision

- 5-year disease-specific survival (DSS) of 100% reported
- May metastasize in approximately one third of patients:
 - Metastasis occurs to liver, bone, lymph nodes, and skin.
 - Metastases may occur late in the disease course.

Atypical Carcinoid

(Figs. 16-63 through 16-67)

Synonym: Moderately differentiated neuroendocrine carcinoma (MDNEC)

Clinical

- Most common laryngeal neuroendocrine carcinoma
- Most patients have a history of heavy tobacco smoking use.

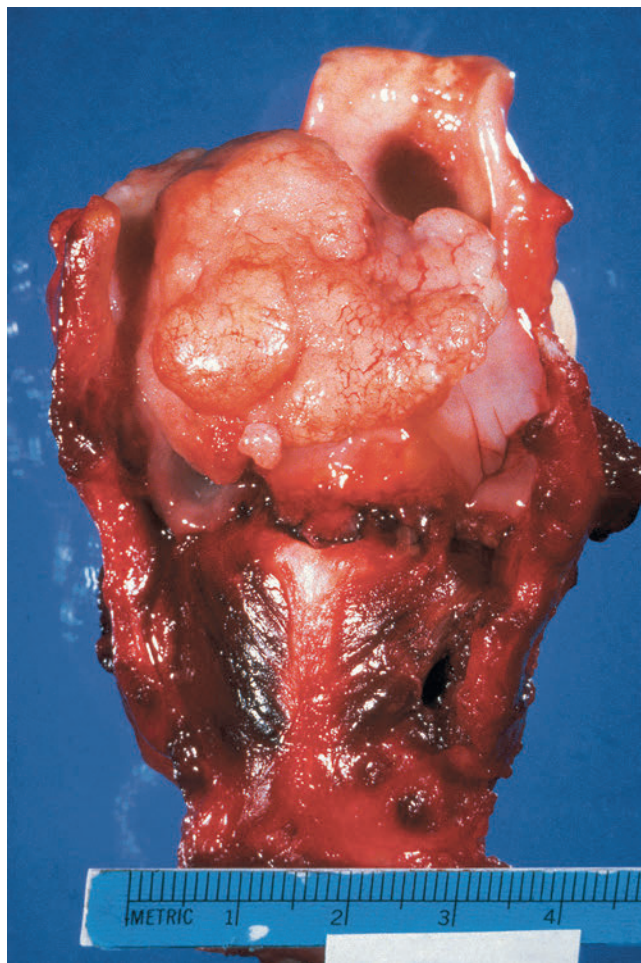


Fig. 16-63. Atypical carcinoid.

Laryngeal atypical carcinoid appearing as a large supraglottic-based mass with extension outside the larynx proper.

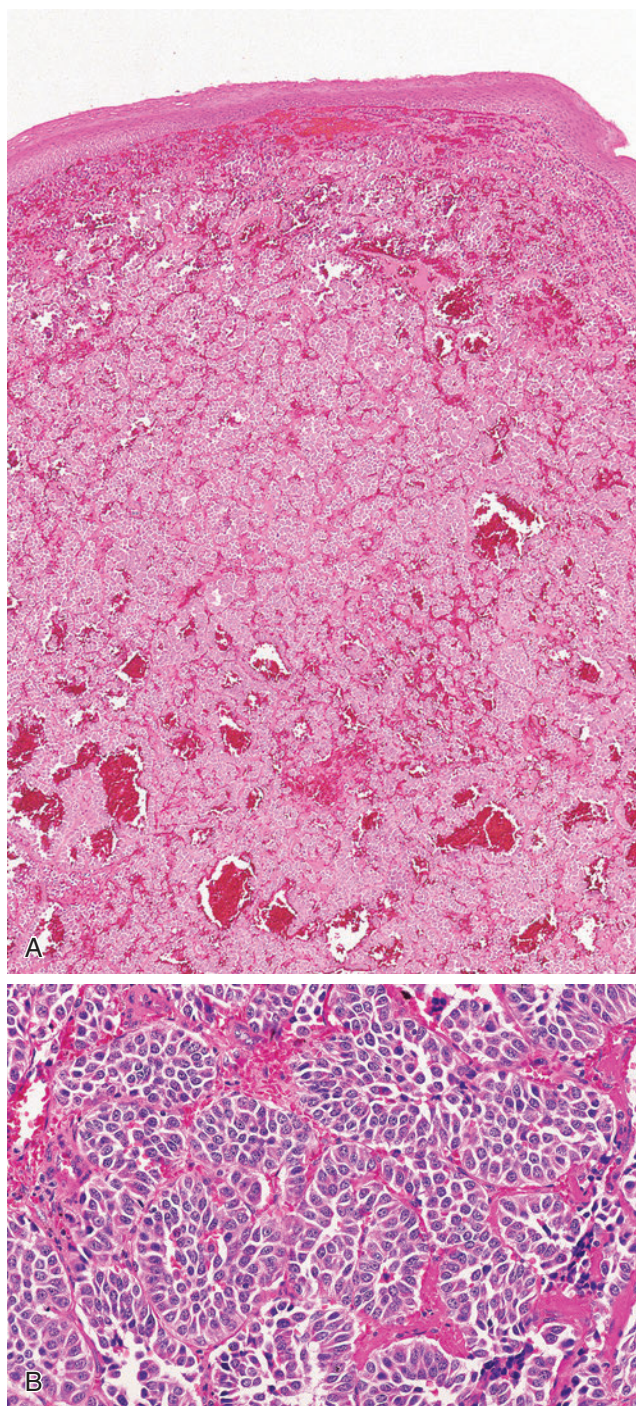


Fig. 16-64. Atypical carcinoid.

A, B, Laryngeal atypical carcinoid characterized by the presence of a submucosal neoplastic proliferation with organoid growth and fibrovascular stroma.

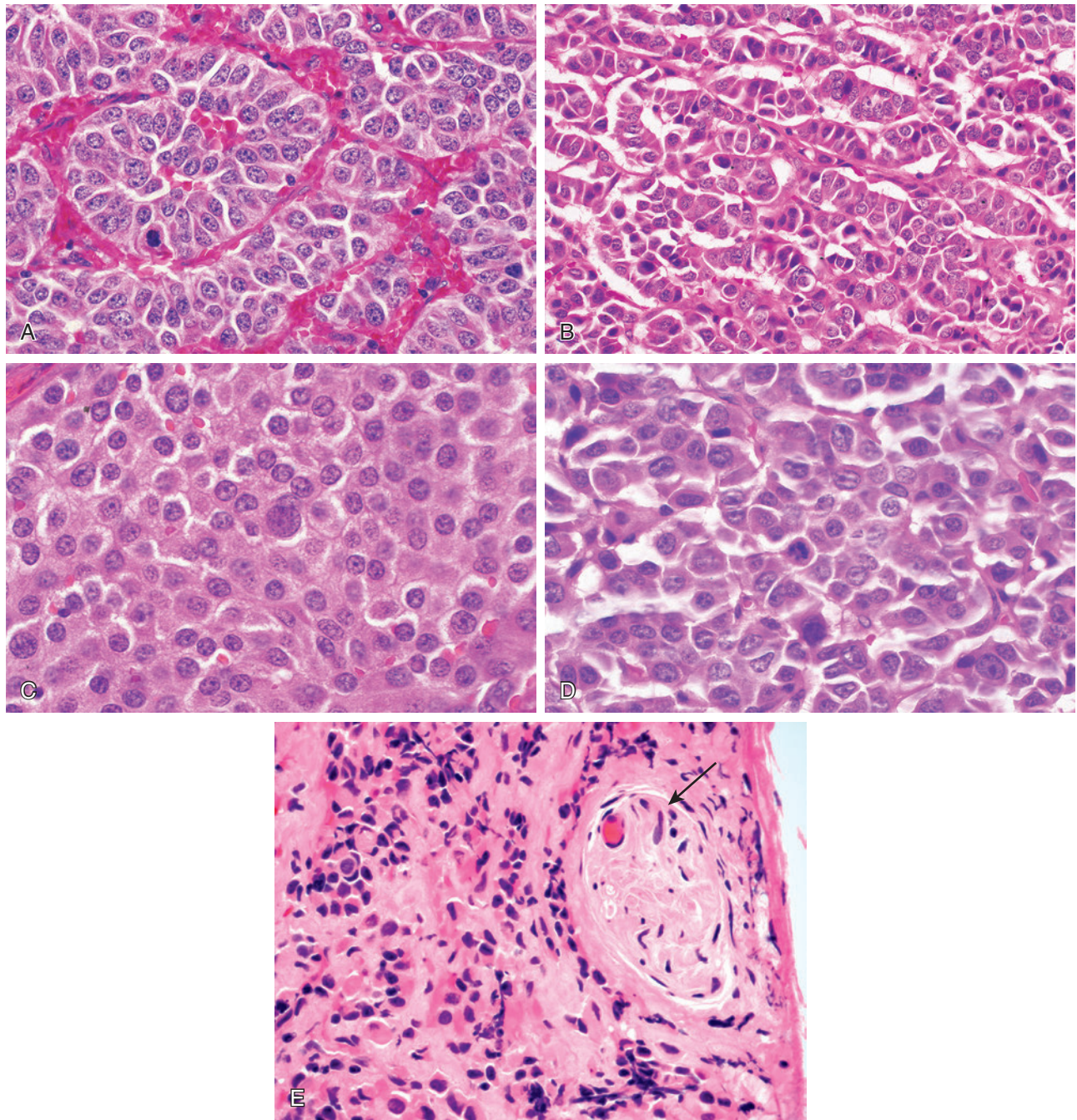


Fig. 16-65. Atypical carcinoid.

A through **D**, Laryngeal atypical carcinoid with organoid or cell nest, trabecular and solid growth patterns composed of cells with round to oval nuclei, dispersed to hyperchromatic nuclear chromatin, inconspicuous to small nucleoli and eosinophilic cytoplasm; variable but definite nuclear pleomorphism is present, and there is increased mitotic activity. The presence of nuclear pleomorphism and mitotic activity is greater than that seen in carcinoid tumor but not as prominent as in small cell and large cell neuroendocrine carcinomas. **E**, Perineural invasion (*arrow*) can be seen in atypical carcinoid representing another feature that would contrast to (typical) carcinoid tumor.

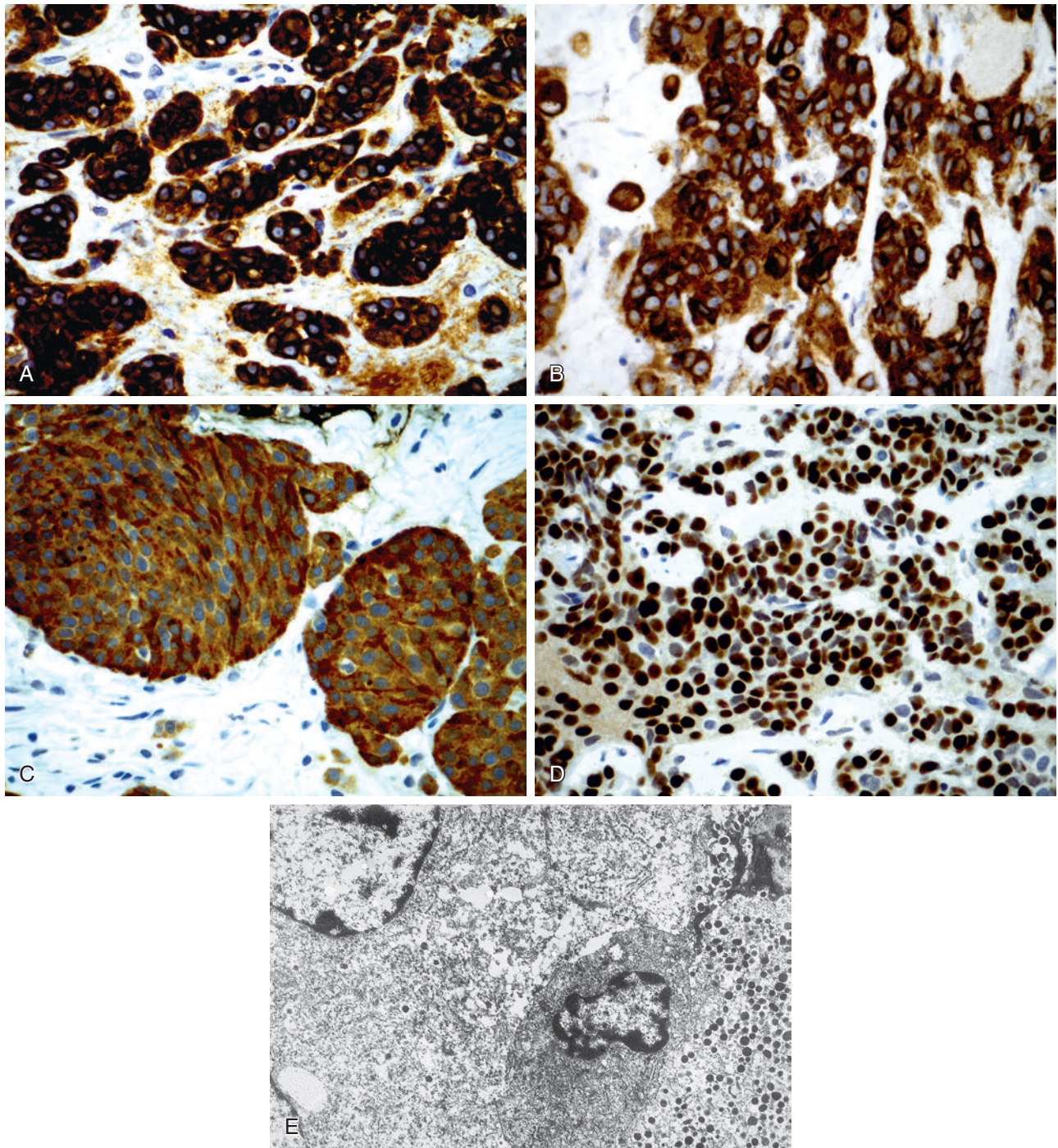


Fig. 16-66. Immunohistochemical staining of atypical carcinoid.

Immunoreactivity in laryngeal atypical carcinoid includes **(A)** cytokeratin (CAM5.2), **(B)** synaptophysin, **(C)** calcitonin, and **(D)** thyroid transcription factor 1. **E**, Ultrastructural findings include the presence of neurosecretory granules (lower right of illustration).

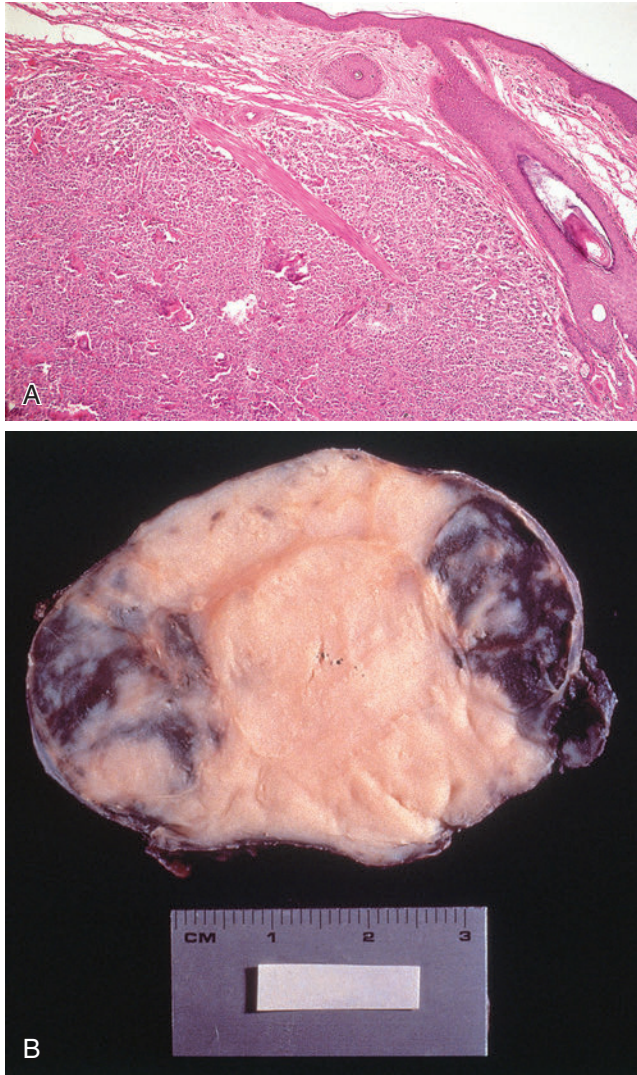


Fig. 16-67. Metastatic atypical carcinoid.

Metastasis from laryngeal atypical carcinoid tumor may include **(A)** subcutaneous metastasis and **(B)** cervical neck lymph node with almost complete replacement of the lymph node by metastatic tumor. In the presence of an unknown primary tumor, the histology and immunohistochemical staining of metastatic laryngeal atypical carcinoid will be similar to those of a metastatic medullary thyroid carcinoma, including immunoreactivity for cytokeratins, neuroendocrine markers, calcitonin, and thyroid transcription factor 1. In contrast to medullary thyroid carcinoma, serum calcitonin levels would not be expected to be elevated in patients with laryngeal atypical carcinoid tumor.

- Carcinoid syndrome rarely occurs in association with atypical carcinoid tumor.

Pathology

Gross

- Submucosal nodular or polypoid mass with a tan-white appearance varying in size from a few millimeters up to 4 cm in diameter.
- Surface ulceration may be present.

Histology

- Submucosal tumor arranged in organoid, trabecular, cribriform, or solid growth with a prominent fibrovascular stroma; infiltrative growth is present, including neurotropism and angioinvasion.
- Neoplastic cells show mild to marked cellular pleomorphism with round to oval nuclei, vesicular to hyperchromatic chromatin, and eosinophilic cytoplasm:
 - Nuclei can be centrally or eccentrically located.
 - Nucleoli may be prominent.
 - Nuclear chromatin described as “salt and pepper” in appearance with absence of nucleoli
 - Oncocytic cytoplasmic changes may be present.
- Mitoses, although uncommon, can be seen:
 - Never reach a level associated with large cell neuroendocrine carcinoma of 10 mitoses per 10 high-power fields (see below)
- Necrosis may be focally identified.
- Glands and squamous differentiation can be identified; neural-type rosettes rarely may be present:
 - May rarely occur in association with squamous cell carcinoma
 - In presence of squamous differentiation, a diagnosis of basaloid squamous cell carcinoma should be excluded.
- Surface ulceration may be prominent.
- Lymph-vascular and/or and perineural invasion may be present.
- Histochemistry:
 - Presence of epithelial mucin (diastase-resistant, PAS-positive, and occasionally mucicarmine positive), argyrophilia; rarely, argentaffin positive
- Immunohistochemistry:
 - Cytokeratins (96%), chromogranin (94%), synaptophysin (100%)
 - Other positive markers may include neuron-specific enolase, CD56, Leu-7 (CD57), neurofilament protein, epithelial membrane antigen, and carcinoembryonic antigen positive
 - Calcitonin is frequently positive (up to 80% of cases).
 - S100 protein, somatostatin, serotonin, adrenocorticotrophic hormone, gastrin, and glucagon may be positive.

- p63 variably positive and when present tends to be focal and weak
- TTF1 and melanoma-related markers are negative.
- Increased proliferation rates seen by Ki67 (MIB1) staining
- p53 overexpression
- p16 and HPV16 by PCR reported positive in a single case:
 - Whether there is any link and/or role of high-risk HPV in pathogenesis remains uncertain.
 - Whether there is any ameliorating effect of HPV on prognosis of LNEC remains uncertain.
- Electron microscopy:
 - Neurosecretory granules are commonly seen (70 to 420 nm); cellular junctional complexes, inter- and intracellular lumina are present.
- Radiotherapy and chemotherapy not considered beneficial as this tumor type is resistant to these therapies.
- Overall survival rates include:
 - 5-year survival rate of 48%
 - 10-year survival rate of 30%
- 5-year disease-specific survival (DSS) of 53%:
 - Patients treated with surgery had better DSS than those treated with radiotherapy.
 - Postoperative radiotherapy did not result in better DSS.
- Fully malignant tumor that often metastasizes to:
 - Cervical lymph nodes (43% of patients)
 - Lungs, bone, liver (44% of patients)
 - Skin and subcutaneous tissue (22% of patients)
- Prognosis is dependent on extent of disease at presentation:
 - When the tumor is confined to the larynx, 62% tumor-free over median of 3 years 9 months
 - Presence of metastatic disease (either at presentation or developing subsequently) is an ominous sign, with death at intervals ranging from 1 to 6 years.
- Size of primary tumor is prognostically important as tumors measuring greater than 1 cm have twice the mortality rate as tumors measuring less than 1 cm.
- Death results from metastatic disease.

Differential Diagnosis

- Carcinoid tumor
- Medullary thyroid carcinoma:
 - Differentiation of atypical carcinoid from a medullary thyroid carcinoma can be problematic in presence of cervical lymph node metastasis of unknown primary origin given overlapping histologic and immunohistochemical features including:
 - Organoid growth with cells showing features of neuroendocrine differentiation
 - Immunohistochemical reactivity for cytokeratins, synaptophysin, and calcitonin
 - Presence of a thyroid-based mass would support a diagnosis of medullary thyroid carcinoma, but in the absence of a thyroid mass, differentiation can be made on basis of increased serum calcitonin levels, which are almost invariably elevated in medullary thyroid carcinoma and almost always within normal limits in atypical carcinoid
- Basaloid squamous cell carcinoma
- Laryngeal malignant melanoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - Depending on site surgery may include partial or total laryngectomy
 - High incidence of cervical lymph node metastasis warrants neck dissection even in clinically N0 necks:
 - Nodal metastasis may be present at time of presentation or subsequently develop nodal metastasis.
 - Patients not undergoing surgical treatment of the neck reported to develop isolated regional recurrence in 30% of cases

Small Cell Undifferentiated Neuroendocrine Carcinoma (SCUNC) (Figs. 16-68 through 16-70)

Synonyms: Poorly differentiated neuroendocrine carcinoma (PDNEC); small cell carcinomas; “oat” cell carcinoma

Clinical

- Second most common laryngeal neuroendocrine carcinoma but represents less than 1% of all laryngeal malignant tumors
- Most patients have a history of heavy tobacco smoking use.
- A paraneoplastic syndrome occasionally may occur in association with SCUNC and may include:
 - Cushing syndrome
 - Eaton-Lambert syndrome
 - Schwartz-Bartter syndrome

Pathology

Gross

- Submucosal mass usually with surface ulceration

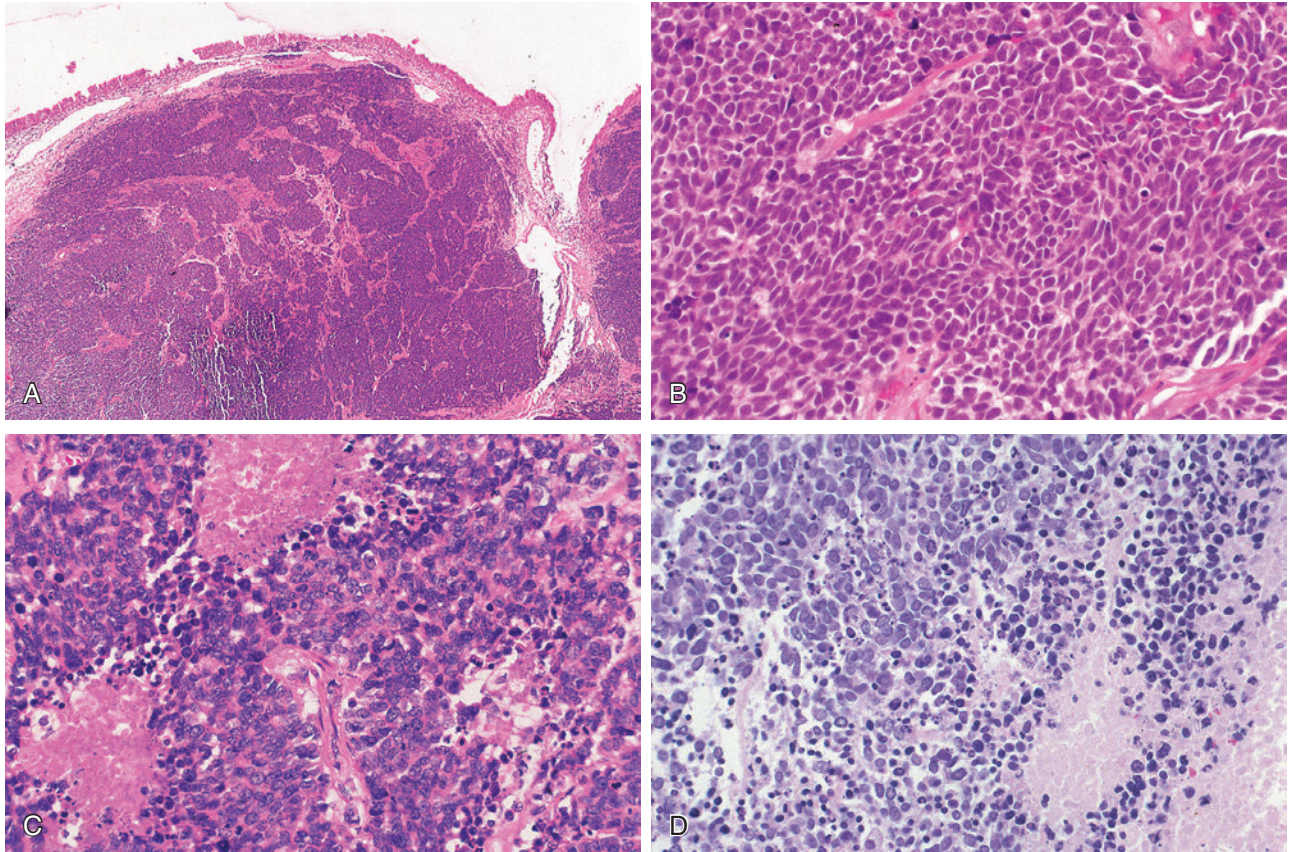


Fig. 16-68. Small cell undifferentiated neuroendocrine carcinoma of the larynx.

A, Submucosal hypercellular tumor with solid, trabecular, and lobular growth. **B,** Small round cell malignant infiltrate composed of hyperchromatic, round to oval to spindle-appearing nuclei with nuclear molding, inconspicuous to small nucleoli, and increased mitotic activity. **C** and **D,** Small round cell (undifferentiated) malignant cellular infiltrate with confluent foci of necrosis as well as individual cell necrosis with numerous mitotic figures present.

Histology

- Submucosal tumor may be arranged in solid nests, sheets, or ribbons with absence of a fibrovascular stromal component.
- Hypercellular with hyperchromatic, pleomorphic, oval to spindle-shaped nuclei, increased nuclear-to-cytoplasmic ratio, nondescript cytoplasm, and indistinct cell borders:
 - Nuclear chromatin may vary from dispersed coarse-appearing described as “salt and pepper” to hyperchromatic.
 - Absence of nucleoli
 - “Crush” artifact is frequently present.
 - Confluent foci of necrosis and individual cell necrosis seen
 - Abundant mitoses, including atypical forms
 - Nuclear molding may be identified.
- Glands and squamous differentiation rarely present
- Neural-type rosettes rarely may be present.
- May occur in association with squamous cell carcinoma and less often with an adenocarcinoma:
 - These tumors are referred to as combined or composite tumors.
- Surface ulceration often present
- Lymph-vascular and/or and perineural invasion may be present.
- In combined or composite carcinoma there is an admixture of small cell neuroendocrine carcinoma and either a squamous cell carcinoma or adenocarcinoma:
 - Squamous carcinoma component includes carcinoma in situ and/or invasive squamous cell carcinoma.
 - In presence of squamous differentiation a diagnosis of basaloid squamous cell carcinoma should be excluded.
- Histochemistry:
 - Argyrophilia rarely present
 - Argentaffin stains usually negative

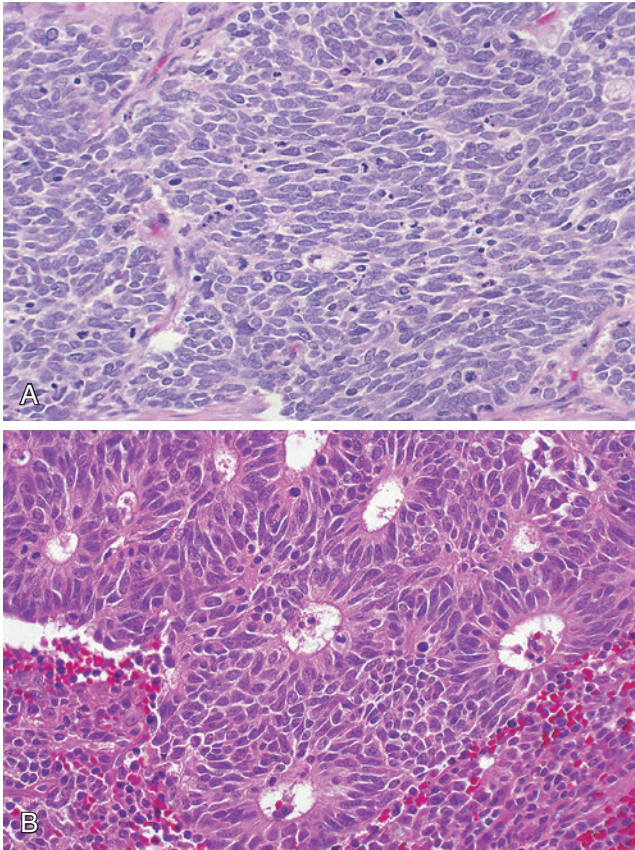


Fig. 16-69. SCUNC.

In addition to the usual morphology, other findings that may be seen in (laryngeal) small cell undifferentiated neuroendocrine carcinoma may include **(A)** prominent spindle-shaped nuclei and **(B)** presence of true (neural-type) rosettes.

- Staining for epithelial mucin (e.g., mucicarmine, PAS with diastase) may be present.
- Immunohistochemistry:
 - Cytokeratins (AE1/AE3, CAM5.2, others) positive:
 - Often characterized by paranuclear (punctate) staining pattern
 - CK7 and CK20 may be positive.
 - High molecular weight cytokeratins, including CK 5/6 and CK903 (34 β E12), typically negative but may be positive and when positive is focal
 - Neuroendocrine markers, including synaptophysin, CD56, neuron-specific enolase positive:
 - Chromogranin may be positive but only focally and may be negative.
 - CD57, neurofilament protein may be positive.
 - TTF1 may be positive.
 - Variability of p63 staining that may include focal to diffuse reactivity
 - Epithelial membrane antigen and carcinoembryonic antigen positive

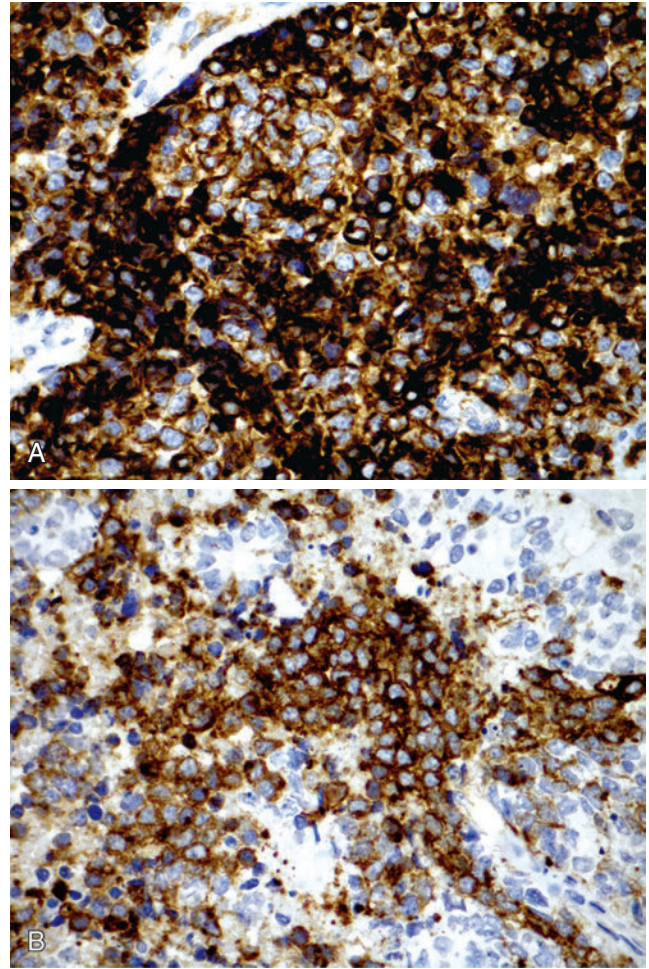


Fig. 16-70. IHC in SCUNC.

Immunoreactivity that can be seen in small cell undifferentiated neuroendocrine carcinoma may include **(A)** cytochrome c oxidase (CytOx) with paranuclear dot-like staining; **(B)** synaptophysin.

- Calcitonin rarely is positive.
- Melanocytic, hematolymphoid, and mesenchymal (e.g., myogenic) markers negative
- In association with laryngeal SCUNC, p16, and HPV16 by PCR reported positive in a single case:
 - Whether there is any link and/or role of high-risk HPV in pathogenesis remains uncertain.
 - Whether there is any ameliorating effect of HPV on prognosis of LNEC remains uncertain.
- In association with oropharyngeal SCUNC, p16, and HPV DNA identified in majority of cases (see Section 3, Pharynx)
- Electron microscopy:
 - Scanty neurosecretory granules (50 to 200 nm); cellular junctional complexes, inter- and intracellular lumina are usually absent.

Differential Diagnosis

- Poorly differentiated squamous cell carcinoma:
 - Cytokeratin staining present but lacks punctate paranuclear staining seen in SCUNC
 - High molecular weight keratins including CK5/6 and CK903 (34 β E12) diffusely and strongly positive
 - p63 diffuse and strong reactivity
- Basaloid squamous cell carcinoma (see Table 16-4)
 - In larynx also predilects to supraglottis
 - Cytokeratin staining present but lacks punctate paranuclear staining seen in SCUNC
 - High molecular weight keratins including CK5/6 and CK903 (34 β E12) diffusely and strongly positive:
 - SCUNC lacks such diffuse and strong staining.
 - p63 diffuse and strong reactivity:
 - SCUNC lacks such diffuse and strong staining.
 - Absence of TTF1 contrasts with the positive immunohistochemical staining pattern for this marker in SCUNC.
- Adenoid cystic carcinoma (see Table 16-4)
- Adenosquamous carcinoma
- Paraganglioma
- Extramedullary plasmacytoma
- Metastatic small cell carcinoma of lung origin
- Primary laryngeal malignant melanoma and metastatic melanoma to the larynx

Treatment and Prognosis

- Preferred treatment is nonsurgical and includes chemoradiotherapy:
 - Many patients have disseminated disease at presentation, obviating the option of laryngectomy and neck dissection.
- Highly lethal tumors with aggressive malignant behavior:
 - Metastases are commonly seen to:
 - Regional lymph nodes in a majority of patients (60% to 90%)
 - Liver, lung, bone, and brain
- Prognosis is poor:
 - 2-year survival of 16%
 - 5-year survival of 5%
- 5-year disease-specific survival (DSS) of 19%
- Treatment for combined or composite carcinoma is same as for small cell undifferentiated neuroendocrine carcinoma without combined squamous cell carcinoma or adenocarcinoma.
- In contrast to the relatively favorable prognosis associated with HPV-associated squamous cell carcinomas of head and neck, findings of HPV-associated neuroendocrine carcinomas suggest aggressive behavior despite association with HPV.

Large Cell Neuroendocrine Carcinoma (LCNEC) (Figs. 16-71 and 16-72)

Definition: Neoplasm fulfilling proposed diagnostic criteria for pulmonary large cell neuroendocrine carcinoma, albeit in the larynx.

- Relatively recently defined subtype of NEC likely previously subsumed within the spectrum of atypical carcinoids but distinct from atypical carcinoid histologically and associated with poorer outcome
- Within the classification of neuroendocrine carcinomas, LCNEC belongs with small cell neuroendocrine carcinoma within the spectrum of poorly differentiated neuroendocrine carcinomas.

Clinical

- To date, fewer than 50 cases reported in the literature
- Laryngeal LCNEC:
 - More common in men than women
 - Occur over a wide age range; average age of 59 years
- Symptoms may include hoarseness, dysphagia, odynophagia, otalgia, weight loss, heartburn (pyrosis), and/or cervical adenopathy
- Sites of origin include larynx > oropharynx, sinusal, hypopharynx, nasopharynx:
 - In larynx predilect to supraglottic region
 - With defined criteria (see below) likely will be recognized in other head and neck sites
- Most patients have history of heavy tobacco smoking.
- No known association with HPV

Pathology

Histology (Table 16-8)

- Criteria for diagnosis include:
 - Presence of features of neuroendocrine differentiation including organoid nesting, trabecular growth, rosettes, and peripheral palisading
 - Presence of enlarged tumor cells with vesicular chromatin, small to prominent nucleoli, and moderate to abundant cytoplasm
 - Increased mitotic activity (greater than 10 mitoses per 10 high-power fields [2 mm²])
 - Confirmation of neuroendocrine differentiation using immunohistochemical staining for chromogranin, synaptophysin, neuron-specific enolase, and/or neural cell adhesion molecule (CD56)
 - All four of requisite criteria must be present to make a diagnosis of LCNEC.
- Immunohistochemistry
 - Reactivity for cytokeratin (AE1/AE3):
 - CK5/6 and 34 β E12 typically negative

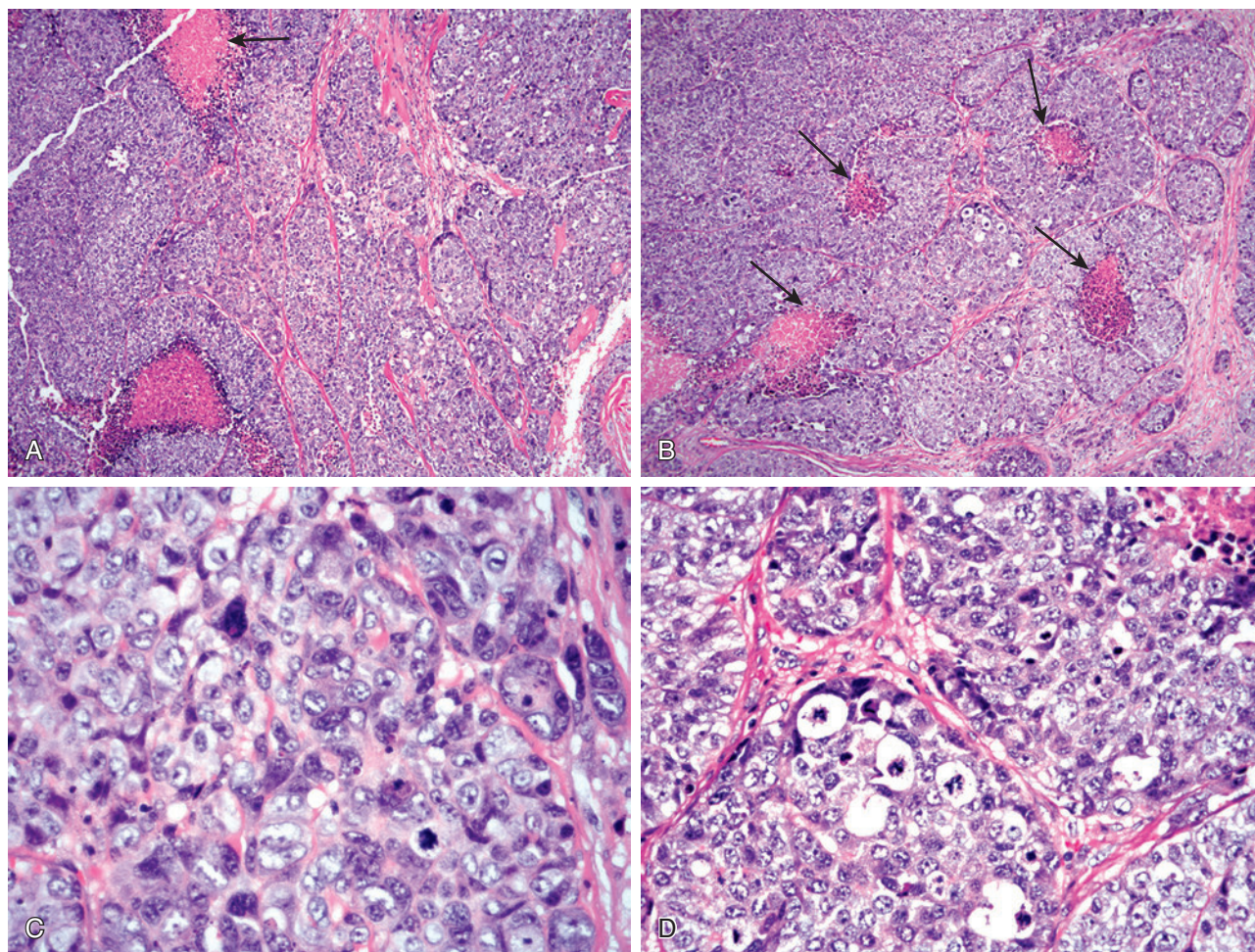


Fig. 16-71. Laryngeal large cell neuroendocrine carcinoma.

The histologic findings seen in large cell neuroendocrine carcinoma of the larynx include (**A** and **B**) presence of features of neuroendocrine differentiation including organoid, cell nest, and/or trabecular growth. **C** and **D**, Presence of large lesional cells vesicular chromatin, identifiable nucleoli, and moderate to abundant cytoplasm as well as increased mitotic activity (overall greater than 10 mitoses per 10 high-power fields [2 mm²]). (Unstained slides provided by James Lewis Jr., MD.)

- Neuroendocrine markers (chromogranin, synaptophysin, and CD56) positive
- Calcitonin and thyroid transcription factor 1 typically negative
- Increased proliferation rates by Ki67 (MIB1) staining typically >20%
- p53 overexpression

Differential Diagnosis

- Atypical carcinoid (AC):
 - Lacks increased mitotic rate, Ki67 labeling indices, p53 immunoreactivity, and low 5-year survival rates associated with LCNEC:
 - Mitotic activity in AC less than 10 mitoses per 10 high-power fields
 - Ki67 indices in AC less than 20% (more on order of less than 10%)

- Absence of p53 overexpression
- 83% 5-year survival as compared with <21% 5-year survival in LCNEC

Treatment and Prognosis

- Preferred treatment is nonsurgical and includes chemoradiotherapy:
 - Many patients have disseminated disease at presentation, obviating the option of laryngectomy and neck dissection.
- Commonly present with advanced stage (stages III and IV):
 - May be metastatic to cervical lymph nodes at presentation
 - May be metastatic to distant sites at presentation (e.g., liver)
- 5-year disease-specific survival (DSS) of 15% to 21%

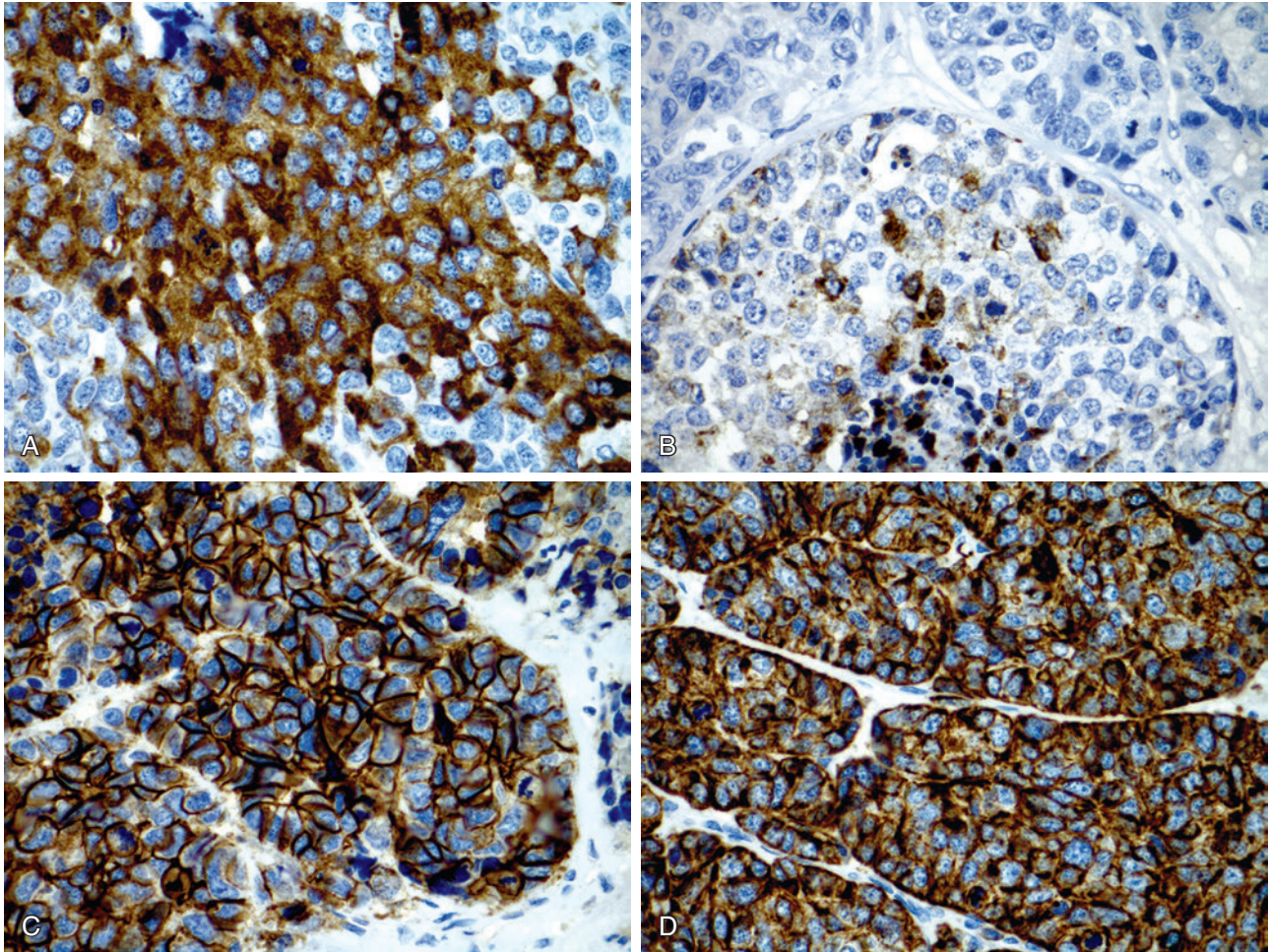


Fig. 16-72. IHC reactivity in laryngeal large cell neuroendocrine carcinoma.

Confirmation of neuroendocrine differentiation by immunohistochemical staining includes reactivity for **(A)** synaptophysin, **(B)** chromogranin (focal positive cells), and **(C)** CD56. **D**, In addition, cytokeratin (CAM5.2) with paranuclear dot-like staining is also present. (Unstained slides provided by James Lewis Jr., MD.)

LARYNGEAL MUCOSAL MALIGNANT MELANOMA

See illustrations under mucosal malignant melanoma of the sinonasal tract.

Definition: Neural crest-derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation.

Clinical

- Approximately 15% to 20% of all malignant melanomas arise in head and neck sites, and of these more than 80% are of cutaneous origin; of the approximate remaining 20%, the majority are of ocular origin.
- Mucosal malignant melanomas (MMM) of the upper aerodigestive tract represent from 0.5% to 3% of melanomas of all sites:

- In the upper aerodigestive tract, the most common site of occurrence is the sinonasal tract.
- Primary laryngeal mucosal malignant melanomas (PLMMM) are rare with fewer than 60 cases reported in the world literature.
- Metastasis to mucosal site must be excluded prior to diagnosing primary mucosal malignant melanoma.

Primary Laryngeal Mucosal Malignant Melanoma (PLMMM)

- Much more common in men than in women, with more than 80% of cases occurring in men; occur over a wide age range from 35 to 86 years of age, with an average age of 58 years, and are most frequent in the sixth and seventh decades of life
- Most cases occur in Caucasians but blacks are also affected.

TABLE 16-8 Pathologic Criteria for Large Cell Neuroendocrine Carcinoma of the Larynx

Requisite Criteria*	Other Typical Features
Tumor cells with moderate to abundant cytoplasm	Nuclei with prominent nucleoli
Features of neuroendocrine differentiation (organoid nesting, trabecular growth, rosettes, and peripheral palisading)	Cellular pleomorphism
Mitotic activity > 10/10 hpf (2 mm ²)	Large areas of necrosis
Confirmation of neuroendocrine differentiation using immunohistochemical staining for chromogranin-A, synaptophysin, neuron-specific enolase, and/or neural cell adhesion molecule (CD56)	

*All four requisite criteria must be present.

From Lewis J, Spence DC, Chiosea S, et al: Large cell neuroendocrine carcinoma of the larynx: definition of an entity, *Head Neck Pathol* 4:198-207, 2010.

- Majority (more than 60% of case in which the site is documented) occur in the supraglottic larynx, including the epiglottis, arytenoids, aryepiglottic folds, ventricle, false vocal cord, and piriform fossa
 - Other less common sites of occurrence include the glottic region along the true vocal cord and the posterior commissure.
 - To date, no documented reports involve the subglottic region.
- Clinical presentation includes hoarseness, dysphagia, sore throat, intermittent hemoptysis, neck or jaw pain, and a cervical neck mass:
 - Symptoms generally occur over short periods of time, ranging from 3 to 6 months.
- Multicentric (synchronous, metachronous) MMM of other upper aerodigestive tract sites are not typically present.
- No known etiologic factors:
 - Occur in patients who smoke tobacco and/or drink alcohol but no definitive link to these risk factors
 - Melanosis, intralaryngeal nevi, and lentigo of the larynx have been reported; given the development of cutaneous malignant melanomas from congenital melanocytic nevi and intradermal nevi, it is possible to suggest that PLMMM may arise from malignant transformation of intralaryngeal melanocytes or melanocytic lesions.

Pathology

Gross

- Nodular, mulberry-like, sessile, polypoid, exophytic, or pedunculated lesions with equally variable color,

including black, brown, red-pink, tan-gray, and white

- Range in size from 3 to 4 mm up to 8.0 cm in greatest dimension

Histology

- Infiltrative tumors composed of epithelioid cells, spindle-shaped cells, or an admixture of cell types
- Epithelioid MMM:
 - Growth patterns vary and include solid, organoid, nested, trabecular, alveolar, or any combination of these patterns.
 - Cells are round to oval, tend to be markedly pleomorphic with increased nuclear-cytoplasmic ratio, vesicular to hyperchromatic nuclei, prominent eosinophilic nucleoli, and eosinophilic to clear-appearing cytoplasm.
 - Nuclear pseudoinclusions and nuclear molding are present.
 - Epithelioid cells may have plasmacytoid features with eccentric located nuclei and an eosinophilic cytoplasm; a paranuclear clear zone is not seen.
- Spindle MMM
 - Growth patterns include storiform or fascicular.
 - Cells are oblong to cigar-shaped, markedly pleomorphic, with large vesicular to hyperchromatic nuclei, absent to prominent nucleoli, and scant eosinophilic cytoplasm.
 - Spindle cells may have an associated myxoid stroma.
 - Tumors with mixed epithelioid and spindle cells can be seen.
- For epithelioid and spindle cell MMM, necrosis and increased mitoses with atypical mitotic figures are common findings; uncommon features include neoplastic giant cells and glandular and squamous differentiation.
- Intracytoplasmic melanin may be present but often melanin pigment is not readily identifiable:
 - May demonstrate presence of heavy melanin deposition but approximately one third of cases have focal, weak pigmentation or are nonpigmented.
 - When present, intracytoplasmic melanin is usually found in scattered cells.
- In the presence of an intact surface epithelium, continuity of the tumor with the surface epithelium (i.e., junctional or pagetoid changes) can be identified; however, even in the presence of intact surface epithelium, junctional changes may not be seen:
 - Given the fact that normal melanocytes may localize to the submucosal compartment within minor salivary glands or within the stroma, junctional change is not required to render a diagnosis of MMM.

- **Histochemistry:**
 - Argentaffin (Fontana stain) and argyrophilic (Churukian-Schenk stain) positive
 - Intracytoplasmic diastase-sensitive, periodic acid Schiff material indicative of glycogen can be seen.
 - Mucin is absent.
- **Immunohistochemistry:**
 - S100 protein positive
 - Melanocytic markers including HMB-45, melan-A, tyrosinase, MiTF, Sox10 positive
 - Vimentin positive
 - Epithelial, neuroendocrine, and hematolymphoid markers are negative.
 - Desmin, actins, myogenin, and myoglobin are negative.
- **Electron microscopy:**
 - The ultrastructural findings of malignant melanoma include the presence of organelles characteristic of melanocytic differentiation; the latter include melanosomes and premelanosomes, both of which are membrane-limited vesicles with distinctive internal structure varying from parallel lamellae to helical to zigzag structures with a periodicity of 8 to 10 nm.

Differential Diagnosis

- Squamous cell carcinoma
- Spindle cell squamous carcinoma
- Neuroendocrine carcinoma
- Inflammatory myofibroblastic tumor

Treatment and Prognosis

- Radical surgical excision is the preferred treatment.
- Adjuvant radiotherapy and chemotherapy of questionable value
- Poor prognosis:
 - 5-year survival rate of less than 20%
- Approximately 80% of patients with PLMMM have metastatic disease to the regional lymph nodes as well as to distant viscera (e.g., brain, lungs, bone).
- Pathologic criteria that are used to predict the biologic behavior in association with cutaneous melanomas, including the depth of invasion, age and gender of the patient, and cytomorphology, generally do not apply for PLMMM; in addition:
 - In some studies prognostic significance has not been found for tumor thickness, level of invasion, ulceration, mitotic index, or nerve/nerve sheath involvement for MMM.
 - Other studies have shown significant adverse prognostic factors for disease-specific survival for MMM of the head and neck linked to advanced clinical stage at presentation, tumor thickness of greater than 5 mm, histologically proven

lymph-vascular space invasion, and metastatic disease (regional and distant).

NONEPITHELIAL MALIGNANT NEOPLASMS OF THE LARYNX

- Nonepithelial malignant tumors of the larynx and trachea are rare and include sarcomas and hematolymphoid malignancies.
- In the larynx, most common sarcoma is chondrosarcoma (see below).
- Other sarcomas that may arise in the larynx and trachea include:
 - Synovial sarcoma
 - Liposarcoma (see below)
 - Rhabdomyosarcoma
 - Leiomyosarcoma
 - Angiosarcoma
 - Malignant peripheral nerve sheath tumor
 - Undifferentiated pleomorphic sarcoma
 - Fibrosarcoma
 - Osteosarcoma
 - Others
- Malignant lymphomas of the larynx and trachea are rare and include:
 - Non-Hodgkin lymphomas:
 - Most are B-cell lymphomas including diffuse large B-cell lymphoma and extranodal marginal B-cell lymphoma of the MALT type
 - Rarely peripheral T-cell lymphomas and NK/T-cell lymphoma of nasal-type
 - Plasmacytoma
 - Hodgkin lymphoma

Chondrosarcoma

(Figs. 16-73 through 16-76)

Definition: Malignant tumor of cartilage.

Clinical

- In general, rare neoplasm in all head and neck sites
- Represents most common nonepithelial malignancy of the larynx, accounting for 75% of all sarcomas of this region, but only represents approximately 1% of all laryngeal tumors:
 - Other sites of involvement include mandible, maxilla, maxillofacial skeleton (nose and paranasal sinuses), nasopharynx.
 - See Section 2, Oral Cavity, for discussion of gnathic chondrosarcomas including mesenchymal chondrosarcoma.
- More common in men than women; may occur over a wide age range but most often occur in the sixth through ninth decades of life

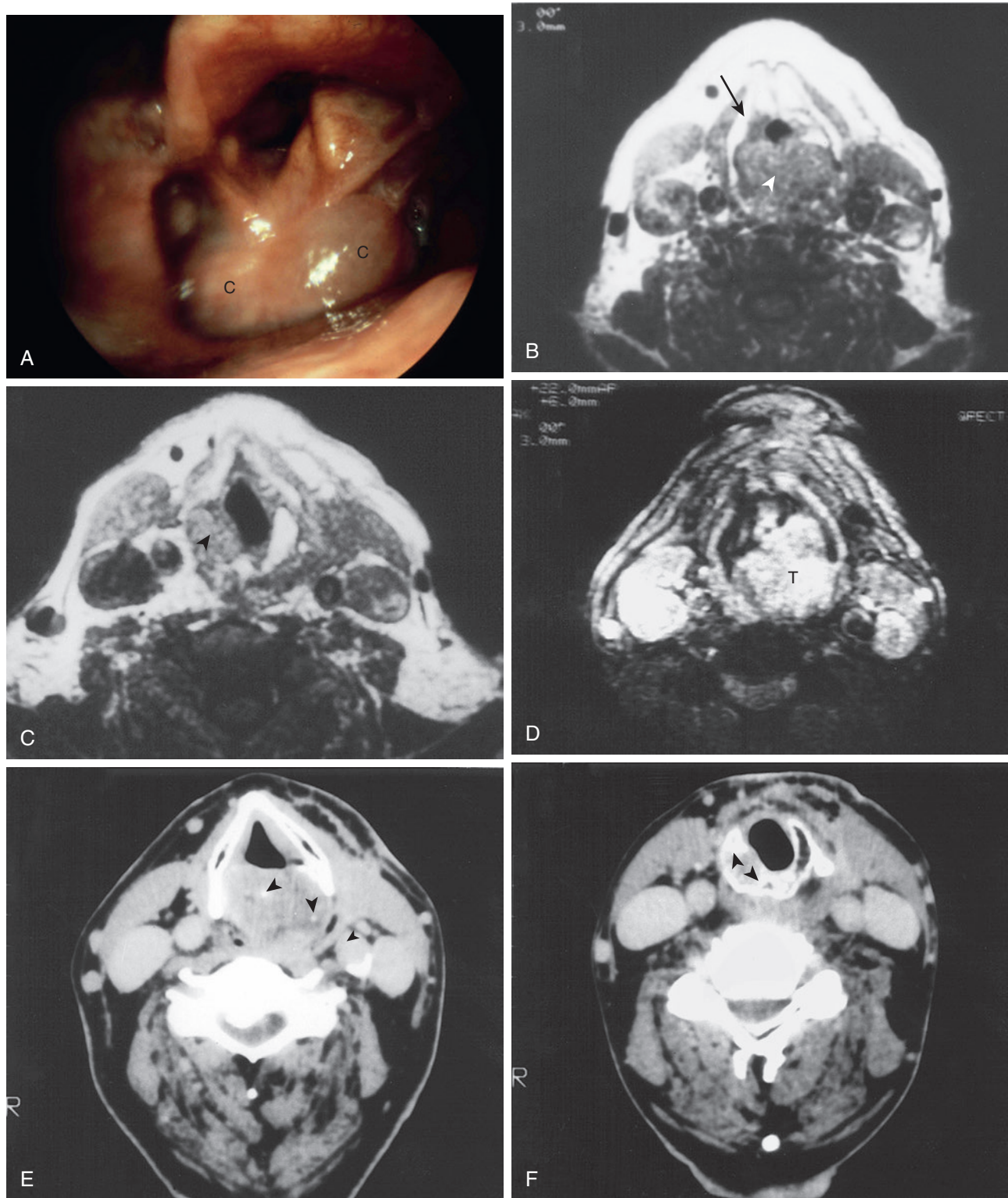


Fig. 16-73. Chondrosarcoma of the larynx.

A, Endoscopic view shows a large bulge in the region of the cricoid (*C*). Note that the mucosa is intact and is not ulcerated. **B**, T1-weighted image shows the large submucosal mass (*arrowhead*). Note its position in the posterior larynx. There is no abnormality in the paraglottic fat (*arrow*). **C**, Slightly lower than **B**. Axial image through the cricoid cartilage shows a well-defined defect (*arrowhead*). The sharp margin would be unusual in invasion by squamous carcinoma. This indicates the origin within the cricoid cartilage. **D**, T2-weighted axial image shows the tumor (*T*) to have the high signal characteristic of chondrosarcoma. **E**, Axial CT shows a large mass with small punctate calcifications (*arrowheads*). This suggests the chondroid nature of the lesion. **F**, Axial scan through the cricoid shows the sharp margin of the lesion (*arrowheads*) as it abuts the normal cartilage. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 31-87, p 1978.)

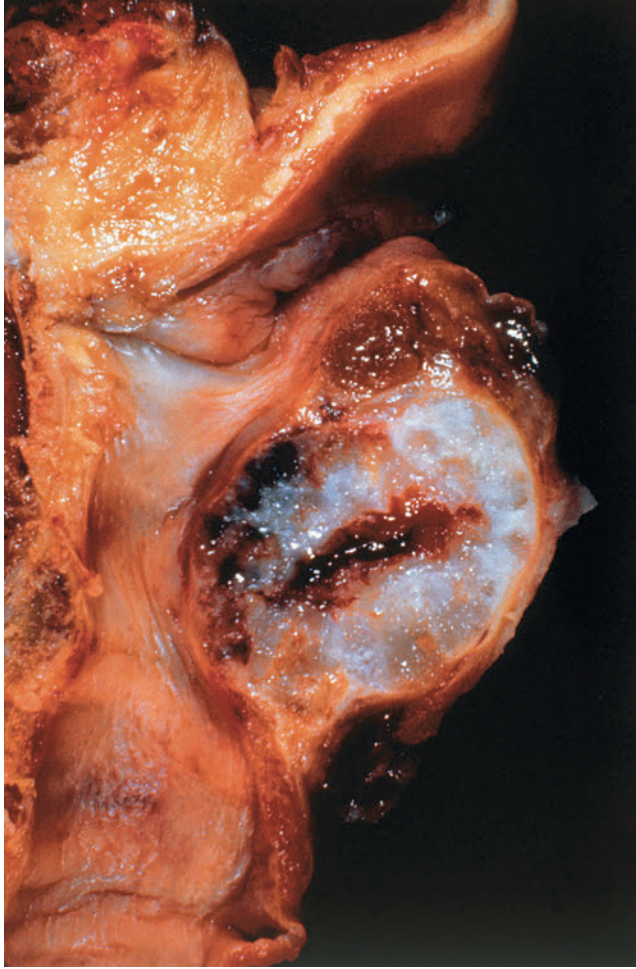


Fig. 16-74. Laryngeal chondrosarcoma.

Laryngeal chondrosarcoma appearing as smooth, lobulated, glistening mass arising from the cricoid cartilage.

- Most common site in the larynx is anterior surface of the posterior lamina of the cricoid cartilage:
 - Less often arises in the thyroid cartilage and arytenoids:
 - Predominantly occur in ossified hyaline cartilages
 - Nearly all cases arise from hyaline rather than elastic cartilage.
- Clinical presentation includes hoarseness, airway obstruction, and dyspnea.
 - Vocal cord paralysis may be present.
 - Involvement of the thyroid lamina may result in the presence of a neck mass.
 - Typically are submucosal appearing endoscopically as a subglottic swelling with overlying intact mucosa
- Radiology:
 - CT scan: circumscribed, hypodense mass with stippled to coarse calcifications resulting in expansion of the affected cartilage
 - MRI: delineates the extent of invasiveness and/or tumor boundaries
- No definitive cause and no link to pre-existing chondroma.

Pathology

Gross

- Bulky tumors that distort site of origin
- On cut section these tumors are solid with a smooth and lobulated appearance, are firm to hard consistency, are gray to white, and often measure greater than 2 cm in diameter.
- Degenerative changes may result in cyst formation, soft areas, and myxoid or gelatinous appearance.
- Fleshy appearance may indicate foci of dedifferentiation.

Histology

- Graded as low-grade or high-grade lesions based on the degree of cellularity, pleomorphism, multinucleated cells, and mitoses:
 - Most laryngeal chondrosarcomas are histologically low grade.
- At low magnification appear lobulated with irregular borders:
 - Invasive growth into adjacent structures can be seen.
- Majority are histologically low-grade that in comparison with chondromas show:
 - Increased cellularity
 - Nuclear hyperchromasia
 - Nuclear pleomorphism
 - Binucleate or multinucleate cells
 - Mitoses are uncommon and necrosis is typically absent.
- High-grade chondrosarcomas are less common:
 - Retaining overall lobular configuration although may only be focally identified
 - Histologically readily apparent as malignant based on the presence of hypercellularity, marked nuclear pleomorphism with bizarre cells, presence of prominent nucleoli, increased mitotic activity, and necrosis.
- In all histologic grades, ossification and/or calcification of hyaline cartilage may be present.
- Can be diagnosed on biopsy but must adhere to strict histologic criteria and clinical/radiologic correlation recommended
- Other histologic subtypes may include clear cell chondrosarcoma and dedifferentiated chondrosarcoma:
 - Clear cell chondrosarcoma:
 - Characterized by chondrocytes with clear cytoplasm and distinct cell membranes

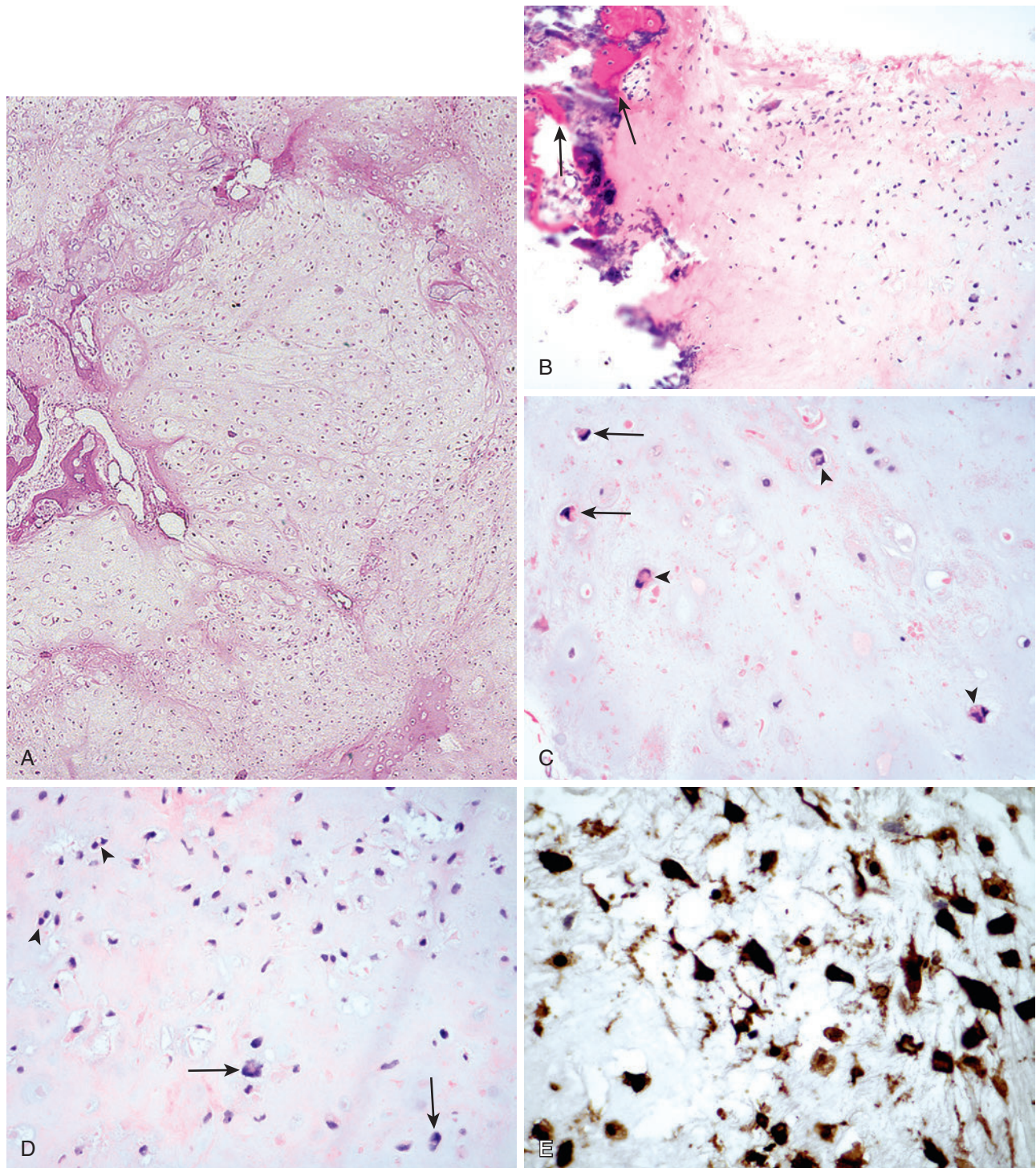


Fig. 16-75. Low-grade laryngeal chondrosarcoma.

Laryngeal chondrosarcoma, low-grade (**A**) lobulated cartilaginous lesion showing increased cellularity; (**B**) occurrence of chondrosarcoma in hyaline cartilage with associated ossification and calcification (*arrows*) is a frequent finding; note the increased cellularity; (**C** and **D**) varying degree of increased cellularity may be present but the presence of binucleate chondrocytes (*arrows*) and nuclear pleomorphism and hyperchromasia (*arrowheads*) is a feature of low-grade chondrosarcoma. These overall findings contrast with those of chondroma, which generally lacks increased cellularity and atypical chondrocytes, but in any given case differentiating low-grade chondrosarcoma from chondroma can be extremely difficult. Lesional cells are immunoreactive for (**E**) S100 protein and

Continued

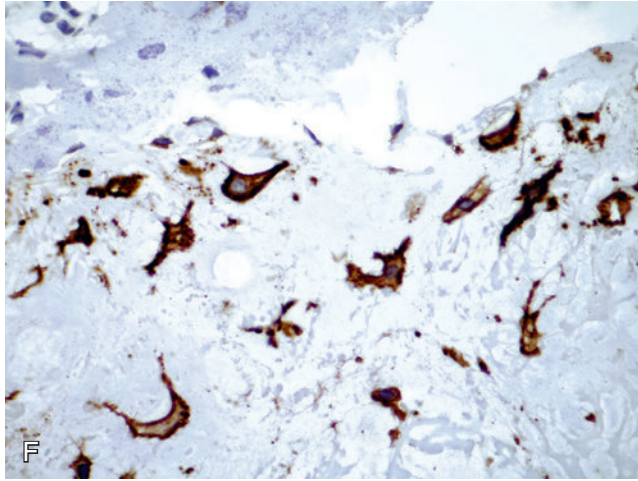


Fig. 16-75, cont'd

(F) podoplanin (D2-40).

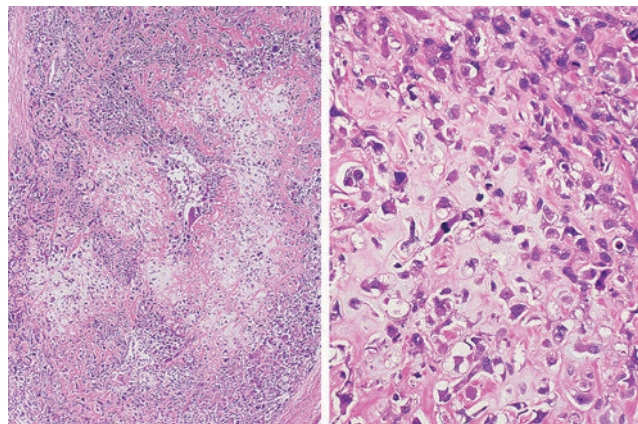


Fig. 16-76. Laryngeal chondrosarcoma, high grade.

Left, Markedly cellular chondroid neoplasm. *Right*, the tumor is composed of pleomorphic cells with hyperchromatic, pleomorphic nuclei, prominent nucleoli, multinucleated cells, and mitoses.

- Dedifferentiated chondrosarcoma:
 - Characterized by the presence of an admixture of differentiated chondrosarcoma with high-grade, noncartilaginous sarcoma
- Immunohistochemistry (all types):
 - Vimentin and S100 protein positive
 - Podoplanin (D2-40) positive

Differential Diagnosis

- Chondroma:
 - May be extremely difficult to differentiate from low-grade chondrosarcoma

- Typically, chondromas are small, measuring less than 1 to 2 cm
- Histologically are characterized by the presence of scattered chondrocytes without nuclear atypia, hyperchromasia, binucleate, or multinucleate cells or mitoses.
- S100 protein and podoplanin (D2-40) positive
- Any purportedly recurrent chondroma likely represents a chondrosarcoma.
- Chondromatous metaplasia/hamartoma (chondro-metaplasia):
 - May present as a nodular mass of the larynx associated with progressive dysphonia, dyspnea, and dysphagia
 - History of laryngeal trauma
 - CT scan shows a rounded and circumscribed mass without infiltration of the surrounding tissues.
 - Histologically characterized by the nodular fibro-elastic cartilaginous tissue surrounded by a thin rim of fibrous tissue; rare hypercellular areas and occasional binucleated cells with slight hyperchromasia and irregular nuclear profiles may be seen but mitotic activity was absent
 - History of laryngeal trauma with the subsequent progressive onset of clinical symptoms helps to distinguish the chondrometaplastic nodule from true laryngeal cartilaginous tumor (e.g., chondroma and chondrosarcoma).
- Chordoma

Treatment and Prognosis

- For laryngeal chondrosarcoma treatment includes wide local (conservation) excision:
 - Conservative (organ sparing) surgery if feasible is recommended:
 - Endoscopic resection can be used for managing selected newly diagnosed cases of cricoid chondrosarcoma.
 - Organ preservation surgery represents a treatment option.
 - Total laryngectomy recommended in presence of high-grade histology, in presence of extensive cricoid involvement, and/or when conservative surgery is not possible
- Radiotherapy and chemotherapy not demonstrated to be effective therapeutic modalities
- In general, cure is achieved following complete excision of the tumor
 - Local recurrence occurs in approximately 25% of cases and can be managed by additional (definitive) surgery.
 - Recurrence is associated with incomplete excision and may occur years after initial diagnosis:
 - Long-term follow-up advised

- Distant metastases are uncommon but can occur (lungs).
 - Presence of higher-grade morphology and/or dedifferentiation more likely to be associated with metastasis
- 1-year, 5-year, and 10-year disease-specific survival reported as 96.5%, 88.6%, and 84.8%, respectively

Liposarcoma (Figs. 16-77 through 16-82)

Definition: Malignant tumor of adipocytes.

- Arise from primitive mesenchymal cells rather than mature adipose tissue, accounting for its presence in areas relatively devoid of fat (e.g., head and neck)

Clinical

- Represent 15% to 25% of all sarcomas
- Approximately 3% to 6% occur in head and neck:
 - In head and neck the most common sites of occurrence include the larynx and hypopharynx followed by the neck.
- For laryngeal and hypopharyngeal liposarcoma:
 - Tends to affect men more than women; occur over a wide age range but are most common in the sixth and seventh decades of life
- For neck liposarcomas:
 - No gender predilection; occur over a wide age range but usually occur in younger ages (approximately a decade younger) than non-head and neck liposarcomas
- Symptoms vary per site of involvement and size of the tumor:
 - Larynx: hoarseness, dysphonia, dysphagia, airway obstruction
 - Pharynx: dysphagia and airway obstruction
 - Neck: slowly growing painless mass
- Arise de novo; rarely originate from a pre-existing lipoma
- No known associated etiologic factors

Pathology

Gross

- Circumscribed and/or encapsulated, lobulated mass varying in appearance from yellow to tan-white and with a myxoid or gelatinous appearance
- Although liposarcomas can attain very large sizes, those identified in the head and neck rarely exceed 10 cm and are generally under 5 cm in greatest dimension.

Histology

- WHO classification includes:
 - Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL)
 - Dedifferentiated liposarcoma (DL)

- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma (PL)

Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma (ALT/WDS)

- Most common morphologic type (30% to 40%) in late adult life
 - Most common morphologic type in relationship to upper aerodigestive tract liposarcomas
- Often diagnosed as lipoma due to its bland histology and only following one or more recurrences is a diagnosis of liposarcoma rendered.
- Histologically resembles a lipoma except for:
 - Greater variation in the size and shape of the adipocytes
 - Presence of scattered lipoblasts:
 - Absence of lipoblasts does not preclude a diagnosis of well-differentiated liposarcoma.
 - Absence of encapsulation
- Term atypical lipoma or atypical lipomatous tumor has been used for superficial (cutaneous or subcutaneous) lipogenic tumors with histologic appearance of well-differentiated liposarcomas that have a tendency to recur.
 - Use of this terminology should be viewed with caution in those well-differentiated liposarcomas occurring in more vital areas (deep neck, nasopharynx, sinonasal cavity, larynx, and hypopharynx) where inadequate excision and subsequent recurrence may result in increased morbidity and mortality.
 - Use of well-differentiated liposarcoma rather than atypical lipoma should convey to the surgeon that the neoplasm requires complete resection in as conservative a manner as to ensure tumor-free margins and not just simple excision.

Dedifferentiated Liposarcoma (DL)

- Histologic progression of ALT/WDL to a higher-grade, less well-differentiated neoplasm in:
 - Primary (de novo) neoplasm (90%)
 - Recurrent neoplasm (10%)
- High-grade component usually is nonlipogenic and only rarely is lipogenic.
- Accounts for 18% of all liposarcomas
- Most common site of occurrence is retroperitoneum >>> extremities
- Less than 20% occur in H&N (and other) sites
- Histology:
 - In approximately 90% dedifferentiated component has appearance of high-grade fibrosarcoma or undifferentiated pleomorphic sarcoma
 - Display range of subtypes including:
 - Most common: storiform-pleomorphic and myxoid forms



Fig. 16-77. Laryngeal liposarcoma.

A, Laryngeal liposarcoma appearing as a circumscribed polypoid, pedunculated mass. **B**, Resected hypopharyngeal liposarcoma with characteristic yellow appearance. **C** and **D**, This patient had a large hypopharyngeal-based mass that he was capable of “bringing up” at will; the tumor was excised via a lateral pharyngotomy approach.

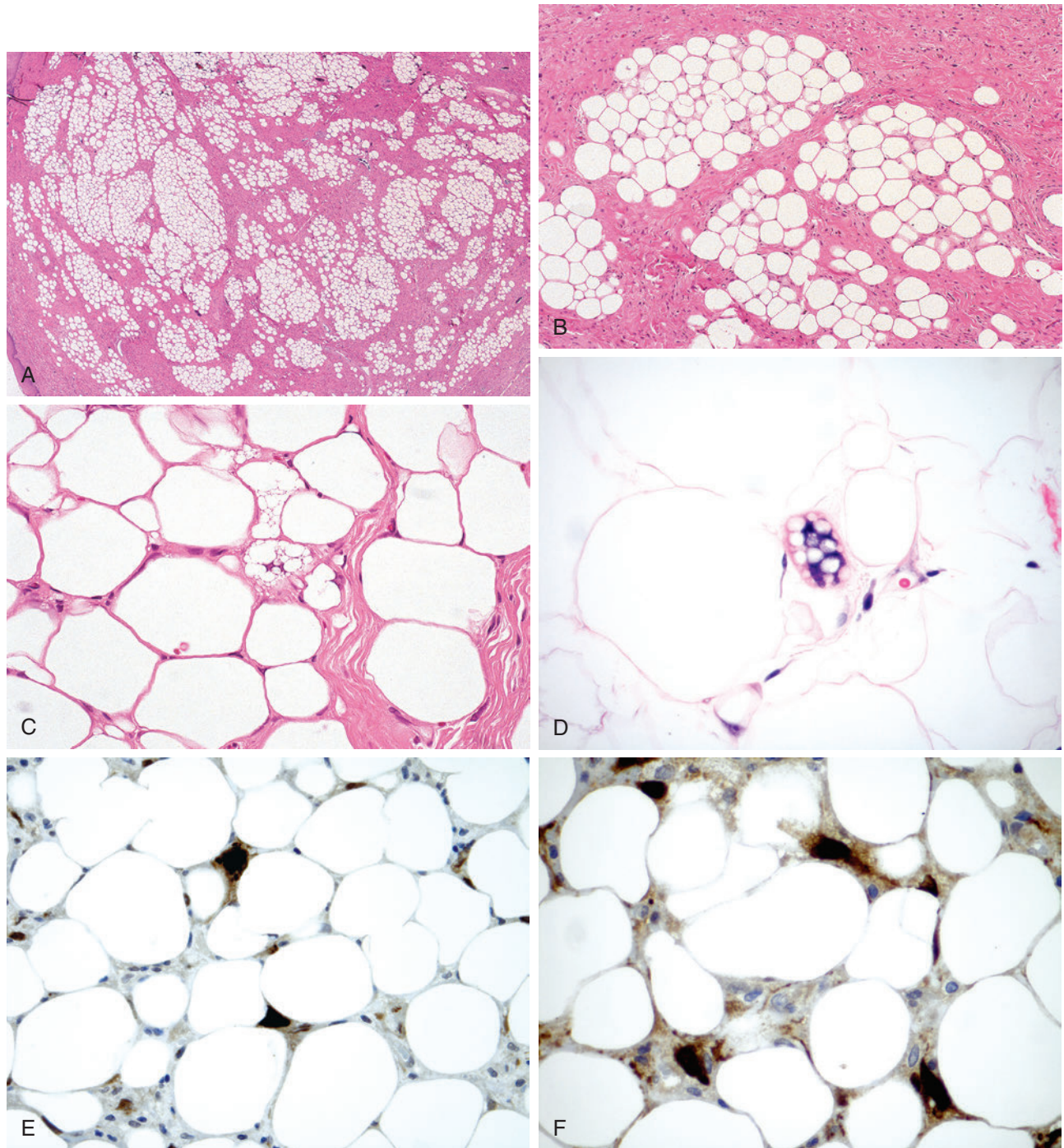


Fig. 16-78. Laryngeal well-differentiated liposarcoma.

Laryngeal atypical lipomatous neoplasm/well-differentiated (lipoma-like) liposarcoma. **A**, Submucosal (surface squamous epithelium in lower left) adipose tissue proliferation composed of nests of fat cells separated by fibrous septa.

B, Adipocytes show variation in size and shape. **C** and **D**, Multivacuolated lipoblasts. Immunohistochemical staining assists in the diagnosis with reactivity for **(E)** MDM2 and **(F)** CDK4. These markers are absent in lipomas.

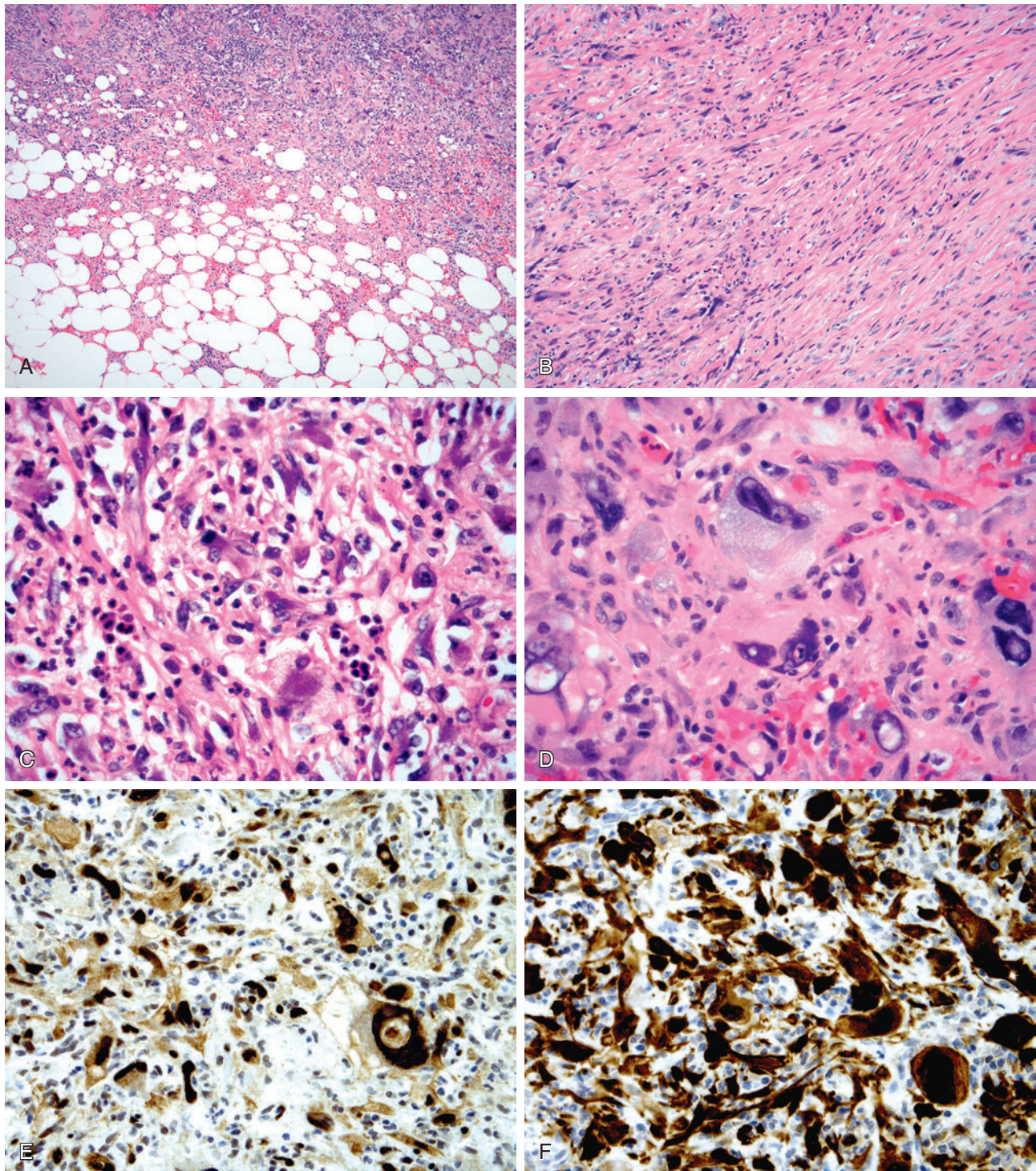


Fig. 16-79. Dedifferentiated liposarcoma.

A, Cervical neck dedifferentiated liposarcoma showing transition or interface between atypical lipomatous tumor/well-differentiated liposarcoma (*bottom half*) and dedifferentiated zone (*top half*). **B**, Area showing appearance of fibrosarcoma. **C** and **D**, Areas resembling undifferentiated pleomorphic sarcoma. The presence of immunoreactivity for **(E)** MDM2 and **(F)** CDK4 supports a diagnosis of dedifferentiated liposarcoma and allows for differentiation from other sarcomas (e.g., fibrosarcoma, undifferentiated pleomorphic sarcoma).

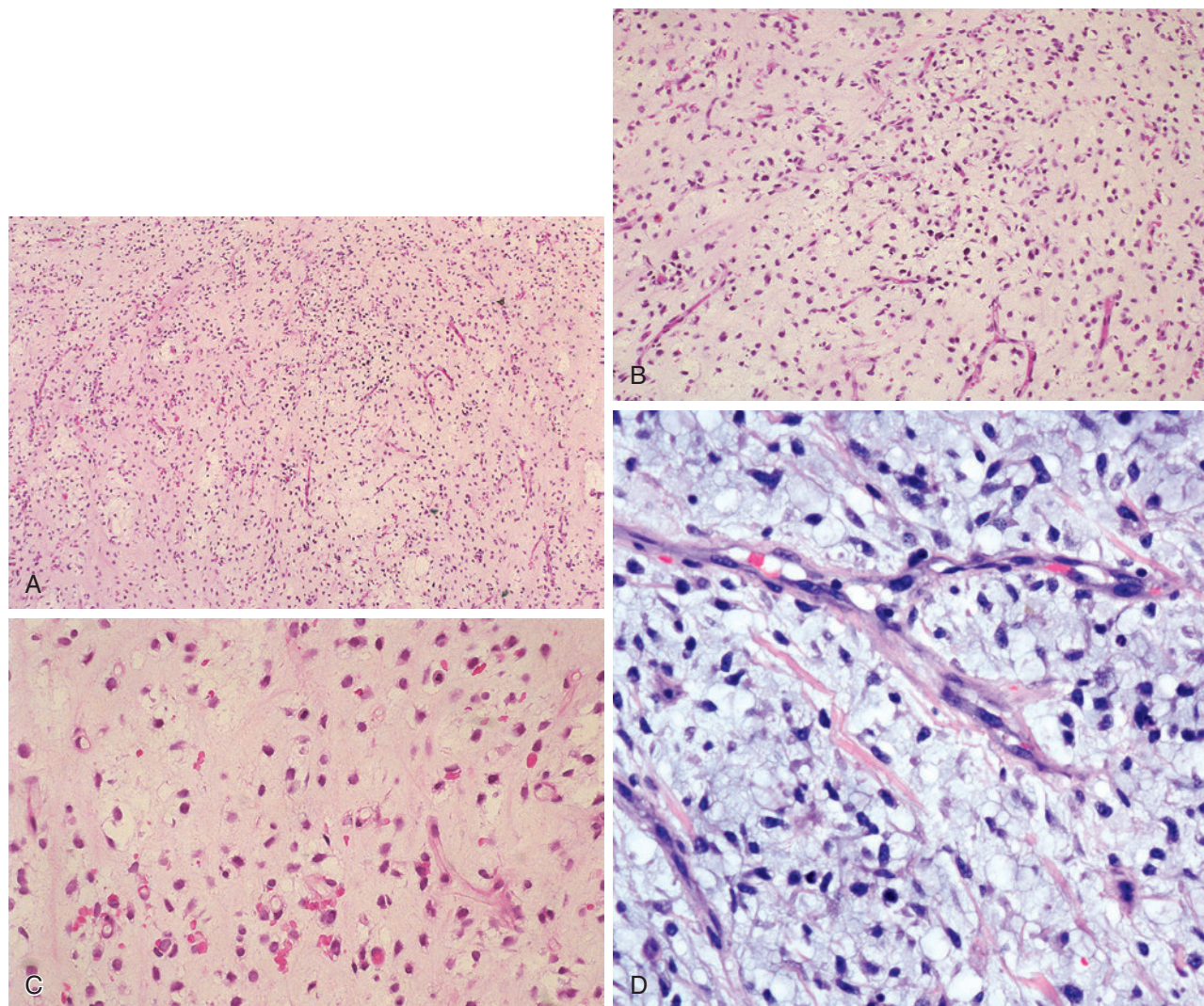


Fig. 16-80. Laryngeal myxoid and round cell liposarcoma.

Cellular myxoid lesion with plexiform capillary pattern plexiform vascularity with a delicate arborizing (capillary-like) pattern and lipoblasts in varying stages of development including signet-ring appearance. Myxoid liposarcoma is typically negative for MDM2 and CDK4.

- Less common: giant cell and inflammatory forms
- In approximately 10% may resemble low-grade fibrosarcoma or fibromatosis

Myxoid Liposarcoma

- Continuum of lesions that include differentiated myxoid tumors with lipoblastic differentiation to poorly differentiated round cell tumors with inconspicuous lipoblastic differentiation; included in this category are lesions previously referred to as round cell liposarcoma.
- Represents one third to one half of all liposarcomas
- Occurs in younger age group than ALT/WDL and DL:
 - Peak incidence in fifth decade of life
- Most common in lower extremity (75% of cases):
 - Medial thigh > popliteal area
 - Less commonly occurs in retroperitoneum
 - Rare in head and neck
- Myxoid liposarcoma characterized by:
 - Lobular or nodular growth
 - Uniform round to oval mesenchymal (nonlipogenic-appearing) cells
 - Variable numbers of signet ring lipoblasts are present:
 - Usually readily identifiable
 - May be most prominent at periphery of nodules
 - Prominent myxoid stroma rich in glycosaminoglycans or hyaluronidase-sensitive acid
 - Mucopolysaccharides

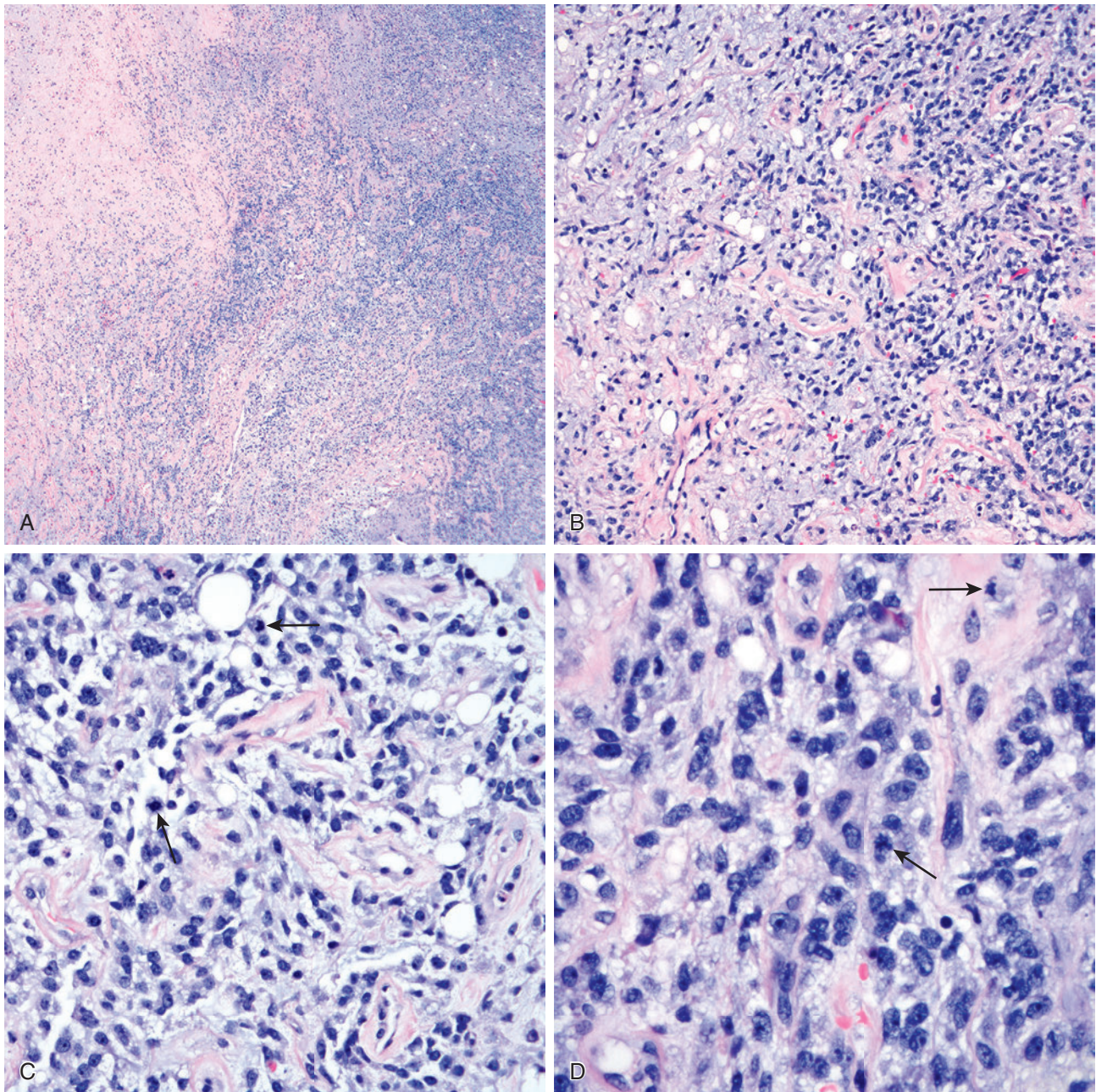


Fig. 16-81. Laryngeal myxoid and round cell liposarcoma.

Laryngeal myxoid/round cell liposarcoma. **A** and **B**, Transition from myxoid area (*left*) to cellular area composed of round cells. **C** and **D**, Densely cellular proliferation solid sheets of primitive round cells with hyperchromatic nuclei, enlarged nucleoli, increased nuclear-to-cytoplasmic ratio, vacuolated-appearing cytoplasm, and increased mitotic activity (*arrows*). Myxoid/round cell liposarcomas are typically negative for MDM2 and CDK4.

- Delicate plexiform capillary vascular pattern present:
 - Represents an important diagnostic clue
 - Assists in differentiating from benign tumors (e.g., myxoma, others)
- Cellular component typically lacks nuclear pleomorphism, significant mitotic activity, or tumor giant cells.
- Extracellular mucin pools or lakes creating a lymphangioma-like appearance can be identified.

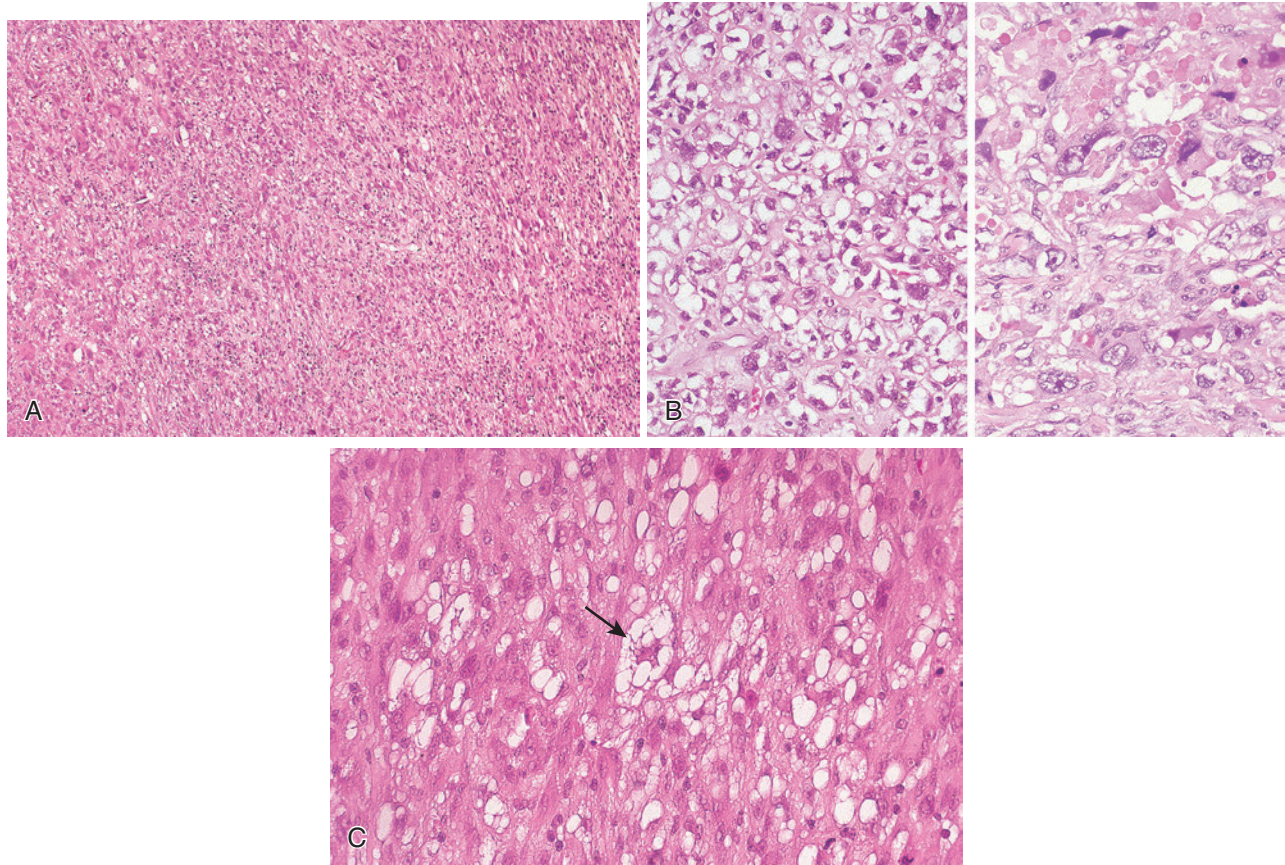


Fig. 16-82. Cervical neck pleomorphic liposarcoma.

A, Cellular tumor composed of spindle and multinucleated giant cells. **B**, *Left*, markedly pleomorphic cells with cytoplasmic vacuolization; *right*, extra- and intracellular eosinophilic hyaline globules. **C**, Multivacuolated lipoblast (arrow). Pleomorphic liposarcomas are typically negative for MDM2 and CDK4.

- Cartilaginous, osseous, leiomyomatous differentiation may occur; rarely, rhabdomyosarcomatous differentiation may be present.
- Round cell liposarcoma:
 - Represents poorly differentiated form of myxoid liposarcoma characterized by the presence of:
 - Densely cellular proliferation solid sheets of back-to-back primitive round cells with hyperchromatic nuclei, prominent nucleoli, increased nuclear-to-cytoplasmic ratio, and granular to vacuolated-appearing cytoplasm
 - Increased mitotic activity as well as necrosis and hemorrhage are present.
 - Sparse to absent intervening myxoid, fibrillar, or myxomucinous stroma
 - Plexiform capillary vascular pattern present but generally compressed by the cellular proliferation
 - Presence of transitional areas from myxoid to hypercellular round cell supports contention that myxoid and round cell liposarcomas represent a histological continuum of myxoid liposarcomas:
- Further support of this consideration is the presence of shared chromosomal aberrations (see below).

Pleomorphic Liposarcoma

- High-grade sarcoma composed of:
 - Variable numbers of pleomorphic lipoblasts characterized by spindle and giant cells with one or more enlarged hyperchromatic nuclei scalloped by cytoplasmic vacuoles
 - Cytoplasmic vacuoles contain lipid droplets.
 - Majority of tumors have fascicles of spindle-shaped cells and smaller, round cells admixed with multinucleated giant cells resembling such tumors as undifferentiated pleomorphic sarcoma, as well as the pleomorphic lipoblasts
 - Limited lipoblastic features may be present.
 - Prominent cytoplasmic eosinophilia may be present and in the presence of limited lipoblastic findings may suggest a diagnosis of rhabdomyosarcoma.

- Extra- and intracellular eosinophilic hyaline globules may be identified and likely represent lysosomal structures.
- Absence of areas of ALT/WDL or other line of differentiation
- Epithelioid variant:
 - Predominantly composed of solid, cohesive sheets and clusters of epithelioid cells with round to oval nuclei, prominent nucleoli, eosinophilic cytoplasm, and distinct cell borders
 - Focally, lipogenic differentiation in the form of pleomorphic lipoblasts is present.
 - Often associated with a higher mitotic rate than is seen in association with pleomorphic (nonepithelioid) liposarcoma.
- Tumor necrosis is present in all morphologic types of pleomorphic liposarcoma.

Mixed Type Liposarcoma

- Extremely rare, representing approximately 5% (or less) of all liposarcomas
- Primarily occur in retroperitoneum
- Histologically defined by the presence of combined:
 - Classic WDL associated with classic pleomorphic liposarcoma
 - ALT/WDL with myxoid/round cell and well-differentiated/dedifferentiated liposarcoma
 - Myxoid/round cell and pleomorphic liposarcoma
- Molecular testing has allowed for classification of some of these mixed-type liposarcomas within one of neoplasm within current WHO classification.

Spindle Cell Liposarcoma

- Considered to represent rare atypical/low-grade malignant lipogenic neoplasm regarded as a variant of atypical lipomatous tumor
- Tends to occur in subcutaneous tissue of the extremities, trunk, and head and neck region
- Histologically, variably cellular neoplasms composed of atypical lipogenic cells showing variations in size and shape, and spindled tumor cells with slightly enlarged, often hyperchromatic nuclei:
 - Multivacuolated lipoblasts may be present.
 - Focal myxoid stromal changes may be present.
- Immunohistochemically:
 - CD34 at least focally positive
 - Only scattered cells in limited cases may show nuclear expression of MDM2.
 - FISH analysis negative for MDM2/CDK4 amplification
- Based on clinicopathologic and molecular findings may represent atypical/low-grade counterpart of spindle cell lipoma rather than morphologic variant of ALT/WDL

General Histologic Considerations

- Lipoblasts:
 - Neoplastic cell recapitulates differentiation cascade of normal fat:
 - Hyperchromatic indented or scalloped nucleus
 - Lipid-rich droplets in cytoplasm
 - Appropriate histologic background
 - Importance overemphasized
 - Few present in ALT/WDL:
 - Pattern and cellular components more important
 - Simulators of lipoblasts:
 - Reactive changes (fat necrosis; atrophy; foreign body reaction)
 - Fixation artifact
 - Signet ring cells in other neoplasms
- Mitoses, necrosis, and hemorrhage can be identified in all histologic variants and generally correlate to the amount of cellular pleomorphism (mitoses are particularly prominent in the pleomorphic variant).
- Histochemistry:
 - Special stains are of little if any assistance in diagnosis.
- Immunohistochemistry:
 - Adipocytes and lipoblasts variable S100 protein immunoreactive
 - Vimentin positive
- Cytogenetics and immunohistochemistry:
 - ALT/WDL:
 - Characterized by giant marker and ring chromosomes:
 - Contain amplified sequences 12q13-15, site of several genes (MDM2, CDK4, others)
 - MDM2 (and HMGA2) consistently amplified
 - CDK4 co-amplified in approximately 90%
 - MDM2 and CDK4
 - IHC:
 - ◻ MDM2 and CDK4 detected in majority of ALT/WDL: (nuclear staining) is a reasonable first tool in diagnosis
 - FISH:
 - ◻ Highly sensitive and specific
 - ◻ Superior to immunohistochemistry
 - ◻ Small false-positive rate
 - Absent in lipomas
 - Small percentage of spindle cell/pleomorphic lipoma express MDM2 and CDK4
 - Recommendation for use:
 - ◻ Lipomatous tumors with equivocal cytologic atypia
 - ◻ Recurrent lipomas
 - ◻ Deep lipomas with atypia >15 cm
 - ◻ Retroperitoneal and intra-abdominal tumors without atypia

- Dedifferentiated liposarcoma:
 - Share similar findings as ALT/WDL although display more extensive chromosomal abnormalities
 - 12q13-15 amplifications more complex than in ALT/WDL
 - IHC:
 - MDM2 and CDK4 reactivity
- Myxoid and round cell liposarcoma:
 - Characterized by reciprocal t(12;16)(q13;p11) translocation:
 - Present in more than 90% of cases
 - Results in fusion of the *DDIT3* gene on chromosome 12 with *FUS* gene on chromosome 16:
 - Presence of *FUS/DDIT3* fusion sensitive and specific for myxoid liposarcoma
 - Chimeric *FUS-DDIT3* gene results in 3 fusion transcripts:
 - Type II identified in most myxoid/round cell liposarcomas
 - Staining for MDM2 and CDK4 typically negative
- Pleomorphic liposarcoma:
 - Various chromosomal gains and losses
 - Dysregulation of several tumor suppressor pathways common
 - No amplification of 12q14-15 region
 - Staining for MDM2 and CDK4 typically negative
- Recurrence is common:
 - Generally occurs within 3 years after the initial treatment
 - Usually same histology as the primary tumor but may “dedifferentiate” with a histologic appearance less differentiated and with a more aggressive biology than the primary tumor.
- Nodal metastasis rare and neck dissection generally not indicated
- Distant metastasis may occur and are more common with the higher-grade histologic variants:
 - Metastases occur to the lungs, bone, and liver.
- 5-year survival rate for all liposarcomas of the head and neck approximately 67%
- 5-year survival rates influenced by histologic type:
 - Well-differentiated:
 - 85% to 100% 5-year survival
 - Myxoid:
 - 71% to 95% 5-year survival
 - Round cell:
 - 12.5% to 55% 5-year survival
 - Pleomorphic:
 - 0 to 45% 5-year survival
- In addition to histologic type, other factors important in prognosis include:
 - Size of the tumor
 - Location of the tumor:
 - Laryngeal/hypopharyngeal and facial tumors have the best prognosis.
 - Mouth and pharynx have the worst prognosis.
- Controversy exists as to the issue of multicentric occurring liposarcomas vs. metastatic liposarcoma:
 - Presence of clonality in multifocal myxoid liposarcoma supportive of metastasis rather than multifocal tumor

Differential Diagnosis

- Lipoma
- Myxoma (intramuscular; nerve sheath)
- Other sarcomas:
 - Rhabdomyosarcoma
 - Undifferentiated pleomorphic sarcoma
 - Myxoid chondrosarcoma
 - PNET/Ewing sarcoma
- Chordoma
- Signet ring cell carcinoma or lymphoma
- Malignant melanoma

Treatment and Prognosis

- Wide local surgical excision is the preferred treatment to include tumor-free margins.
 - More aggressive surgical procedures may be indicated for the other histologic variants.
- Utility of radiotherapy remains controversial, but evidence supports the use of postoperative radiotherapy as an adjunct to surgery:
 - In cases in which the tumor cannot be completely resected
 - In cases in which surgical margins are close

SECONDARY TUMORS

- Metastatic tumors to the larynx and trachea are rare.
- Most common tumor types to metastasize to this region include malignant melanoma and various carcinomas including those originating from the kidney, breast, lung, prostate, gastrointestinal tract (e.g., colon, stomach); less frequently, metastasis may originate from the female genital tract, kidney, thyroid gland, and other sites.
- In the larynx, most common site of metastasis is supraglottis followed by the subglottis:
 - Supraglottis and less so the subglottis are richly vascularized as compared with the glottic

region, accounting for the greater incidence of metastasis to the supraglottic and subglottic larynx.

- Symptoms vary per site of involvement:
 - Larynx: hoarseness, dysphagia, and/or pain
 - Trachea: cough, dyspnea, stridor, and hemoptysis
- Metastasis usually localizes to the submucosa or to cartilage that has undergone ossification.

- Metastasis to the larynx and trachea often occurs in the setting of disseminated disease in terminal or near-terminal patients.

FURTHER READING

References may be accessed online at [ExpertConsult.com](#).

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Intraoperative Consultation of Laryngeal Lesions

- Issues relative to intraoperative consultation of laryngeal mucosal margins are similar to those discussed for intraoperative consultation of oral cavity mucosal lesions. The reader is referred to Section 2 for more detailed discussion, including illustrations.
- This section is an overview of the overlapping issues with the intraoperative consultation of laryngeal mucosal lesions and those of the oral cavity previously discussed in Section 2, Oral Cavity.

INDICATIONS

- Indications for intraoperative consultation of mucosal lesions of the upper aerodigestive tract include:
 - Render a histologic diagnosis (e.g., carcinoma/dysplasia) when definitive therapeutic intervention is planned immediately:
 - In laryngeal tumors most frequent indication for use of frozen section is documentation of residual tumor status
 - Intraoperative consultation with the purpose of primary tumor diagnosis is less common and discouraged.
 - Assessment of the adequacy of resection (i.e., surgical resection margins)
 - Preliminary assessment of the nature of a planned procedure based on the extent and distribution of the neoplasm (e.g., subtotal versus total laryngectomy)
 - Adequacy for diagnostic purposes (e.g., lymphoma)
 - Determination for special handling (e.g., immunohistochemistry, flow cytometry, microbiologic cultures)
 - Determination of neurotropism, lymph-vascular space invasion (LVI), or soft tissue involvement that may necessitate a more extensive resection
 - If lymph nodes are excised, then a frozen section may be requested to exclude the presence of metastatic disease and the need for a neck dissection.

SURGEON'S EXPECTATIONS

- Establish diagnosis of carcinoma/dysplasia and differentiate it from look-alike lesions.
- Confirm presence or absence of lesional tissue at the margins of resection.
- When applicable, identify the presence of osseous involvement.
- When applicable, identify the presence of nodal metastasis.

SPECIMEN HANDLING AND ORIENTATION

- Evaluation of surgical margins of resection for the presence or absence of lesional tissue falls under the purview of the surgical pathologists; however, how the specimen is removed and the orientation of the specimen is the responsibility of the surgeon:
 - Particularly true for those cases in which the tumor is initially excised and the designated margins are separately removed, the tumor is removed in multiple parts or the specimen is a complex en bloc excision requiring proper orientation by the surgeon for those margins that are of critical concern.
- Once removed and properly oriented, the specimen becomes the responsibility of the surgical pathologist.
- There is no standard method by which surgeons remove tissue and thereby request intraoperative consultation of the surgical resection margins; some approaches include:
 - Excision of the entire lesion, designation of specific margins, and tissue selection by the pathologist for frozen section
 - Circumferential resection margins are submitted for frozen section regardless of the number of frozen sections that may be required to completely evaluate the circumferential margins.
 - A limited number of frozen sections (e.g., up to four: anterior, posterior, medial, and lateral) are submitted as determined by the pathologist.

NOTE: Anatomy of the head and neck is complex, and in any given resection the risk posed by removing the entire lesion and surrounding structures for intraoperative consultation includes:

- Loss of the three-dimensional orientation of the specimen
- Erroneous sampling of the areas of concern
- Submission of biopsies from areas of clinical concern following the main resection and these biopsies are entirely submitted for frozen section.

DEFINITION OF A “POSITIVE” MARGIN

- Specimens in which no tumor or dysplasia is present at the surgical margins of resection are considered as completely excised.
- “At the margin of resection” means the neoplastic cells are seen in contact with or lie within millimeters of the pigment that was painted along the margin prior to sectioning (i.e., tumor across or up to the resection margin):
 - In this situation, the specimen is considered incompletely excised, requiring a wider excision to be assured that all viable tumor cells have been adequately removed.
- Sole reliance of margins as assessed on the resected specimen should be discouraged and, when feasible, intraoperative evaluation of tissue surrounding the specimen should be made and have that regarded as the “true margin.”
- Histologic definition of what constitutes a “positive” margin should be uniformly accepted and applied:
 - Discrepancy in the literature as to what constitutes a positive or negative resection margin
 - Some authorities include only invasive carcinoma at the margin as positive, excluding carcinoma intraepithelial dysplasia/carcinoma in situ and gross residual disease.
 - Most pathologists would agree with the classification of positive margins as defined by:
 - Presence of lesional tissue within 0.5 mm of the surgical margin (so-called close margins) with the exception of laryngeal lesions
 - Significant dysplastic epithelium at the margin:
 - High-grade squamous intraepithelial dysplasia to include moderate dysplasia and severe dysplasia/carcinoma in situ at a margin of resection is considered a positive margin
 - Invasive carcinoma at the margin
- Although frozen section diagnosis of surgical margins is extremely accurate, it is not entirely reliable in eliminating positive margins in the final diagnostic report.

ADEQUACY OF RESECTION MARGINS

- Presence of lesional tissue within 5 mm of the inked surgical margin regardless of whether it is invasive carcinoma or carcinoma in situ/severe dysplasia places a patient at a nearly equal risk for local recurrence:
 - These margins are associated with approximately 80% incidence of recurrent disease.
 - Absence of positive margins does not guarantee local control of disease nor is it a reliable guide to the biologic behavior of a tumor.
 - Presence of positive margins increased the likelihood of local recurrence but does not affect survival because subsequent surgery and/or irradiation may control tumor recurrence in some of their patients.
- The question of how wide a tumor should be excised is the responsibility of the surgeon:
 - For some specimens such as the larynx, free margins up to 5 mm may be sufficient:
 - Laryngeal margins with margins of ≤ 2 mm have 5-year survival rate similar to patients with tumor at the resected margin.
 - Patients with resected larynges including margin clearance >2 mm have essentially similar outcomes as patients with wider margin clearance.
 - With a similar tumor at another extralaryngeal site, such as the oral cavity and pharynx (oropharynx, hypopharynx), wider margins (1.0 cm) are optimal.

FURTHER READING

References may be accessed online at ExpertConsult.com.

FURTHER READING

Intraoperative Consultation of Laryngeal Lesions

Please also see references for Intraoperative Consultation listed in Section 2, Oral Cavity.

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Embryology, Anatomy, and Histology of the Salivary Glands

- Salivary gland system composed of exocrine glandular tissue that include major salivary glands and minor salivary glands:
 - Major salivary glands include:
 - Parotid gland
 - Submandibular (submaxillary) gland
 - Sublingual gland
 - Minor salivary (seromucous) glands include:
 - Small aggregations within the submucosa of the upper aerodigestive tract
- All salivary glands share basic structure but vary per site in their function, secretions, gross and microscopic features:
 - Major and intraoral minor salivary glands produce fluids that constitute oral saliva.
 - Minor salivary (seromucous) glands outside the oral cavity including sinonasal tract, pharynx, larynx, trachea, bronchi are morphologically and functionally similar to oral minor salivary glands but in contrast do not contribute to saliva

EMBRYOLOGY OF THE SALIVARY GLANDS

- All salivary glands develop as solid proliferations or buds from the epithelium of the stomodeum during the fifth and sixth weeks of gestation:
 - Stomodeal epithelium is part ectoderm and part endoderm.
- Parotid gland:
 - First to form in humans
 - Arise from the ectodermal lining of the stomodeum from which the ducts, lumina, and acini evolve
 - Capsule and connective tissue develop from the surrounding mesenchyme
- Submandibular gland:
 - Develops from buds of the endoderm in the floor of the stomodeum from which the ducts, lumina, and acini evolve
- Sublingual gland:
 - Appears later than the other glands
 - Develop from buds of the endoderm in the paralingual sulcus from which the ducts, lumina, and acini evolve

- Minor salivary glands (seromucous glands):
 - Develop later in gestational life (third month)
 - Endodermally derived

NOTE: Parotid gland is last of the salivary glands to be encapsulated resulting in either incorporation/entrapment of lymphoid tissue within the parotid or incorporation/entrapment of parotid ducts and acini within the periparotid lymph nodes epithelium. (See next chapter for discussion and illustrations.)

ANATOMIC BORDERS OF THE SALIVARY GLAND

- See [Fig. 18-1](#).
- Parotid gland
 - Largest gland (average weight of 25 g)
 - Encapsulated and pyramidal-shaped palpable between the ramus of the mandible and the mastoid process
 - Artificially divided into two lobes by the coursing of the facial nerve through the gland:
 - Superficial lobe (largest portion)
 - Deep lobe situated adjacent to the lateral pharyngeal space
 - Anterior border:
 - Overlies the superficial surface of the masseter muscle
 - Posterior border:
 - Overlaps the sternocleidomastoid muscle and wraps around the lower ear
 - Lateral or superficial border:
 - Skin and dermis of the face
 - Medial or deep border:
 - Buttressed by the styloid process and its associated muscles (styloglossus, stylohyoid, stylopharyngeal) and by the carotid sheath and its contents (internal carotid artery, internal jugular vein, cranial nerves IX, X, XII)
 - Superior border:
 - Zygomatic arch
 - Inferior border:
 - Sternocleidomastoid muscle (oblique anterior border)
- Parotid (Stensen) duct:
 - Approximately 4 to 7 mm long
 - Originates from the anterior portion of the parotid coursing forward over the masseter

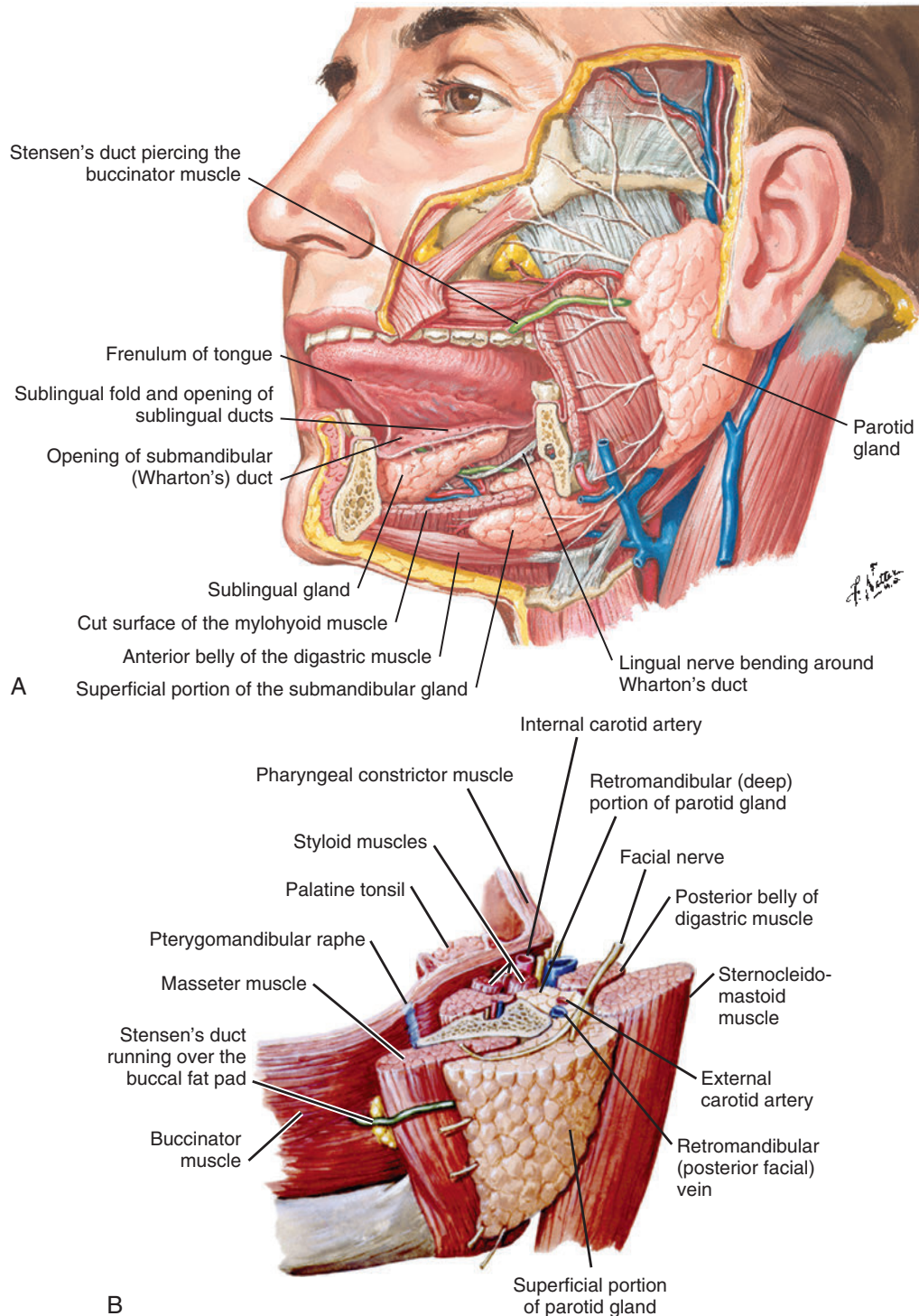
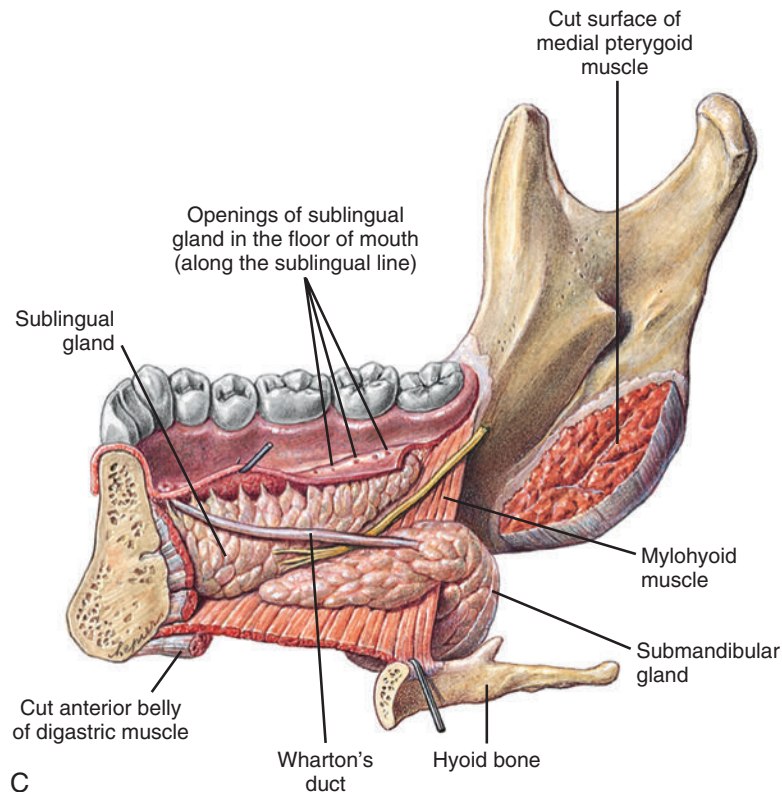


Fig. 18-1. Salivary glands and related anatomy.

A, Left lateral drawing of the face with the body of the mandible resected to show the floor of mouth structures. The relationships of the parotid gland, submandibular gland, and sublingual gland are shown. **B**, Left oblique view drawing from above shows the relationships of the left parotid gland to the mandibular ramus, pterygoid muscles, carotid sheath, and pharyngeal wall. Note the course of the facial nerve artificially dividing the parotid gland into a superficial lobe (largest portion) and deep lobe (smallest portion).

**Fig. 18-1, cont'd**

C, Left lateral view of the floor of mouth as seen with a midline cut. The submandibular gland can be seen to extend around the back edge of the mylohyoid muscle. The multiple ducts of the sublingual gland can be seen draining into the lateral floor of the mouth. (**A**, Modified from www.netterimages.com. **B**, From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, p 2450, Fig. 40-1. **C**, Modified from Sobota Atlas of Human Anatomy © Elsevier GmbH, Urban & Fischer, Munich.)

- muscle, enters the buccal fat pad piercing the buccinator muscle, and opens in the oral cavity opposite the second maxillary molar (parotid papilla)
- In approximately 20% of the population, accessory parotid tissue is found along the anterior portion of the gland and Stensen duct.
- Submandibular (submaxillary) gland
 - Each gland weighs from 10 to 15 g.
 - Encapsulated and walnut-shaped, located in the submandibular triangle, situated below the angle of the mandible
 - Divided into superficial and deep lobes; the latter can only be palpated in the floor of the mouth
 - Anterior border:
 - Anterior belly of the digastric muscle
 - Posterior border:
 - Stylomandibular ligament, which separates it from the lower part of the parotid
 - Lateral border:
 - In relation to the submandibular fossa on the inner surface of the body of the mandible
 - Medial border:
 - Bounded by several muscles (mylohyoid, styloglossus, hyoglossus, stylohyoid, and posterior belly of the digastric) and nerves (hypoglossal, glossopharyngeal, and lingual)
 - Superior border:
 - Inferior border of the body of the mandible
 - Inferior border:
 - Skin, platysma, and deep fascia
 - Submandibular (Wharton) duct:
 - Runs forward along the inner surface of the mandible, in parallel with the lingual nerve passes medial to the lower border of the sublingual gland, at which point the duct may receive the major sublingual duct (Bartholin) prior to opening in the oral cavity at the sublingual caruncle or papilla lateral to the frenulum

- Sublingual gland
 - Smallest of the major salivary glands, weighing between 2 and 4 g
 - Almond-shaped, located submucosally in the floor of the mouth
 - Anterior border:
 - Opposite sublingual gland
 - Posterior border:
 - Deep part of the submandibular gland
 - Lateral border:
 - Internal aspect of the body of the mandible
 - Medial border:
 - Genioglossus muscle
 - Superior border:
 - Mucosa of the floor of the mouth, which it raises to form the sublingual fold
 - Inferior border:
 - Mylohyoid muscle
 - Has several ducts connecting to the oral cavity:
 - Several ducts unite to form the common sublingual (Bartholin) duct, the largest duct, which merges with the submandibular duct prior to opening in the oral cavity lateral to the frenulum
 - Smaller ducts known as Rivinus ducts open into the oral cavity proper.
- Minor salivary (seromucous) glands
 - Located beneath the mucosal epithelium throughout the submucosa of entire upper aerodigestive tract:
 - Are unencapsulated arranged in lobules
 - In tongue and lips lie in close contact with structures around them, including:
 - Skeletal muscle
 - Nerves
 - Anterior hard palate and gingiva generally devoid of seromucous glands

INNERVATION OF THE SALIVARY GLANDS

- Parotid gland
 - Auriculotemporal branch of the IX cranial nerve traverses the parotid gland and provides its sensory and secretomotor functions:
 - Frey syndrome, or auriculomotor nerve syndrome: occurs after parotidectomy when misdirected regeneration of the secretomotor fibers with innervation of the cutaneous sweat glands results in facial sweating during eating
 - VII (facial) nerve passes through the deep and posterior aspects of the parotid gland prior to dividing into its branches to the face:
 - Any surgical procedure to remove portions of the parotid gland, unless it involves only the superficial part, carries the danger of damage

to the nerve; maintaining the integrity and function of the facial nerve in the face of a total parotidectomy is a difficult and delicate procedure.

- Submandibular and sublingual glands:
 - Facial nerve (VII) provides the sensory and secretomotor function of these glands via the chorda tympani accompanying the lingual nerve (a branch of the mandibular division of V nerve) passing through the submandibular ganglion.
- Blood supply and lymphatic drainage
 - Parotid gland:
 - Arterial supply is via branches of the external carotid artery and includes the posterior auricular, maxillary, superficial temporal, and transverse facial arteries.
 - Venous structures parallel those of the arteries and empty into the external jugular vein
 - Lymphatic drainage is to the superficial and deep cervical lymph nodes via the superficial parotid lymph nodes.
 - Submandibular and sublingual glands:
 - Arterial supply to the submandibular gland is via branches of the external carotid artery the facial and lingual arteries; arterial supply to the sublingual gland is by the sublingual and submental arteries branches of the lingual and facial arteries, respectively.
 - Venous structures parallel those of the arteries and empty into the external and internal jugular veins.
 - Lymphatic drains to the superficial and deep cervical lymph nodes via submandibular and sublingual lymph nodes.

HISTOLOGY OF THE SALIVARY GLANDS

- See [Figs. 18-2 through 18-5](#); [Tables 18-1 and 18-2](#).
- Common to all salivary glands is their arborizing epithelial ductal system with production of saliva from the specialized secretory cells in the distal segments and delivery of these secretions via the complex branching structures to the oral cavity:
 - Main secretory duct of the gland divides into progressively smaller striated ducts that, in turn, branch into smaller intercalated ducts, which terminate in the terminal secretory end structures.
- From distal to proximal the system includes:
 - Acini represent the terminal secretory cells and include serous and/or mucous cells, which produce the saliva:
 - Serous cells:
 - Triangular to pyramidal cells with a narrow apex toward the luminal aspect, round nuclei near the basal one third of the cell, and

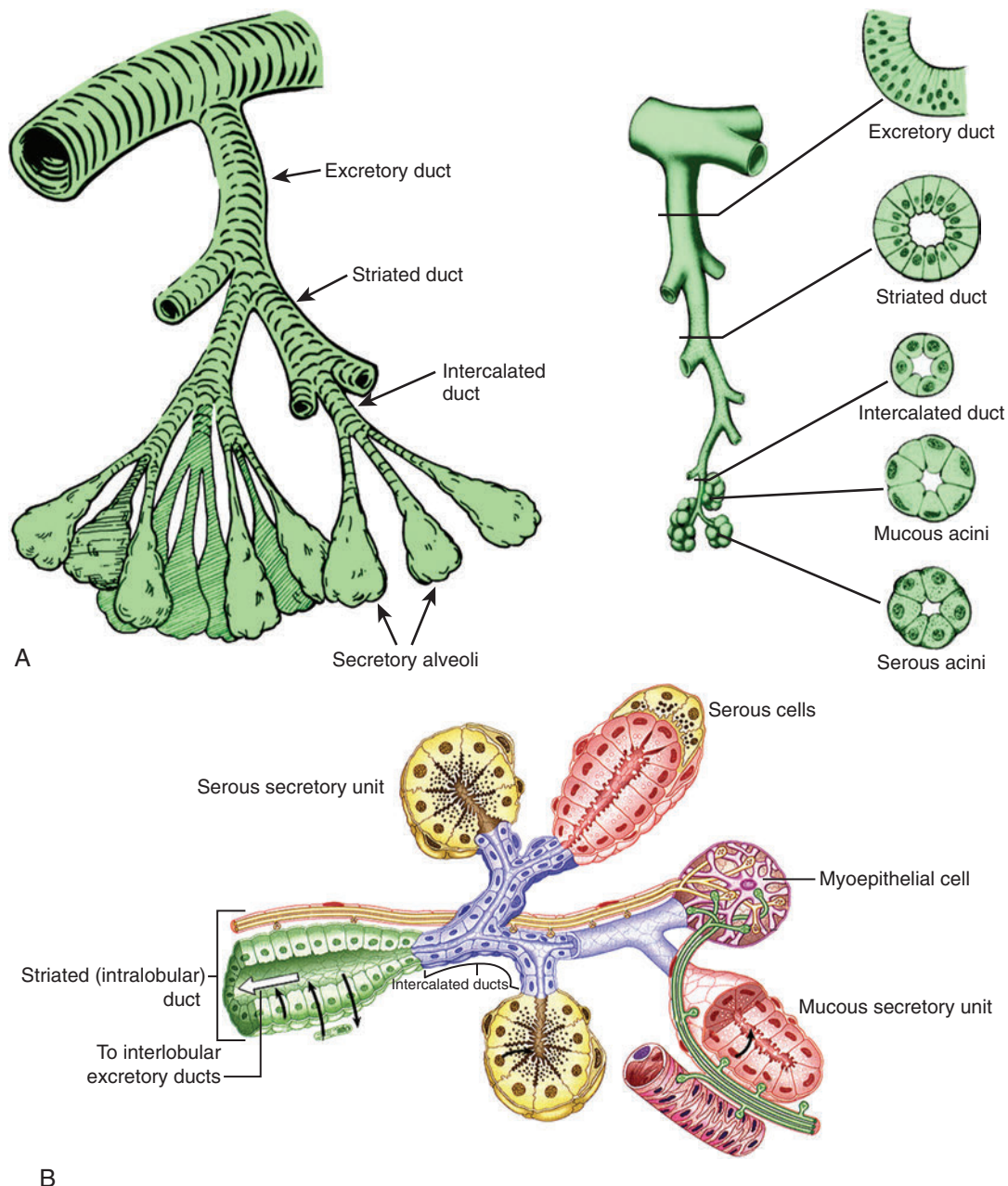


Fig. 18-2. Schematic drawing of salivary duct system.

A, The drawing shows the major salivary gland ductal system. **B**, The ductal system is shown with cross-sections at the various ductal levels. (**A**, Modified from Batsakis JG: *Tumors of the head and neck: clinical and pathological considerations*, ed 2, Baltimore, 1979, Williams & Wilkins. **B**, From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, 2454, Fig. 40-7B.)

- abundant cytoplasm containing numerous basophilic zymogen granules situated at the apical portion
- Zymogen granules are diastase-resistant, periodic acid Schiff positive, and mucicarmine negative.

- Mucous cells:
 - Pyramidal cells with basally located, flattened nuclei and clear to faintly basophilic, finely granular-appearing cytoplasm
 - Mucicarmine, alcian blue, and diastase-resistant, periodic acid Schiff positive

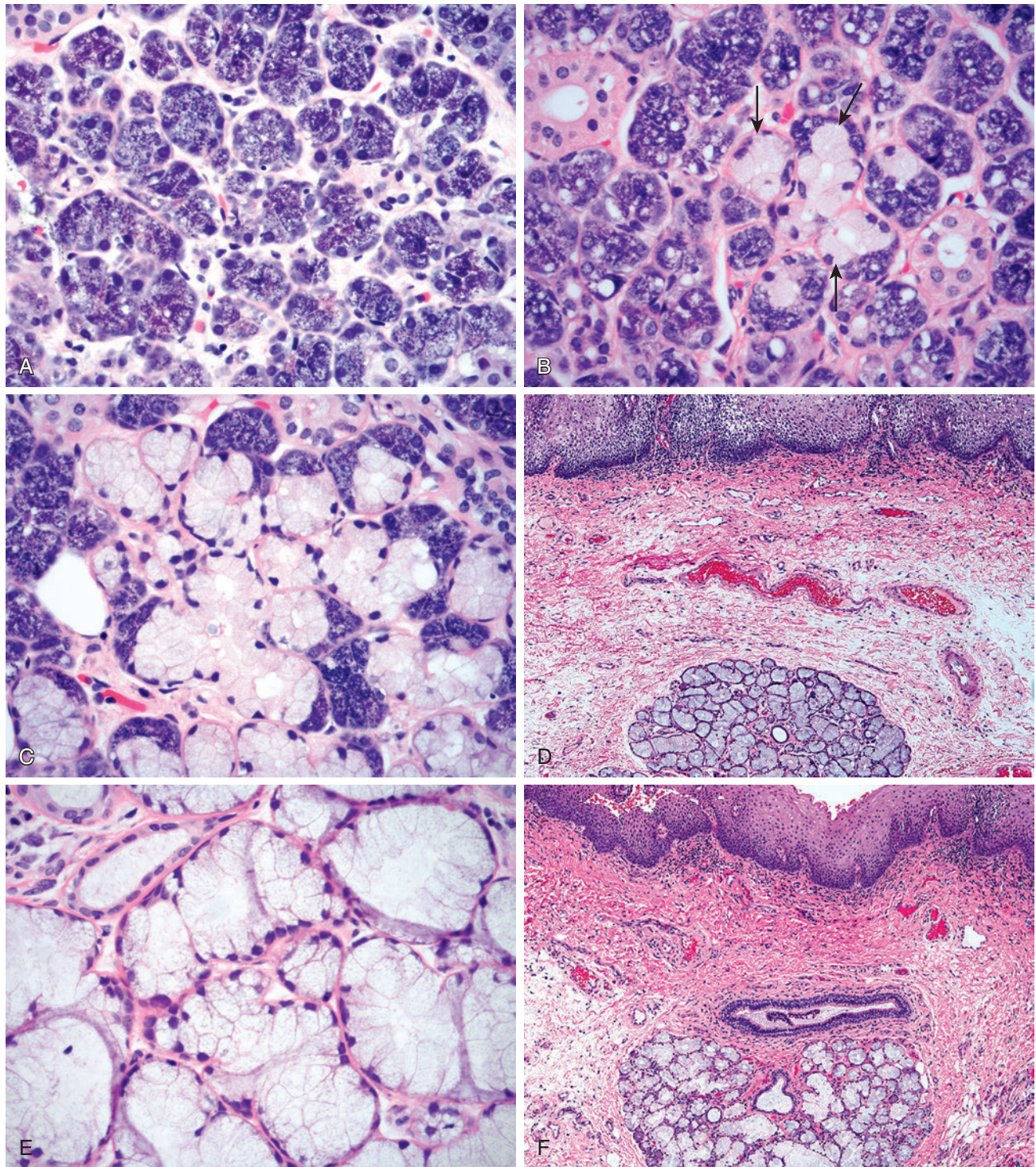
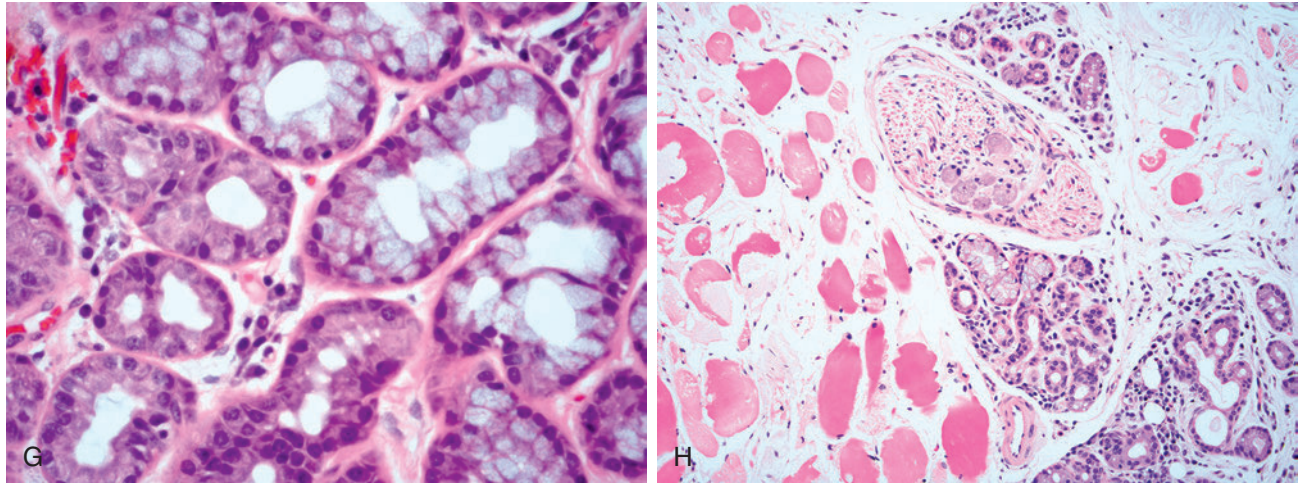
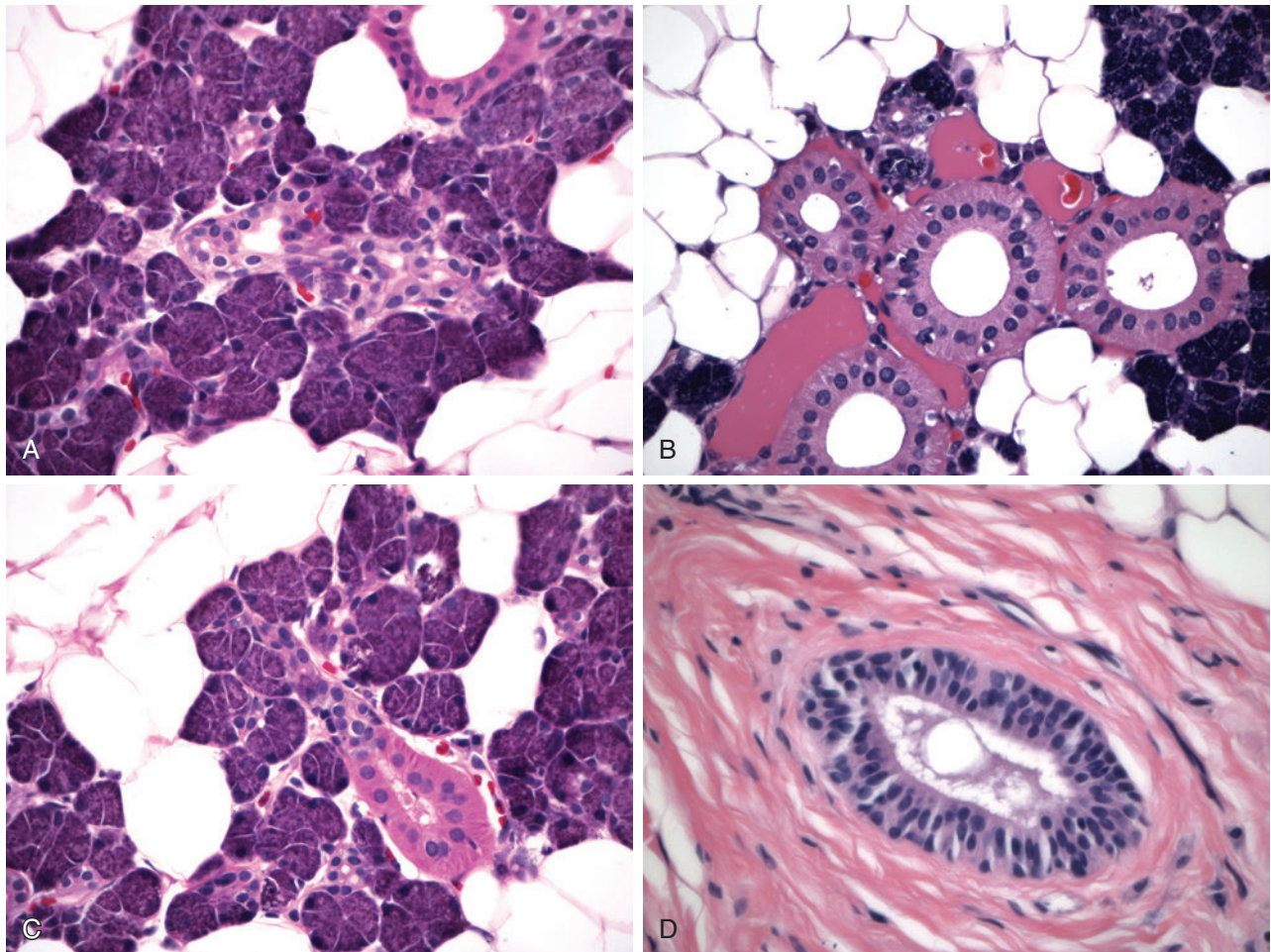


Fig. 18-3. Histologic features of acinar cell types in various salivary glands.

A, The parotid gland is composed of serous acini characterized by triangular to pyramidal cells with a narrow apex toward the luminal aspect, round nuclei near the basal one third of the cell, and abundant cytoplasm containing numerous basophilic zymogen granules situated at the apical portion. **B**, Although considered to be wholly composed of serous acini, mucous cells (arrows) can be seen in parotid gland parenchyma. **C**, The submandibular (and sublingual) gland is composed of an admixture of mucous and serous acini; serous cells typically arranged as crescent-shaped caps (referred to as demilunes) along the periphery of the mucous acinar cells. **D** and **E**, Palatal minor salivary glands are situated in the submucosa with a lobular arrangement and are wholly composed of mucous acini-appearing pyramidal cells with basally located, flattened nuclei and clear to faintly basophilic, finely granular-appearing cytoplasm. **F** and **G**, Minor salivary glands (seromucous glands) are situated in the submucosa with a lobular arrangement and composed of an admixture of mucous and serous cells.

**Fig. 18-3, cont'd**

H, Lingual and labial minor salivary glands can be seen in close contact with structures, around them including skeletal muscle and nerves, the latter including ganglion cells.

**Fig. 18-4. Histology of salivary gland ducts.**

A, Intercalated ducts are lined by low cuboidal cells with centrally located oval nuclei and scant amphophilic to eosinophilic cytoplasm. **B,** Striated ducts are larger than intercalated ducts and are lined by columnar cells with centrally located round nuclei displaying deep basal vertical striations. **C,** Transition from intercalated duct to striated duct. **D,** Small interlobular excretory duct lined by pseudostratified columnar cells and located within dense fibrous connective tissue.

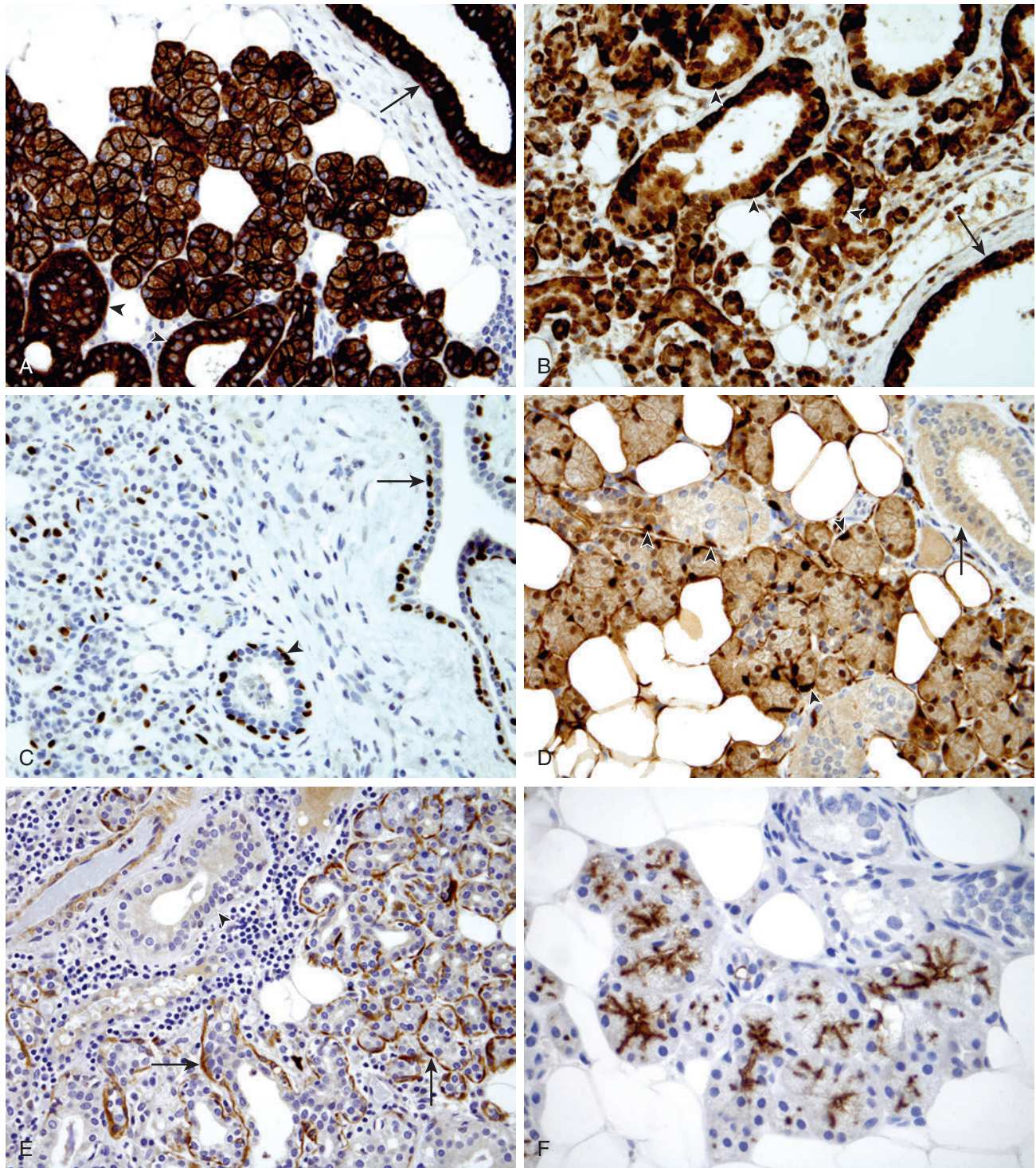


Fig. 18-5. Immunohistochemical staining of salivary gland parenchyma.

Immunohistochemical reactivity in normal salivary gland structures include **(A)** high and low molecular weight cytokeratin (CAM 5.2) expression in acinar cells, intercalated cells and striated duct cells (*arrowheads*), and interlobular duct cells (*arrow*); myoepithelial and basal cells are also reactive; **(B)** high molecular weight cytokeratin (CK5/6) expression of myoepithelial cells of both acini and striated ducts (*arrowheads*) and basal cells of interlobular duct (*arrow*); **(C)** p63 expression seen in myoepithelial cells of acini (*left*) and basal cells of striated duct (*arrowhead*) and interlobular duct (*arrow*); **(D)** S100 protein expression in myoepithelial cells of acini and striated ducts (*arrowheads*) but negative in basal cells of interlobular duct (*arrow*); note adipocytes are also S100 protein positive; **(E)** calponin expression is similar to that of S100 protein, including expression in myoepithelial cells of acini and striated ducts (*arrows*) but negative in basal cells of interlobular duct (*arrowhead*); **(F)** discovered on GIST-1 (DOG1) expression is primarily restricted to acinar cells with moderate apical membranous staining.

- Immunohistochemical staining of acinar cells includes:
 - Pancytokeratins and low molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19), EMA and CEA positive
 - Amylase positive
 - Discovered on GIST-1 (DOG-1) positive:
 - Diffuse moderate (2+) apical membranous staining pattern in normal serous acini, 1+ apical membranous pattern in mucous acini
 - Myoepithelial cells, striated and excretory ducts negative
 - p63, calponin, smooth muscle actin, S100 protein, and vimentin negative
 - High molecular weight keratins (e.g., CK5/6) typically negative
- Intercalated ducts
 - Lined by low cuboidal cells with centrally located oval nuclei and scant amphophilic to eosinophilic cytoplasm
 - More conspicuous in the parotid gland than in other salivary glands
 - Immunohistochemical staining of intercalated duct cells includes:
 - Pancytokeratins and low molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19), EMA, CEA, and estrogen receptor positive
 - p63, calponin, smooth muscle actin, S100 protein, and vimentin negative
 - DOG-1 positive in distal intercalated cells:
 - Weak to moderate (1-2+) apical staining
 - Amylase negative
 - High molecular weight keratins (e.g., CK5/6) typically negative
- Myoepithelial cells:
 - Ectodermally derived, flat, elongated cells lying at the periphery of the acinar cells and the intercalated cells in the space between the basement membrane and the basal plasma membrane
 - Generally, myoepithelial cells are difficult to identify by light microscopy; appear as flattened, stellate, and spindle-shaped cells with cellular processes that extend around acini and intercalated ducts
 - Their contractile function is similar to smooth muscle, assisting in the movement of saliva through the duct system.
 - Immunohistochemical staining of myoepithelial cells includes:
 - Pancytokeratins, low and high molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19) positive

TABLE 18-1 Salivary Gland Acinar Cell Types

Salivary Gland	Acinar Type*
Parotid	Serous (scattered mucous cells can be found)
Submandibular (submaxillary)	Serous and mucous
Sublingual	Mucous and serous
Palate	Mucous
Tongue	Mucous and serous
Buccal	Mucous and serous
Lip	Mucous and serous
All other upper aerodigestive tract sites	Mucous and serous

*Predominant type first.

Adapted from Ellis GL, Auclair PL: The normal salivary glands. In Silverberg SG, editor: Tumors of the salivary glands. AFIP Atlas of tumor pathology, series 4, fascicle 9, Washington, 2008, ARP Press.

TABLE 18-2 Immunohistochemistry: Normal Salivary Gland Structures

Cell	PanK	LMWK	HMWK	EMA	CEA	S100	p63	SMA	CAL	VIM	GFAP	DOG1
ED	+	+	–	+	+	–	–	–	–	–	–	–
SD	+	+	–	+	+	–	–	–	–	–	–	–
ID	+	+	–	+	+	–	–	–	–	–	–	+*
A	+	+	–	+	+	–	–	–	–	–	–	+ [†]
M	+	+	+	–	–	+	+	+	+	+	V+	–
B	+	+	+	–	–	–	+	–	–	+	–	–

A, Acinar cells; B, basal cells; CAL, calponin; CEA, carcinoembryonic antigen; DOG1, discovered on GIST 1; ED, excretory duct; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; HMWK, high molecular weight cytokeratin (e.g., CK5/6); ID, intercalated duct; LMWK, low molecular weight cytokeratins (e.g., CK7, CK8, CK19); M, myoepithelial cells; PanK, pancytokeratin (AE1/AE3; CAM5.2); SD, striated duct; SMA, smooth muscle actin; V+, variably positive; VIM, vimentin.

*Weak to moderate apical staining.

[†]Moderate apical membranous staining.

- p63, calponin, smooth muscle actin, S100 protein, and vimentin positive
- Variable GFAP reactivity
- EMA and CEA negative
- DOG-1, amylase negative
- Striated ducts:
 - Larger than intercalated ducts
 - Lined by columnar cells with centrally located, round nuclei displaying deep basal vertical striations representing basal folds in plasma membranes for which these ducts are named
 - Due to large numbers of cytoplasmic mitochondria the cells of striated ducts:
 - Have prominent eosinophilic granular cytoplasm
 - Are intensely reactive with phosphotungstic acid-hematoxylin
 - Immunohistochemical staining of striated duct cells includes:
 - Pancytokeratins and low molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19), EMA and CEA positive
 - p63, calponin, smooth muscle actin, S100 protein, and vimentin negative
 - DOG-1, amylase negative
 - High molecular weight keratins (e.g., CK5/6) typically negative
- Excretory (interlobular) ducts:
 - Lined by pseudostratified columnar cells adjacent to the striated duct cells
 - Goblet cells may be present intermixed among the pseudostratified columnar cells.
 - Lined by stratified squamous cells as these ducts merge with the oral mucosal epithelium
 - Immunohistochemical staining of excretory (interlobular) duct cells includes:
 - Pancytokeratins and low molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19), EMA and CEA positive
 - p63, calponin, smooth muscle actin, S100 protein, and vimentin negative
 - DOG-1, amylase negative
 - High molecular weight keratins (e.g., CK5/6) typically negative
- Basal cells:
 - Located around striated and excretory (interlobular) ducts
 - Differ from myoepithelial cells by absence of myoid markers by immunohistochemistry and myofilaments on ultrastructural evaluation
 - Play role in regeneration and metaplastic changes
 - Immunohistochemical staining of basal cells includes:
 - Pancytokeratins, low and high molecular weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19) positive
 - p63 positive
 - Calponin, smooth muscle actin, S100 protein, and GFAP negative
 - EMA and CEA negative
 - DOG-1, amylase negative
- Salivary glandular component separated into lobules by fibrous tissue septa.
- Histologic differences between the salivary glands rests with the composition of their respective acinar cells:
 - Parotid gland:
 - Entirely serous although mucinous acini may be identified
 - Sebaceous glands and/or scattered sebaceous cells may be identified:
 - Stains for mucin are negative.
 - Mature adipose tissue is a normal finding in parotid gland parenchyma, and it proportionally increases with age.
 - Submandibular (submaxillary) gland:
 - Mixed serous and mucous with the majority of acinar cells being serous
 - Serous cells typically arranged as crescent-shaped caps (referred to as demilunes) along the periphery of the mucous acinar cells
 - Sublingual gland:
 - Mixed mucous and serous (demilunes) with the majority of acinar cells being mucous
 - Minor salivary glands vary depending on site:
 - Most of upper aerodigestive tract including oral cavity, sinonasal tract, pharynx, and larynx is seromucous, with the majority of acinar cells being mucous.
 - In anterior ventral portion of tongue (referred to as Blandin or Nunn glands) composed of pure mucous type
 - In the region of the circumvallate papillae on the posterior and lateral portions of the tongue (referred to as von Ebner glands) composed of pure serous type
 - Palate is purely mucous.
- Age-related and/or reactive cellular changes may include:
 - Oncocytes:
 - Characterized by cells with abundant eosinophilic granular cytoplasm owing to presence of abundant mitochondria
 - Uncommon cell type in salivary gland in patients under 50 years of age but presence increases with age
 - See Chapters 19 and 20 for more detailed discussion and illustrations.

- Sebaceous cells:
 - Present in most parotid glands but generally are few in number
 - Appear as small collections of sebaceous cells
 - Do not stain with mucicarmine.
 - Immunoreactive for EMA
- Fatty infiltration:
 - In particular relative to parotid gland represents a normal finding and proportionally increases with age
 - Presence increased under other conditions including but not limited to malnutrition (see next chapter)
- Metaplasia may include presence of:
 - Squamous cells with keratinization and intercellular bridges
 - Mucous cells
 - Metaplastic changes not infrequently seen after a traumatic event such as prior fine-needle aspiration or biopsy but may occur spontaneously unrelated to a traumatic event
- Hyperplasia
- Atrophy
- Age-related and metaplastic changes of salivary gland discussed in Chapter 19

FURTHER READING

References may be accessed online at [ExpertConsult.com](#).

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Non-Neoplastic Diseases of Salivary Glands

CLASSIFICATION OF NON-NEOPLASTIC SALIVARY GLAND LESIONS

BOX 19-1 Classification of Non-Neoplastic Salivary Gland Lesions

Developmental Lesions

- Heterotopias

Hyperplasia and Metaplasia

- Adenomatoid hyperplasia
- Squamous metaplasia
- Necrotizing sialometaplasia
- Oncocytic changes (oncocytic metaplasia, oncocytosis)
- Intercalated duct lesions (intercalated duct hyperplasia; [intercalated duct adenoma])

True Cysts

- Lymphoepithelial cyst
- Salivary duct cyst
- Polycystic (dysgenetic) disease

Nondevelopmental Cysts

- Mucus extravasation phenomenon
- Mucus retention cyst
- Ranulas

Infectious, Inflammatory, and Autoimmune Disease

- Bacterial sialadenitis
- Mumps
- HIV salivary gland disease
- Chronic sialadenitis
 - Nonobstructive
 - Infectious
 - Noninfectious
 - Obstructive
 - Sialolithiasis
 - Sialadenosis
- IgG4-related sialadenitis
- Lymphoepithelial sialadenitis
 - Sjögren syndrome

DEVELOPMENTAL LESIONS

Heterotopic Salivary Glands

See Section 7, The Ear and Temporal Bone.

Definition: Salivary gland tissue located in sites other than those appropriate for the normal anatomic distribution of salivary glands.

Synonyms: Ectopic salivary glands; salivary gland choristoma

Clinical

- Majority of heterotopic salivary gland tissue occurs in head and neck sites.
- Most common locations include the periparotid lymph nodes, the middle ear, and the lower neck; less frequent sites of occurrence include:
 - Upper neck
 - External ear (auditory canal), middle ear
 - Intraosseous sites (e.g., mandible)
 - Cerebellopontine angle
 - Pituitary gland

- Salivary gland tissue has been reported in thyroglossal duct, capsules of the thyroid gland and parathyroid glands, mediastinum, tonsils, and gingiva, as well as more distant sites, including the prostate gland, vulva, and rectum.

Heterotopic Salivary Gland Tissue in the Lower Neck

- Most of these examples occur in the lower anterolateral neck along the medial border of the sternocleidomastoid muscle.
- Most common presenting symptom is a draining sinus on the anterior aspect of the neck along the medial border of the sternocleidomastoid muscle near the sternoclavicular joint.
- Sinuses drain saliva-like material, usually a very limited quantity but the amount may increase during meals.
- Localized nontender swelling associated with the sinus may be the only complaint.

- Histologically, the tissue includes normal salivary gland tissue either purely serous or mixed serous and mucinous glands.

Intranodal Periparotid Salivary Gland Tissue (Fig. 19-1)

- Not technically heterotopic but represents normal development
- Generally accepted explanation for the occurrence of salivary gland tissue in periparotid lymph nodes is entrapment during embryonic development rather than true ectopia, although this issue is still the subject of debate.

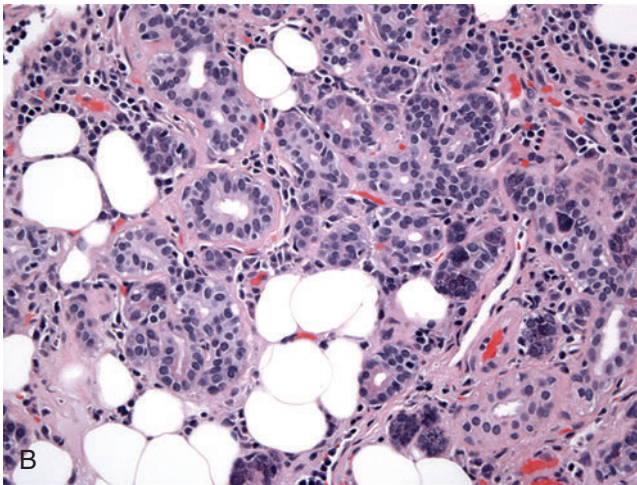
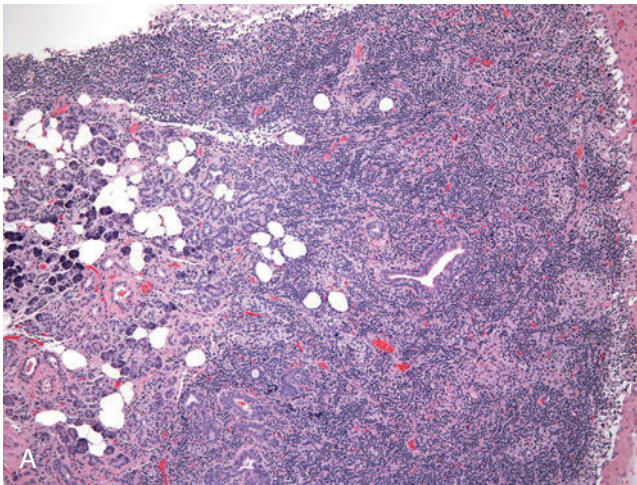


Fig. 19-1. Intranodal parotid parenchyma.

A, B, Periparotid lymph node with intranodal salivary gland parenchyma composed of all components of salivary gland parenchyma including serous acini and ducts. This is a normal and fairly frequent finding in periparotid lymph nodes believed to represent entrapment of salivary gland parenchyma during embryonic development rather than true ectopia.

- Ontogenically, the parotid gland is the last of the salivary glands to be encapsulated, resulting in either incorporation/entrapment of lymphoid tissue within the parotid or incorporation/entrapment of parotid ducts and acini within the periparotid lymph nodes epithelium.
- Histologically, the salivary gland tissue includes all components of the salivary gland unit including ducts and acini but more often consists of serous glands with scattered, well-formed ducts.
- All pathologic lesions (non-neoplastic and neoplastic) may originate from the intranodal salivary gland tissues, including:
 - Cysts, metaplasia, hyperplasia, and benign epithelial ductal proliferations
 - Benign and malignant salivary gland neoplasms:
 - Represent primary intranodal neoplasms with the gland proper being devoid of tumor
 - A malignancy arising from intranodal salivary gland tissue:
 - May present as mass lesion within the node separate from adjacent major salivary glands
 - In the absence of an identifiable primary neoplasm from an adjacent salivary gland, these intranodal foci can be considered as the primary site for the development of the malignancy.

Heterotopic Salivary Gland Tissue in the Middle Ear

See Section 7, The Ear and Temporal Bone.

- Heterotopic salivary gland tissue in the middle ear is discovered in the evaluation of patients for conductive hearing loss.
- Most cases are associated with ossicular abnormalities of the incus and stapes.
- Patients range in age from the first to sixth decades but most are under 21 years of age.
- Because the ossicles originate from the first (malleus and incus) and second (stapes) branchial arch, the presence of salivary gland tissue is considered a developmental abnormality involving the branchial arches.
- Heterotopic salivary gland tissue has been seen in association with anomalies that suggest the branchio-otorenal (BOR) syndrome; in addition, a syndrome including salivary gland choristoma in association with branchial arch abnormalities, most commonly the second, as well as abnormalities of the facial nerve, has been identified.
- Salivary gland tissue in the middle ear:
 - May extend into the eustachian tube, involve the mastoid bone, and may be intimately associated with the facial nerve

- Represents an admixture of seromucinous glands and adipose tissue; the latter contributes to the yellow appearance of the tissue
- Recapitulates the acinar arrangement of normal salivary glands; ducts may be identified
- Is situated within the submucosa
- In general conservative surgical resection is curative; however, this tissue is slow growing and in conjunction with potential complications from surgery, particular to the facial nerve surgical intervention may not be advised.
- A biopsy may be required to establish a diagnosis.

Intraosseous Heterotopic Salivary Gland Tissue

- Intraosseous salivary gland tissue is uncommon and tends to occur in the posterior mandible near the angle beneath the mandibular canal and less frequently in the anterior mandible.
- Intraosseous salivary gland tissue is asymptomatic and is an incidental radiographic finding.
- No treatment is required.

Salivary Gland Heterotopia and Salivary Gland Tumors

- Salivary gland neoplasms occurring in sites that normally do not contain salivary gland tissue are usually considered to originate from heterotopic salivary gland tissue.
- An exception to the above statement includes those salivary gland tumors arising in periparotid lymph nodes without an identifiable parotid gland mass:
 - Clinical setting is one in which the intranodal salivary gland tumor, specifically a malignant tumor, is considered as being of “unknown primary origin.”
 - Clinical and radiologic search for the primary salivary gland tumor proves negative.
 - Entrapment of salivary gland parenchyma within lymph nodes during embryonic development accounts for the intranodal salivary gland tissue.
 - Salivary gland neoplasms, benign and malignant, may originate within periparotid nodal salivary gland parenchyma presenting as a mass separate from adjacent major salivary glands (i.e., parotid gland).
 - In the absence of an identifiable primary neoplasm from an adjacent salivary gland, these intranodal foci can be considered as the primary site.
- A wide variety of tumor types occur in salivary gland heterotopia, including (but not limited to):

- Pleomorphic adenoma, monomorphic adenomas (e.g., Warthin tumor), acinic cell adenocarcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma not otherwise specified, carcinoma ex pleomorphic adenoma, sialoblastoma, others

Accessory Parotid Gland

- Represent isolated lobules of parotid gland parenchyma separated from the main body of the gland situated along a major salivary duct
- Incidence reported up to 56% in an autopsy series
- Accessory parotid tissue is spheric or oblong, measuring from 0.5 to 3 cm in greatest dimension.
 - Accessory tissue can be seen anterior to the border of the masseter situated on the buccal fat pad.
 - Accessory tissue is normally connected to Stensen duct by a single accessory duct, although more than a single duct may be found.
- Clinically, lesions of accessory parotid tissue present with mass in the cheek.
- Histologically, accessory tissue is identical to the normally situated parotid tissue and reflects similar pathologic processes that the main gland may exhibit (e.g., inflammation, fatty infiltrate, other).
- Benign and malignant salivary gland tumors may arise in accessory parotid glands:
 - Benign tumors may include pleomorphic and monomorphic adenomas, Warthin tumor, others.
 - Malignant tumors reported include a wide variety of types, including (but not limited to) mucoepidermoid carcinoma, acinic cell adenocarcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, others.
- Magnetic resonance imaging is helpful in the diagnosis and treatment of accessory parotid gland tumors.
- Best surgical approach to tumors in the accessory parotid region is via a standard parotid incision and concomitant superficial parotidectomy; this approach to accessory parotid gland tumors is superior in that it provides a better margin of resection and minimizes functional and cosmetic deformities.

HYPERPLASIA AND METAPLASIA IN THE SALIVARY GLANDS

Adenomatoid Hyperplasia of Mucous Salivary Glands (Fig. 19-2)

Definition: Hyperplastic or hamartomatous proliferation of the mucous acini of salivary gland tissue.

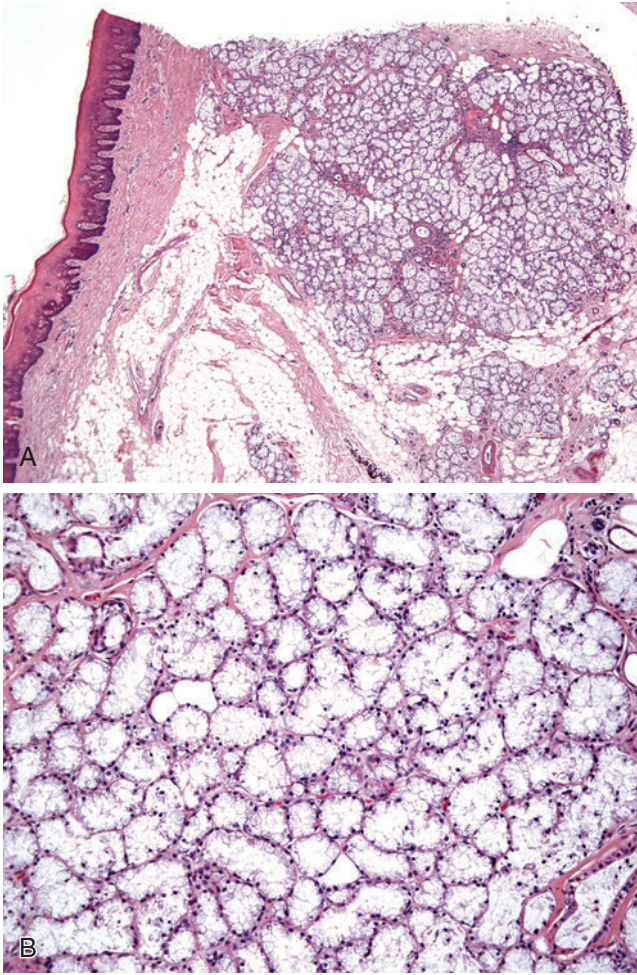


Fig. 19-2. Adenomatoid hyperplasia.

A, B, Adenomatoid hyperplasia showing submucosal proliferation of hyperplastic lobules of normal-appearing mucinous acini without significant inflammation or fibrosis; the overlying squamous epithelium (**A**) is unremarkable.

Clinical

- Relatively uncommon lesion that tends to occur slightly more often in men than in women
- Occurs in all age groups, although it is more common in adults than in children
- Majority of cases involve the hard or soft palates; less common sites of occurrence include the retromolar mucosa; involvement of major salivary glands has not been reported.
- Clinical presentation includes a localized painless mass often discovered during routine dental examination; ulceration of the overlying mucosa is not present:
 - Often mistaken for a salivary gland neoplasm
- Cause is unknown and there is no association with sialadenitis or trauma.

Pathology

Gross

- Lesions are firm and sessile, varying in size from 0.5 to 3 cm.

Histology

- Submucosal proliferations of hypertrophied and/or hyperplastic lobules of otherwise normal-appearing mucinous acini
- No significant inflammation or fibrosis are seen.
- Overlying epithelium is unremarkable, although pseudoepitheliomatous hyperplasia may be present.

Differential Diagnosis

- Salivary gland neoplasms:
 - Submucosal lobular configuration composed of a single cell type (i.e., mucinous acini) should allow for differentiation from benign and malignant salivary gland neoplasms.

Treatment and Prognosis

- Surgical excision is curative.

Squamous Metaplasia and Mucous Cell Metaplasia

- Relatively common metaplastic changes that can be seen in a wide variety of lesions, including non-neoplastic lesions and neoplasms (benign and malignant)
- May occur spontaneously or occur as secondary to a traumatic event such as fine-needle aspiration biopsy or biopsy
- For illustrations see Chapter 20 under Pleomorphic Adenoma and Warthin Tumor.

Necrotizing Sialometaplasia (NS)

(Figs. 19-3 through 19-6)

Definition: Benign, self-healing (reactive) inflammatory process of salivary gland tissue, which clinically and histologically may be mistaken for a malignant neoplasm.

Synonym: Adenometaplasia

Clinical

- Tends to affect men more than women; occurs over a wide age range with the average age of occurrence in the fifth and sixth decades of life
- Most commonly involves the intraoral minor salivary glands, particularly involving the palate:
 - Major salivary glands, as well as minor salivary glands of virtually every site in the upper aerodigestive tract, can be affected.

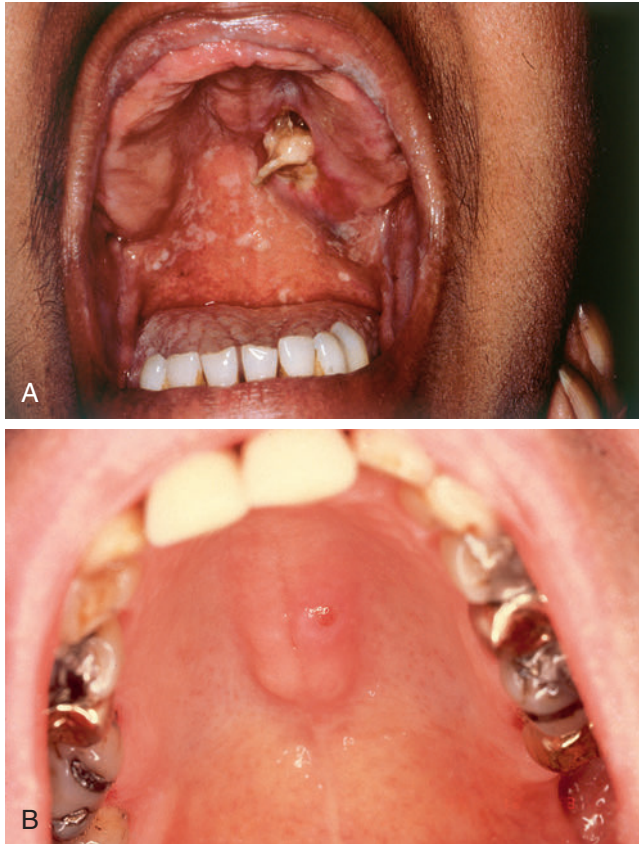


Fig. 19-3. Necrotizing sialometaplasia.

A, Necrotizing sialometaplasia (NS) of the palate appearing as a deep, crater-like ulcerative lesion. **B**, Less commonly NS may appear as a submucosal nodular swelling.

- Larynx may be affected but is a rare site of occurrence.
- Most common presenting problem is that of a painless ulcerated lesion or a nodular swelling, which is usually unilateral but may be bilateral:
 - May be associated with pain, numbness, or a burning sensation and dysphagia
 - Uncommonly, may present with anesthesia of the greater palatine nerves
- Pathogenesis:
 - Believed to be secondary to trauma and/or an ischemic event with compromise of the vascular supply to salivary glands leading to ischemic necrosis:
 - Ischemia may be iatrogenically induced after an operative procedures (surgery, postintubation, postbronchoscopy), anesthesia, or radiotherapy.
 - Mean duration of 18 days from the time of the insult to the development of the lesion
 - In experimental studies on rat submandibular and sublingual glands, the induction of

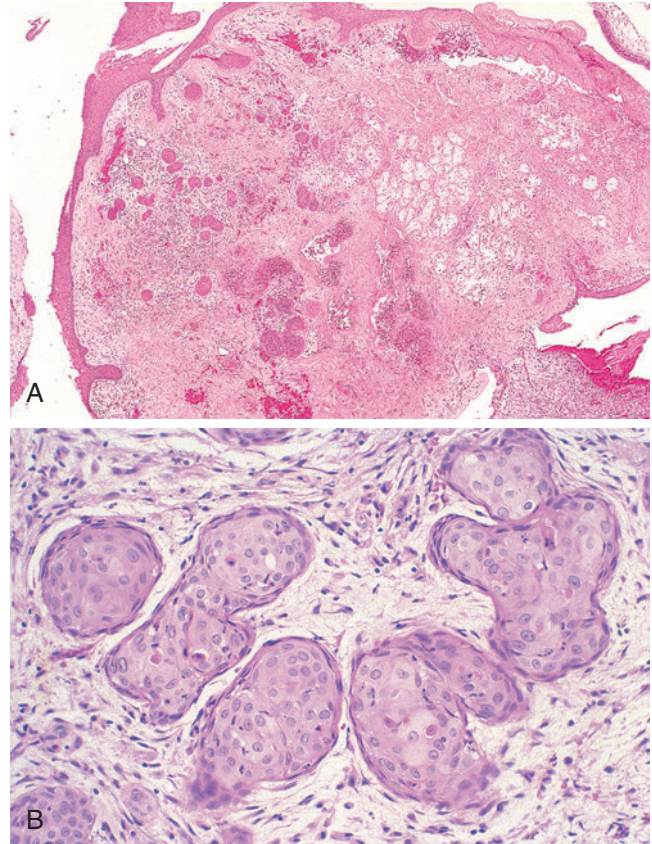


Fig. 19-4. Necrotizing sialometaplasia.

A, Low magnification shows submucosal lobular necrosis of the salivary glands consisting of acinus-sized pools of mucin with preservation of the lobular architecture; the surface squamous epithelium is intact. **B**, At higher magnification, the metaplastic minor salivary glands show rounded, smooth borders with bland squamous epithelial cells, uniform nuclei, and abundant eosinophilic cytoplasm with occasional preservation of ductal lumina; mucous cells are not seen.

sialometaplasia occurred 6 to 8 days after arterial ligation.

- Inciting event is primarily but not exclusively thought to be due to ischemia.
- May occur de novo unassociated with a traumatic event or it may occur in association with other non-neoplastic lesions or in association with a neoplasm (benign or malignant)

Pathology

Gross

- Typically appears as a deep, crater-like ulcerative lesion, measuring from 1 to 3 cm:
 - May appear as a submucosal nodular swelling that may slough, leaving a crater-like ulcer

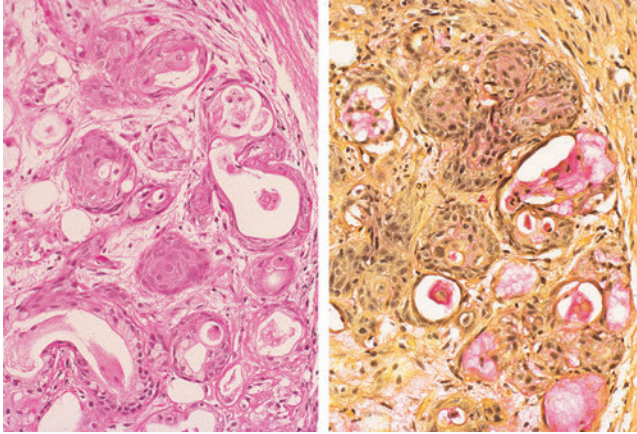


Fig. 19-5. Necrotizing sialometaplasia.

Left, The features on routine sections are usually diagnostic but *(right)* mucin stains may be helpful in delineating the presence of residual mucous cells.

Histology

- At low magnification there is preservation of the lobular architecture of the minor salivary glands.
- Histologic hallmark is squamous metaplasia of residual acinar and ductal elements:
 - Squamous cells are typically bland in appearance with uniform nuclei and abundant eosinophilic cytoplasm.
 - Preservation of ductal lumina and/or scattered mucocytes may or may not be identified.
 - Lobular architecture is maintained and metaplastic lobules vary slightly to moderately in size and shape, have smooth edges.
 - Metaplastic foci may be surrounded by granulation tissue and mixed acute and chronic inflammatory reaction.
 - In some examples, the squamous metaplastic foci may be atypical, including irregular contours of metaplastic lobules with nuclear hyperchromasia, increased nuclear-to-cytoplasmic ratio, dyskeratosis, and mitoses, suggesting a possible diagnosis of squamous cell carcinoma:
 - Preservation of lobular architecture of the involved minor salivary glands should allow for differentiation from carcinoma but in any given example it may be challenging differentiating NS from squamous cell carcinoma.
 - Low proliferation rate (<10%) by Ki67 staining and absence of p53 reactivity may support a diagnosis of NS but do not unequivocally differentiate NS from squamous cell carcinoma.
 - Presence of myoepithelial cells along the periphery of the metaplastic lobules as determined by reactivity for myoepithelial

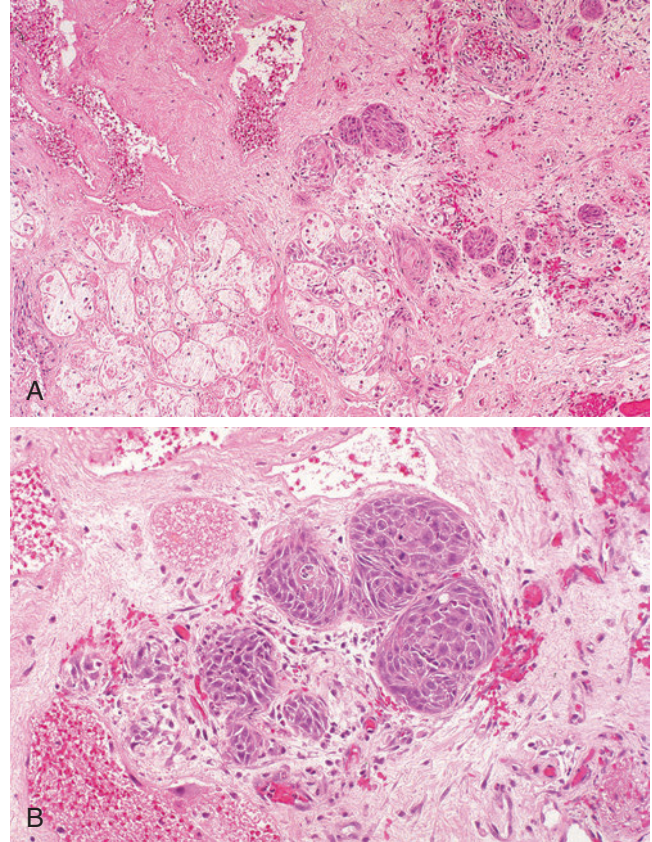


Fig. 19-6. Necrotizing sialometaplasia of the sinonasal tract.

A, Presence of lobular necrosis (*bottom left and center*) with adjacent metaplastic seromucous glands. **B**, At higher magnification the metaplastic epithelial cells are atypical characterized by the presence of nuclear pleomorphism, hyperchromasia, increased nuclear-to-cytoplasmic ratio and individual cell necrosis raising the concern for a possible diagnosis of squamous cell carcinoma. However, based on the overall architectural findings including preservation of lobular architecture of the minor salivary glands and absence of definitive evidence of invasive growth, the findings support a diagnosis of necrotizing sialometaplasia. Long-term follow-up of the patient proved the lesion to be benign with no recurrence or progression of disease.

cell-related markers (e.g., p63, calponin, smooth muscle actin) and keratin subtypes in NS suggested as possible differentiating findings from squamous cell carcinoma but do not unequivocally differentiate NS from squamous cell carcinoma

- Necrotic lobules consist of acinus-sized pools of mucin, which may extend into adjacent tissue, eliciting a granulation tissue reaction with associated acute and chronic inflammation:
 - Necrotic lobules may not be present in all cases so that the designation of sialometaplasia without

“necrotizing” would be more appropriate in such a situation.

- With regeneration, mitoses, individual cell necrosis, enlarged nuclei, and prominent nucleoli can be seen.
- Associated findings include ulcerated mucosa and pseudoepitheliomatous hyperplasia (PEH):
 - PEH results when the metaplastic lobules present in excretory ducts and merge with surface epithelium.
 - This reaction may be so striking, presenting a diagnostic nightmare in separation from an infiltrating squamous cell carcinoma.
- Histochemistry:
 - Intraluminal and/or intracytoplasmic mucicarmine and diastase-resistant, PAS-positive material may be identified.

Differential Diagnosis (Table 19-1)

- Mucoepidermoid carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma

NOTE: The retention of the overall lobular architecture, bland appearance of the squamous nests with rounded or smooth edges, and retention of residual ductal lumina and mucocytes help in differentiating NS from the malignant neoplasms listed above.

Treatment and Prognosis

- NS are self-limiting lesions that heal by secondary intention:
 - Depending on the size of the lesion, the healing process in most cases occurs from 3 to 12 weeks.
 - Debridement and saline rinses may aid in the healing process.
- Recurrences do not usually occur.

Subacute Necrotizing Sialadenitis (SANS)

- Nonspecific inflammatory condition of unknown cause affecting oral minor salivary glands:
 - Some authorities believe that SANS should not be included within the spectrum of necrotizing sialometaplasia and most likely represents an infectious process or perhaps an immune response to an unknown allergen.
 - Other authorities believe SANS may represent the early or minimal form of NS.
- In either case, SANS most often is characterized by a localized palatal swelling, accompanied by an abrupt onset of pain.
- Patients range in age from 15 to 45 years, with a mean age of 21.9 years.

TABLE 19-1 Necrotizing Sialometaplasia: Differential Diagnosis

	NS	MEC, Low-Grade	SCC
Architecture/growth	Retention of lobular architecture	Cystic and solid; may be circumscribed to encapsulated without invasion or show infiltrative growth	Haphazard, infiltrative growth
Cellular components	Smooth round to oval nests of metaplastic squamous epithelium with bland cytology; may show residual ductal lumina with mucous cells	Admixture of mucous, intermediate (“basaloid”) and epidermoid (squamous) cells; bland cytology; irregular cell nests	Nests and cords of squamous cells with irregular outlines and variable amount of cytologic atypia; may entrap residual glands but the tumor itself contains no mucin
Cyst formation	Absent	Present (prominent component)	Absent
Surface epithelium	May show PEH; usually not connected with NS	Uninvolved; not connected with tumor	Often dysplastic and/or in direct continuity with the carcinoma; may be ulcerated
Extravasated mucin	May be present	May be present	Absent
Necrosis of salivary gland lobules	May or may not be present	Absent	Absent
Inflammation	May be prominent	May be prominent with mucin extravasation	May be present; associated desmoplasia
Cytogenetics	None known	<i>CRTC1-MAML2</i> translocation	None known

MEC, Mucoepidermoid carcinoma; NS, necrotizing sialometaplasia; PEH, pseudoepitheliomatous hyperplasia; SCC, squamous cell carcinoma.

- SANS most often affects intraoral sites, including the hard palate, soft palate, buccal mucosa, and tonsils.
- Lesions typically are nonulcerated swellings, develop over a short period of time (7 to 10 days), and range in size from 0.3 to 2.5 cm in diameter.
- Histopathologic features include:
 - Diffuse involvement of minor salivary glands by lymphocytes, histiocytes, neutrophils, and variably by eosinophils
 - Loss of acinar cells, early acinar cell necrosis surrounded by a dense polymorphous inflammatory infiltrate, and atrophy of ductal cells
 - Squamous metaplasia is not usually seen.
- Appears to be a self-limiting process with most cases resolving 2 to 3 weeks after biopsy without recurrences
- Main differences between SANS and NS include:
 - SANS is usually a smaller-sized lesion than lesions of NS.
 - Scarcity of ulceration in SANS but typically present in NS
 - Absence of squamous metaplasia in SANS but present in NS

Oncocytic Alterations

- Oncocytic cells in the salivary glands occur in the following settings:
 - Oncocytic metaplasia
 - Oncocytosis (nodular or diffuse)
 - Oncocytoma; oncocytic carcinoma
 - Warthin tumor
 - Variety of other lesions/tumors that may have oncocytic cells including but not limited to:
 - Pleomorphic adenoma
 - Basal cell adenoma
 - Myoepithelioma
 - Canalicular adenoma
 - Mucoepidermoid carcinoma
 - Acinic cell carcinoma
 - Others

Oncocytic Metaplasia (Fig. 19-7)

- Non-neoplastic transformation of ductal and acinar epithelium to oncocytes:
 - Oncocytes are histologically characterized by cytoplasmic alteration (metaplasia) of epithelial and/or myoepithelial cells with swelling of the cytoplasm by mitochondrial hyperplasia giving the cell a characteristic granular eosinophilic appearance by light microscopy.
- Represents an aging phenomenon:
 - Oncocytic metaplasia is generally not seen in patients less than 50 years of age from which time

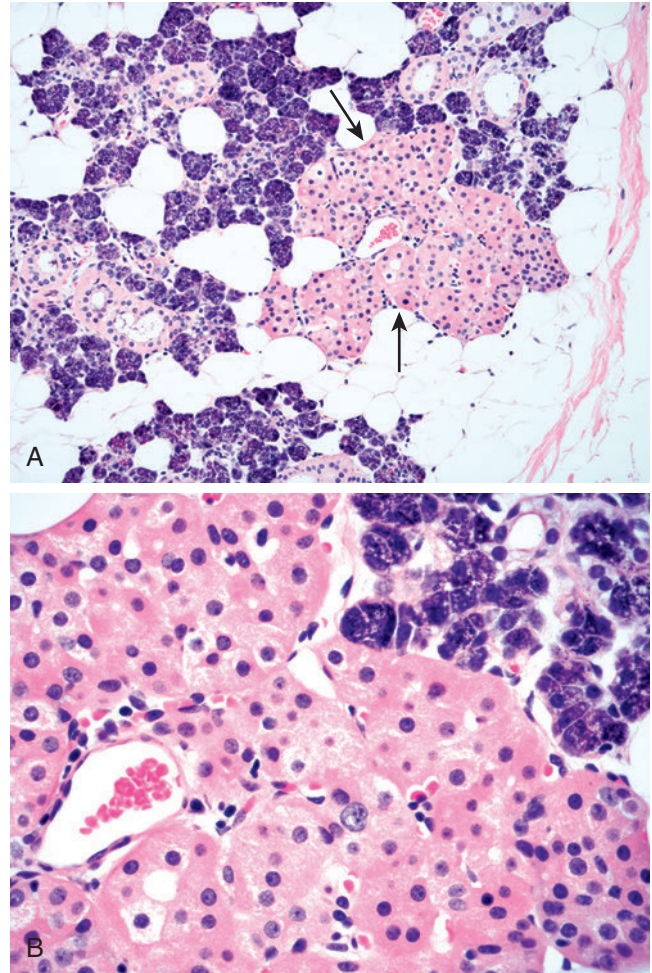


Fig. 19-7. Oncocytic metaplasia.

A, Incidentally identified focus of oncocytic metaplasia (arrows) in a parotid gland from an older aged individual.
B, Oncocytic cells are characterized by the presence of granular eosinophilic cytoplasm.

the percentage of the population with oncocytic metaplasia increases.

- In contrast to oncocytoma (and oncocytosis), oncocytic metaplasia is non-mass-forming focal or limited changes in one or more areas within the salivary gland.
- Appear as isolated clusters of oncocytic cells within otherwise normal-appearing parenchyma
- Clear cell changes may be present.
- Usually represents incidental histologic findings in salivary glands excised for other reasons
- Oncocytic cells may be seen in other non-neoplastic processes (see oncocytosis immediately following), as well as in numerous salivary gland tumors, including pleomorphic adenomas, Warthin tumor, oncocytoma, mucoepidermoid carcinoma, acinic cell carcinoma, oncocytic carcinoma, others.

Oncocytosis (Fig. 19-8)

- Oncocytosis (also referred to as oncocytic [adenomatous] hyperplasia) represents a non-neoplastic mass-forming proliferation of oncocytic cells within the salivary gland.
- Typically appear as nodular foci, referred to as nodular oncocytic hyperplasia or nodular oncocytosis
- Less commonly, may represent a diffuse alteration in the affected salivary gland referred to as diffuse oncocytosis
- In either nodular or diffuse form may present as a clinically detectable mass lesion presenting difficulties in differentiation from oncocytoma
- Histologically, oncocytotic foci:
 - Include multiple (often two or more) separate nodules
 - Unencapsulated
 - Gradual merge with and/or contain residual (nononcocytic) salivary gland parenchyma, including ductular epithelium and serous acinar cells
 - Such histologic findings assist in differentiating oncocytosis from oncocytoma, the latter entirely composed of oncocytes without identifiable residual normal parenchyma.
 - May show clear cell change
- Differentiation of oncocytosis from oncocytoma may not be possible due to overlapping histologic features, and this differentiation may be more of an academic than practical issue because treatment and prognosis are essentially similar (i.e., cured by excision).

Intercalated Duct Lesions (IDL)

(Fig. 19-9)

Definition: Rare lesions that include hyperplasia, adenoma, or both (hybrid) that may be a precursor lesion of salivary gland neoplasms:

- Proposal that IDL may represent precursor lesion to salivary gland neoplasms based on presence of small foci of IDL in cases of basal cell adenoma, epithelial-myoepithelial carcinoma, pleomorphic adenoma, mucoepidermoid carcinoma, basal cell adenocarcinoma, Warthin tumor, acinic cell carcinoma, others
- Role as a precursor lesion not definitively proven

Clinical

- Rare lesion
- More common in females than in males; occur over a wide age range from second to ninth decades with a mean in the sixth decade
- Majority occur in the parotid gland > oral cavity > submandibular gland.

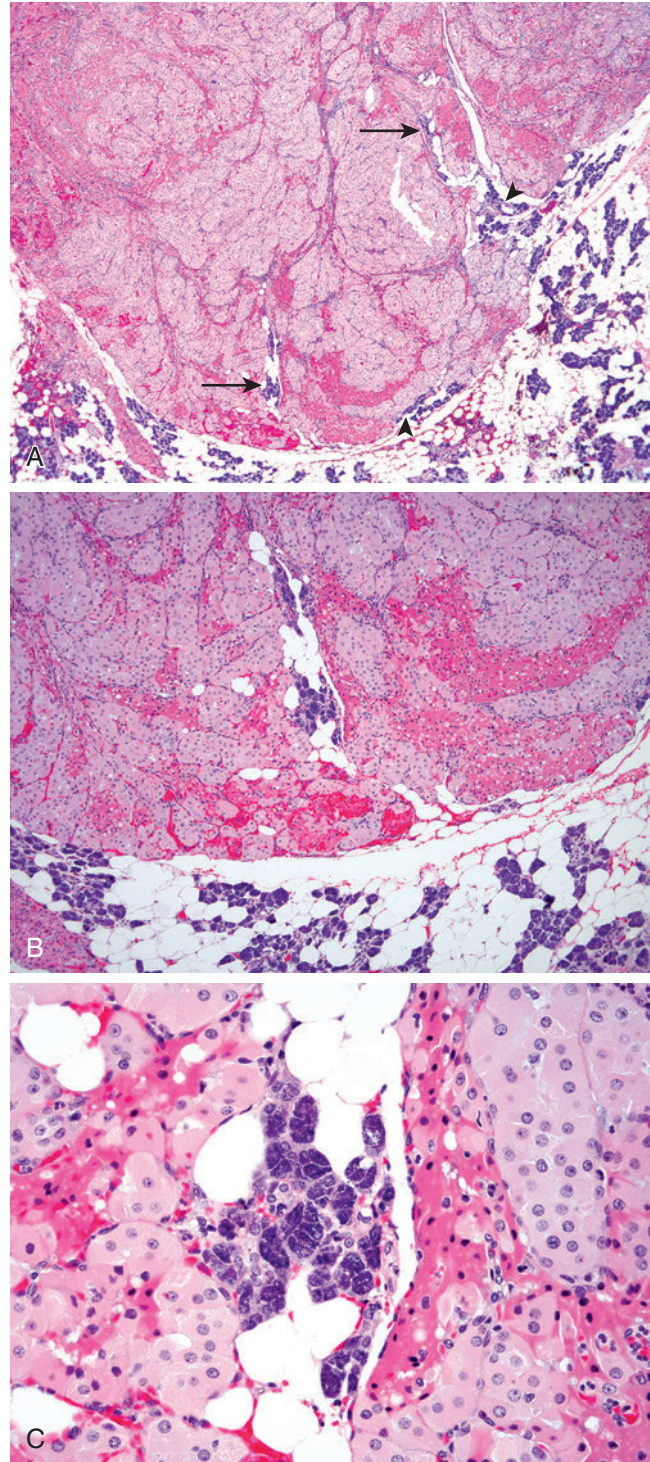


Fig. 19-8. Oncocytosis.

A, Mass-forming oncocytic nodule that is circumscribed but not encapsulated gradually merging with (*arrowheads*) and incorporating (*arrows*) residual salivary gland parenchyma. Higher magnification shows the (**B**) absence of a capsule and (**C**) presence of acini within oncocytic cells characterized by the presence of cells with granular eosinophilic cytoplasm.

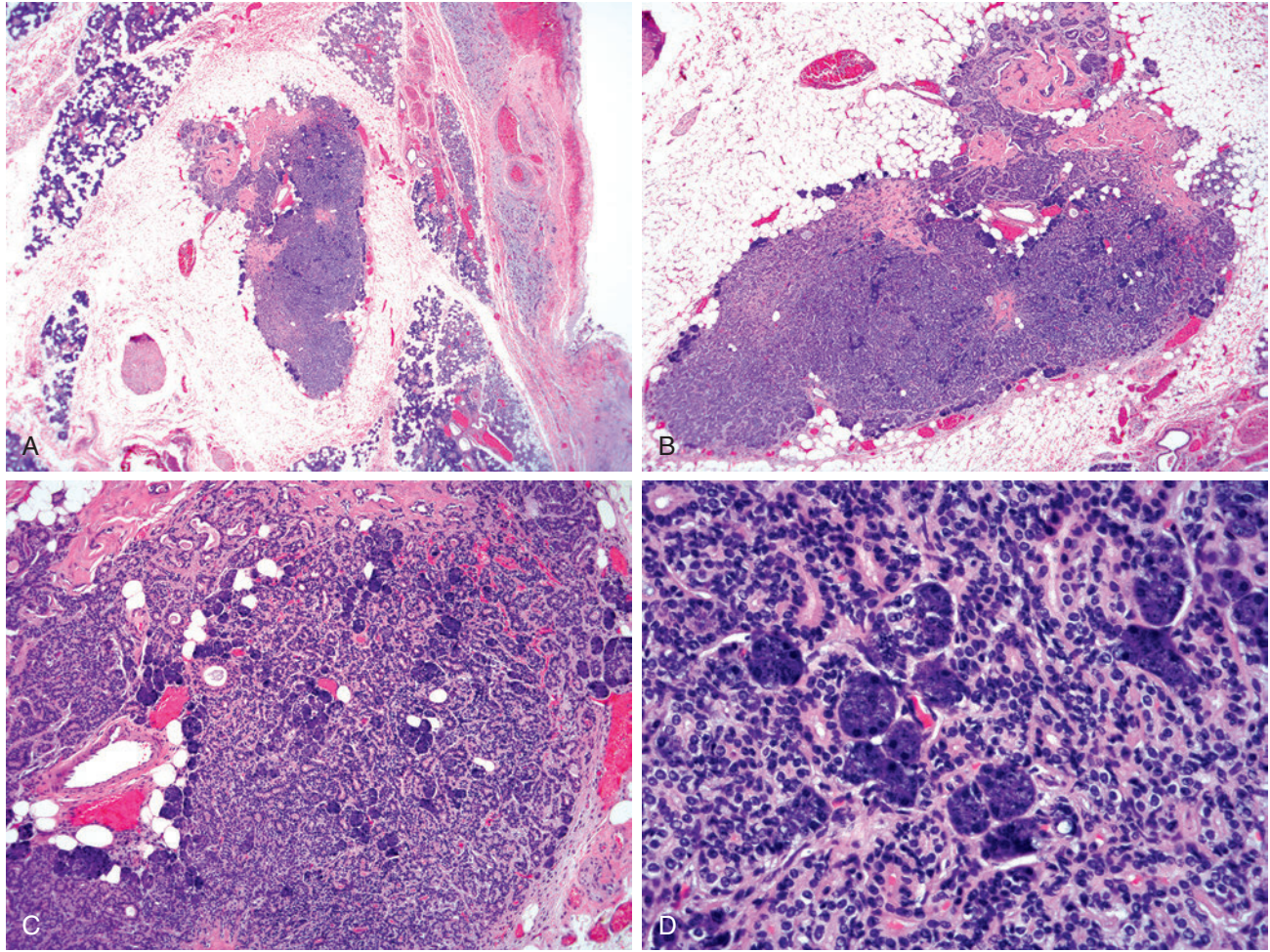


Fig. 19-9. Intercalated duct hyperplasia.

A and **B**, Intraparotid relatively circumscribed but unencapsulated cellular proliferation composed of closely packed ducts that includes acinar cells along the periphery as well as within the lesion; stromal hyalinization focally around ducts is present. **C**, Closely packed ducts and incorporation of acinar cells within and along the periphery of the proliferation. **D**, Ducts are lined by cuboidal cells with small round nuclei and eosinophilic cytoplasm. There is an absence of nuclear pleomorphism or increased mitotic activity; acinar cells characterized by intracytoplasm basophilic (zymogen) granules are seen.

- Typically represent incidental finding found in association with another lesion
- Usually a small lesion measuring less than 5 mm in greatest dimension

Pathology

Intercalated Duct Hyperplasia

- Most common type of IDL
- Characterized by unifocal or multifocal (and diffuse) unencapsulated proliferation of small ducts with minimal intervening stroma merging/blending imperceptively with acinar and mucous cells of surrounding salivary gland parenchyma
- At low magnification appear as irregular pale foci contrasted with the surrounding darker-appearing salivary gland parenchyma:
 - In multifocal lesions, foci vary in size and shape.
- Intercalated ducts are lined by single layer of cuboidal to columnar cells with small round nuclei and eosinophilic to amphophilic cytoplasm:
 - There is an absence of nuclear pleomorphism or increased mitotic activity.
- Acinar cells may be incorporated within the proliferation and/or also identified at the periphery of most lesions.
- Myoepithelial cells are consistently present around the ducts but are not discernible by light microscopy requiring immunohistochemical staining with p63 or other markers (e.g., calponin, CK14, others) for identification.
- Stromal hyalinization that may be periductal can be identified.

- Other uncommon features may include:
 - Perilesional follicular lymphoid hyperplasia
 - Clear myoepithelial cells
 - Entrapment of nerve within the lesion
 - Presence of focal luminal eosinophilic secretions
 - Cystic change
 - Basal lamina-like material with a cribriform pattern
 - Absence of fat cells or intralesional inflammatory infiltrates

Intercalated Duct Adenoma

- Presence of discrete, rounded, partially to completely encapsulated nodules with well-defined contours
 - Fibrous capsule may vary in thickness and may contain entrapped, irregular-appearing ducts.
- Composed of intercalated ducts lined by a single layer of cuboidal to columnar cells with small round nuclei and eosinophilic to amphophilic cytoplasm:
 - There is an absence of nuclear pleomorphism or increased mitotic activity.
 - Minimal intervening stroma present
- Occasionally acinar cells may be interspersed among the ductular structures.

Hybrid Intercalated Duct Lesion

- Least common type of IDL
 - Partially round, encapsulated adenoma-like appearance admixed with irregular hyperplasia-like areas
 - Give the impression of a transition from hyperplastic intercalated ducts to adenomatous areas
- Alternatively may include a completely encapsulated adenoma with separate discrete, hyperplastic foci immediately adjacent to the capsule.
 - Entrapped irregular ductal structures can be identified within capsule of the adenoma.
- Clear intercalated duct cells may be present.
- Immunohistochemistry
 - CK7, S100 protein, estrogen receptor, lysozyme positive; progesterone receptor negative
 - Myoepithelial cells positive for calponin and CK14

Treatment and Prognosis

- No specific treatment required
- Given their usual small size typically cured in the excision without known untoward biology
- More critical issues relative to treatment and prognosis relate to associated neoplasms some of which include malignant salivary gland neoplasms (see under definition earlier).

TRUE CYSTS OF MAJOR SALIVARY GLANDS (SIALOCYSTS)

- Most cystic lesions of major salivary glands represent cystic neoplasms.
- True cysts differ from pseudocysts by the presence of an epithelial lining.
- Most true cysts of major salivary gland arise in the parotid gland and are divided into three general categories:
 - Lymphoepithelial cyst
 - Salivary duct cyst
 - Polycystic (dysgenetic) disease

Lymphoepithelial Cyst (LEC)

(Fig. 19-10)

Definition: Benign true cystic lesion of the parotid gland of uncertain origin with characteristic histology and unrelated to human immunodeficiency virus (HIV) infection.

Clinical

- Uncommon acquired parotid gland cyst
- Slightly more common in men than in women; occurs over a wide age range including at birth to the eighth decade of life; the average age is in the fifth decade of life
 - May be present at birth but the clinical manifestations may not become apparent until adult life
- Presents as painless swelling of the parotid gland
- Majority are unilateral although bilateral lesions may occur.
- May occasionally be tender or painful, which may be due to secondary infection
- Rarely, may be associated with facial paralysis
- Histogenesis remains controversial:
 - Suggested to originate from the branchial apparatus and/or develop from salivary gland inclusions in lymph nodes
 - Designation of lymphoepithelial cyst is histologically accurate and is more appropriate than branchial cleft cyst.
 - Some authors believe that LECs, as well as salivary duct cysts and dysgenetic or congenital cysts, arise from salivary ducts and have no relation with the branchial apparatus.

Pathology

Gross

- Cyst is usually sharply circumscribed, fluctuant and unilocular, rubbery to firm ranging in size from 0.5 to 6 cm in greatest dimension
- Multilocular cysts are uncommon.

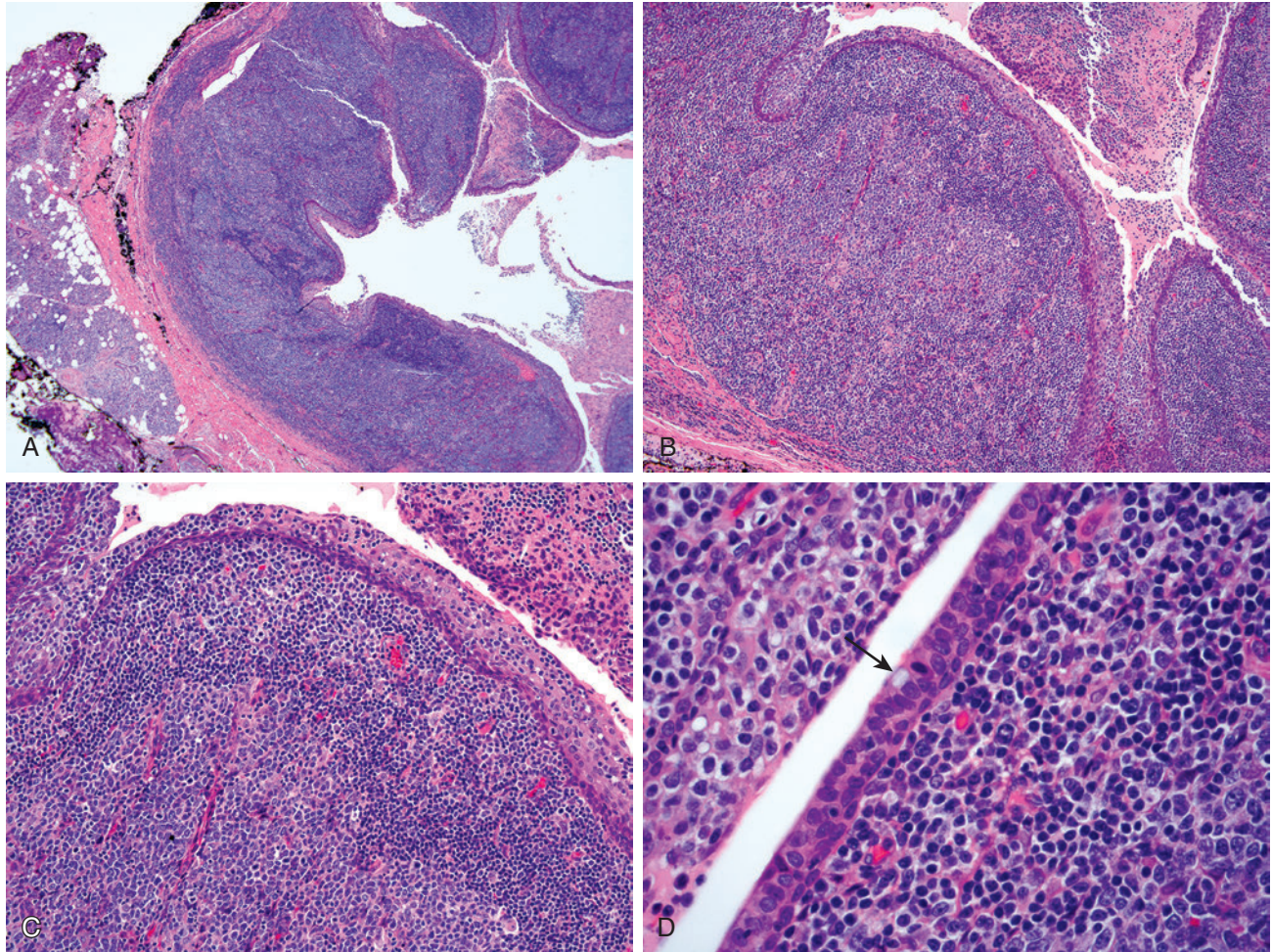


Fig. 19-10. Parotid gland lymphoepithelial cyst.

A, The cystic proliferation is sharply delineated from the parotid parenchyma (*lower left*). **B** and **C**, Cyst is lined by benign squamous epithelium and the cyst wall includes a dense lymphoid cell proliferation including germinal centers. **D**, Intraepithelial mucous cells (*arrow*) can be found.

- On cut section, small intracystic protrusions may be present, imparting a granular appearance to the lesion; the latter correlate to the presence of the lymphoid component in the cyst wall (see later).
- Usually contain caseous material with a yellow-white appearance

Histology

- Sharply circumscribed from the surrounding parotid parenchyma and is separated from the parotid tissue by fibrous tissue
- Lined by a variety of epithelial cell types, including squamous, cuboidal, columnar, and pseudostratified types; mucous (goblet) cells, sebaceous cells, and oncocytic metaplasia may be present.
- Cyst wall composed of an abundant mature lymphoid cell proliferation with readily identifiable germinal centers

Immunohistochemistry:

- Lymphoid component shows expression for B-cell (CD20, others) and T-cell (CD3, others) markers.
- Absence of Epstein-Barr virus (e.g., in situ hybridization for Epstein-Barr encoded RNA)
- Absence of p24 staining (marker for HIV infection)

Differential Diagnosis

- Other salivary gland true cysts, as well as cystic neoplasms:
 - LECs may be mistaken for cystic lymphoepithelial sialadenitis (LESA):
 - In contrast to LECs, the cystic LESA has:
 - Characteristic lymphoepithelial cell lesions
 - Tendency of the lymphocytes to migrate through the epithelial component
 - Cystic LESA lack features that can be seen in LECs, including mucous (goblet) cells.

- HIV-salivary gland disease (see later in this chapter):
 - Histology of LECs is similar to cystic lymphoepithelial lesions in HIV-associated salivary gland disease.
 - Absence of features that might suggest associated with HIV infection including absence of:
 - Florid follicular hyperplasia
 - Multinucleated giant cells
 - Lymphoepithelial cell islands
 - Presence of p24 immunoreactivity in HIV-associated lesions
 - Marked decrease in interfollicular CD4:CD8 ratio observed in HIV+ compared with the HIV negative cases
- Among the cystic neoplasms of the parotid that LECs may be confused with is Warthin tumor and cystic mucoepidermoid carcinoma (cystic MEC):
 - In contrast to Warthin tumor, LECs are unilocular, lack papillary architecture, and lack an epithelial cell component with oncocytic cytoplasmic changes.
 - Cystic MECs are usually low-grade malignancies characterized by the presence of an admixture of mucous cells, epidermoid cells, and intermediate cells.
 - These three cell types are absent in LEC.
 - Further, MECs tend to be infiltrative neoplasms, a feature that is not present in LECs.
- Confusion with metastatic cystic squamous cell carcinoma may occur, but LECs lack the cytologic atypia and increased mitotic activity usually seen in metastatic cystic squamous cell carcinoma.

Treatment and Prognosis

- Surgical excision is curative.

Salivary Duct Cyst (Fig. 19-11)

Definition: Acquired cyst believed to develop due to ductal obstruction with marked cystic dilation of a salivary gland duct.

Synonyms: Acquired, simple, and retention cyst

Clinical

- Most common salivary gland cysts
 - Represent approximately 2% to 3% of all parotid gland lesions
- No gender predilection; occur over a wide age range from early childhood to older adults but most patients are over 30 years of age
- Clinical presentation includes unilateral painless swelling.

- Approximately 85% occur in the parotid gland with 10% in submandibular gland; remainder in various other salivary gland sites.
- Obstructive changes that may result in the development of the salivary duct cyst include neoplasms, postinflammatory strictures, calculi, and mucus plugs.

Pathology

Gross

- Well-circumscribed and are usually uniloculated containing thin, watery, to viscous brown fluid
- Majority are 1 to 3 cm, although may reach as large as 10 cm.

Histology

- Sharply demarcated from the adjacent salivary gland parenchyma
- Epithelium lining of the cysts may be single or multilayered cuboidal, columnar, or squamous epithelium; mucus-containing goblet cells and oncocytic metaplasia may be seen.
- Cyst wall is composed of collagenized connective tissue of varying thickness.
- Sparse to minimal chronic inflammatory cell infiltrate can be present.
- Granulomatous inflammation may be present in the cyst wall and in the adjacent gland.
- Adjacent salivary gland parenchyma may show duct ectasia with inspissated secretions and chronic inflammation.

Differential Diagnosis

- Lymphoepithelial cyst:
 - Marked inflammatory cell component typically seen in lymphoepithelial cysts is not seen in salivary duct cysts.
- Cystic neoplasms in particular mucoepidermoid carcinoma:
 - In contrast to cystic mucoepidermoid carcinoma (MEC), salivary duct cysts lack the proliferative (hyperplastic) cellular features as well as combination of cell types (i.e., epidermoid cells, mucocytes and intermediate cells) seen in MEC:
 - Infiltrative growth would further support a diagnosis of a malignant neoplasm but a number of malignant salivary gland neoplasms including MEC may not be infiltrative and still represent a carcinoma (see Chapter 20 for more complete discussion).

Treatment and Prognosis

- Surgical excision is curative.
- Rarely, salivary gland neoplasms have been associated with salivary duct cysts.

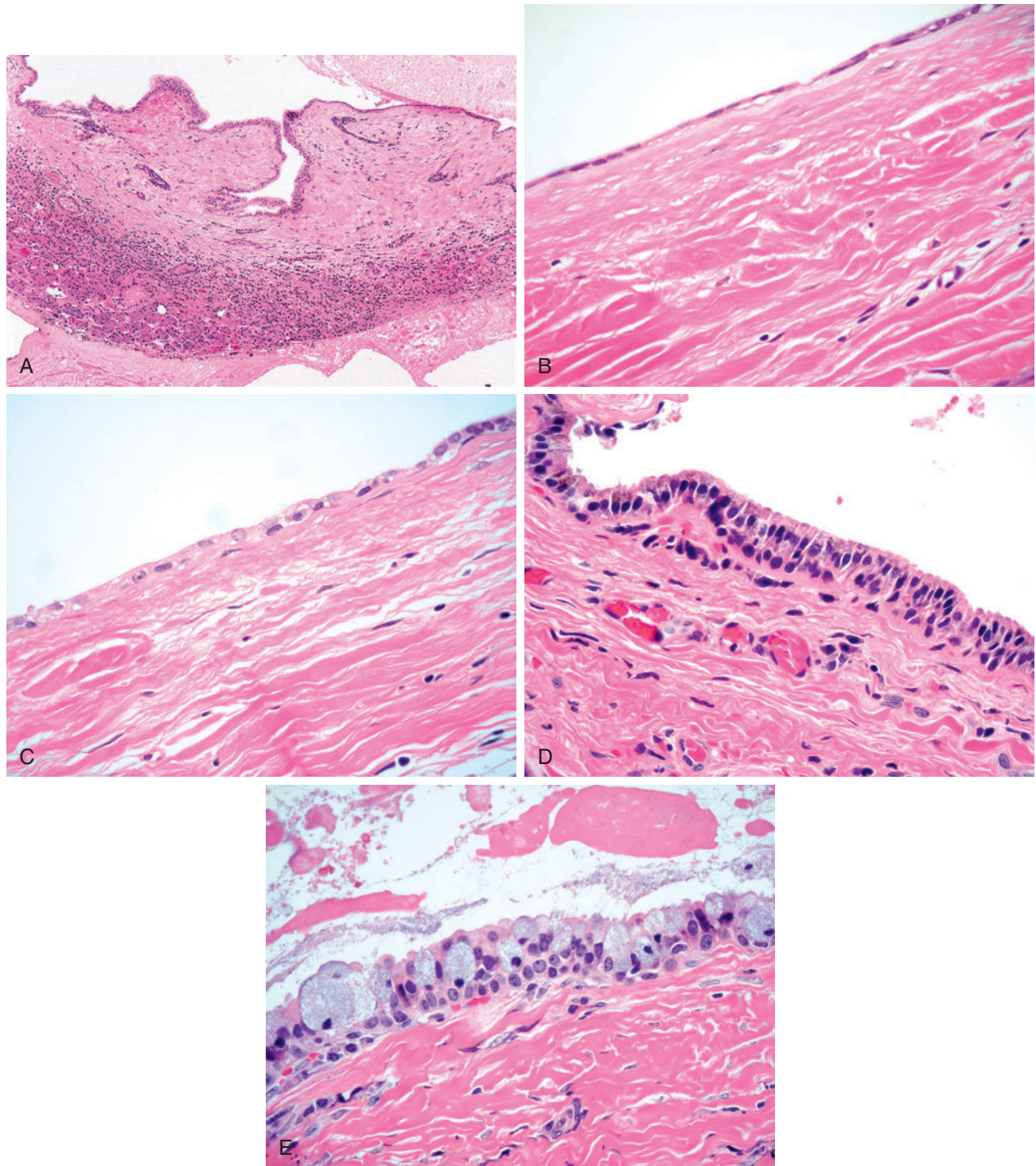


Fig. 19-11. Salivary duct cyst.

A, Unilocular cyst with fibrotic wall delineated from atrophic-appearing parotid parenchyma (*bottom*). The cyst is variably lined by **(B)** flattened (attenuated) epithelium, **(C)** cuboidal epithelium; **(D)** single to multilayered columnar epithelium; **(E)** mucous cells usually interspersed with nonmucous cells.

Polycystic (Dysgenetic) Disease (Fig. 19-12)

Definition: Rare developmental abnormality of the salivary gland duct system histologically similar to polycystic diseases of other organs (e.g., kidney, liver, pancreas, and lungs).

Clinical

- Polycystic disease represents approximately 0.2% of benign salivary gland cysts with less than 20 cases reported in the world literature.
- The overwhelming majority of the reported cases involve the parotid gland with rare involvement of the submandibular gland.

- Women are almost always affected and the majority of cases occur in childhood although patients range in age from the first to the seventh decade of life.
- Most patients have bilateral gland involvement, but occasionally only a single gland is involved.
- The clinical presentation includes recurrent, painless swelling with abnormalities in the flow of saliva.
- Based on a single case of familial occurrence, an autosomal dominant mode of transmission has been suggested.

Pathology

Cytology

- Aspirate smears characterized by relatively clean background, in which are distributed histiocytes, red

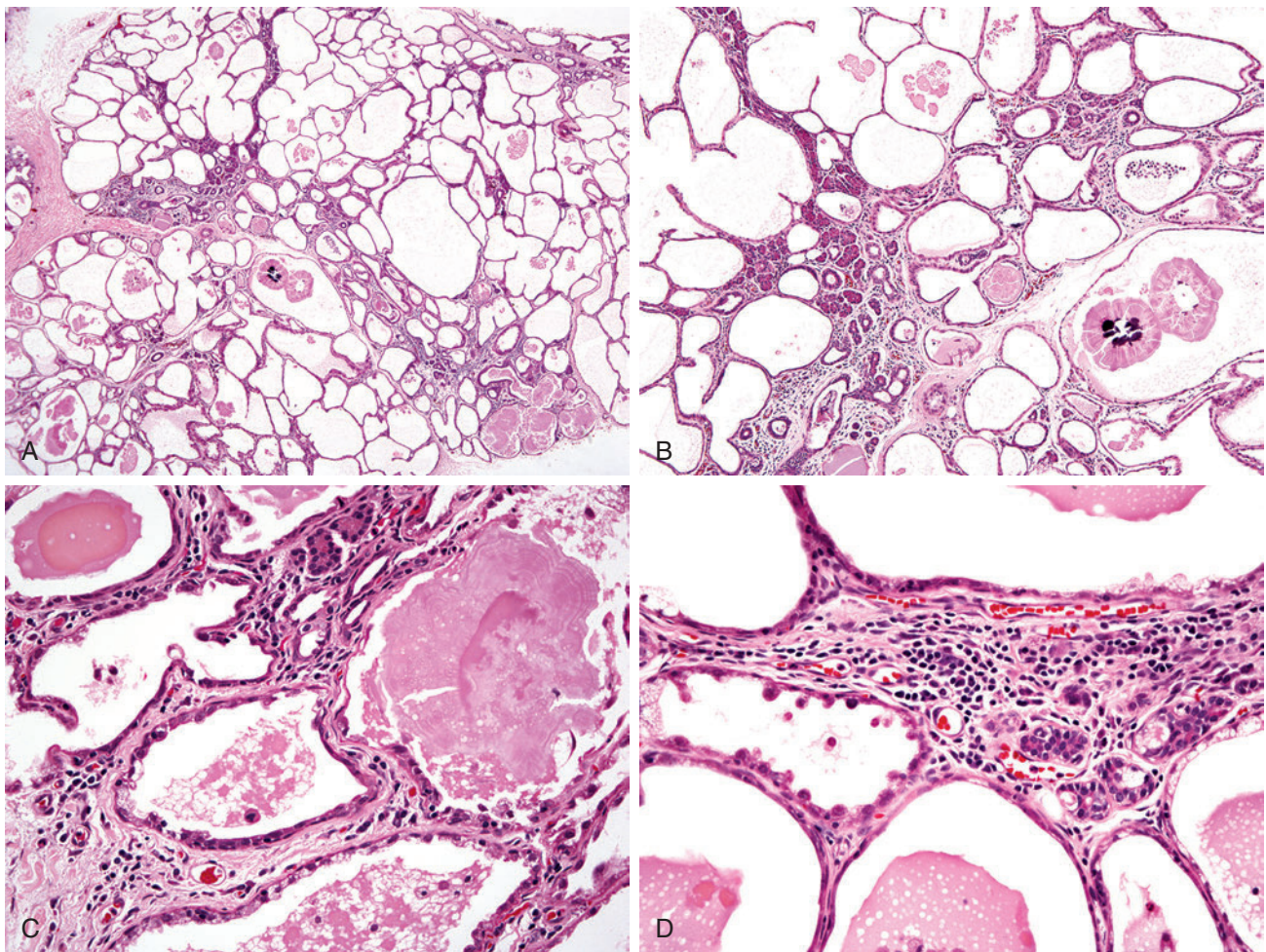


Fig. 19-12. Polycystic dysgenetic disease.

A and B, The involved gland is diffusely replaced by multiple varying-sized epithelial-lined cysts creating a honeycomb or lattice-like appearance. **C,** Cysts are lined by flattened to cuboidal to columnar-appearing epithelium; intraluminal proteinaceous and eosinophilic concretions with concentric laminations resembling microliths are present. **D,** Apocrine-like snouting may be present; entrapped salivary gland acini and ducts can be seen in between the cysts. Minimal inflammation is present.

blood cells, and small clusters of ductal epithelial cells

- Characteristic eosinophilic laminated spheroliths lie in many of the cystic spaces.

Gross

- On cut section the enlarged gland is spongy in consistency with apparent variable-sized cysts.

Histology

- Dominated by the presence of multiple varying-sized epithelial-lined cysts diffusely involving the affected gland(s):
 - Cysts have honeycomb, lattice-like appearances.
- Cysts are lined by flattened to cuboidal to columnar-appearing epithelium with apocrine-like snouting, and cytoplasmic eosinophilia.
- Some cells may contain lipid, creating a vacuolated or microvesicular appearance to the cytoplasm.
- Cysts vary in size and may be empty or contain inspissated proteinaceous material, as well as eosinophilic concretions that may demonstrate concentric laminations resembling microliths:
 - Eosinophilic concretions are diastase-resistant periodic acid Schiff positive.
 - Concretions may also stain for amyloid.
- Cysts replace the parenchyma, creating a honeycomb appearance.
- Despite parenchymal replacement, the overall lobular architecture of the gland is retained.
- Cysts often interconnect with incomplete fibrous septa.
- Parenchyma in between the cysts is fibrous but residual (entrapped) salivary gland acini and ducts can be seen.
- Inflammation is minimal to absent; no association with acute or chronic sialadenitis.

Differential Diagnosis

- Sclerosing polycystic adenosis (see Chapter 20):
 - Unilateral well-circumscribed and partially encapsulated lesion considered to be a neoplasm based on evidence of clonality and capability to harbor dysplasia and carcinoma in situ of ductal epithelium
- Cystic salivary gland neoplasms, including cystadenoma, cystadenocarcinoma, mucoepidermoid carcinoma:
 - In contrast to a neoplastic proliferation where the disease process is localized, the changes associated with polycystic disease diffusely involve the affected gland(s).
 - Absence of the constituent cells of mucoepidermoid carcinoma, including mucous cells, epidermoid cells, and intermediate assist in excluding a diagnosis of mucoepidermoid carcinoma.

Treatment and Prognosis

- Polycystic disease can be managed conservatively without surgical resection; however, surgical intervention may be required to establish a diagnosis or for cosmesis.
- This is a benign disorder with excellent long-term prognosis.
- To date, there is no evidence to suggest that polycystic salivary gland disease is associated with cystic lesions of other organs.

NONDEVELOPMENTAL CYSTS

- Salivary gland mucocele is a general term used to describe minor salivary gland lesions resulting from obstruction secondary to a mucous plug or intraluminal sialolith resulting in a mucus retention cyst, or due to trauma resulting in mucus extravasation phenomenon.

Mucus Extravasation Phenomenon

(Figs. 19-13 and 19-14)

Definition: Dilatation of minor salivary glands with accumulated mucus secretion often associated with mucus extravasation into the connective tissue without an associated epithelial lining.

Synonyms: Mucus escape phenomenon; extravasation mucocele

Clinical

- Relatively common lesion
- No gender predilection; occur in all age groups but are most common in the second to third decades of life
- Most common site of occurrence is lower lip, although other sites may be affected, including the buccal mucosa, floor of mouth, palate, tongue, retromolar fossa, tonsillar region, and upper lip.
- Clinical presentation varies but most common presentation is that of a painless swelling developing from days to week, then ruptures and disappears only to recur within several weeks.
- Superficial lesions present as raised swelling that is fluctuant on palpation.
- If the lesion is close to the surface, the overlying epithelium may be thin and the lesion has a translucent, bluish appearance; deeper-seated lesions located in soft tissues are more nodular and depending on the depth:
 - Superficial lesions are movable, smooth, soft to firm, raised vesicles with a blue or green appearance measuring in size from a few millimeters to several centimeters.

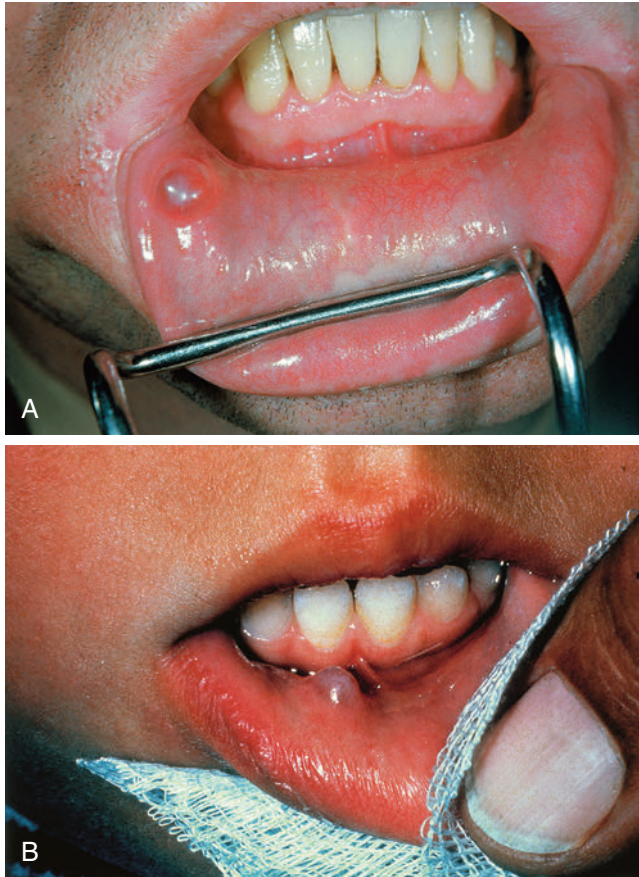


Fig. 19-13. Mucus extravasation phenomenon.

A, B, Mucus extravasation phenomenon of the lip appearing as superficial raised vesicles with a bluish appearance.

- Deeper-seated lesions are movable, firm, nodular, and covered by normal-appearing mucosa.

Pathology

Histology

- Characterized by extravasation of mucus into adjacent tissue intermixed with granulation tissue and inflammatory cells:
 - Lined by granulation tissue
 - Inflammatory cells may include numerous foamy histiocytes.
- Associated minor salivary glands show variable degree of atrophy, ductal dilatation, fibrosis, and a chronic inflammatory cell infiltrate.
- Overlying epithelium of the involved site is intact and often thinned.
- Histochemistry:
 - Intraluminal and intramural mucus material is mucicarmine and diastase-resistant, PAS positive.
 - These stains are useful for identifying residual mucus in the lesion.

Differential Diagnosis

- Diagnosis is usually straightforward and given the absence of epithelial lining essentially excludes all epithelial-lined cystic lesions (non-neoplastic and neoplastic).

Treatment and Prognosis

- Surgical excision is the preferred treatment to include excision of the associated salivary gland acini to prevent recurrence.
- Except in cases treated by inadequate surgery (incision), recurrences rarely occur.

Mucus Retention Cyst (Fig. 19-15)

Definition: Obstructive disorder of salivary glands resulting in ductal dilatation with increased intraluminal pressure; mucus retention cyst represents a true cyst in that an epithelial lining is present.

Synonyms: Retention mucocele; oral sialocyst

Clinical

- Relatively uncommon
- Tend to be slightly more common in men than in women; occur over a wide age range but most often occur in the sixth to eighth decades of life
- May occur in minor and major salivary glands but most common site of occurrence is the floor of mouth, buccal mucosa, and the lips
- Usually slow-growing and painless, appearing as a circumscribed and often fluctuant swelling; rarely, associated pain or a burning sensation may be present.
- Exact classification is subject of some debate:
 - Some classify this lesion with the more common mucus extravasation phenomenon.
 - Others consider it as a separate unique entity.
 - Given differences in clinical and histologic findings, there is justification for separating these entities.

Pathology

Gross

- Superficial lesions appear vesicular and bluish; deeper situated lesions are nodular and have the same color as the associated soft tissue.

Histology

- Cysts usually unilocular but may be convoluted simulating a multilocular or multicystic pattern
- True epithelial lined cysts:
 - Typically, epithelial lining consists of a uniform layer of cuboidal, columnar, or nonkeratinizing squamous epithelium; occasional mucus-secreting cells can be found.

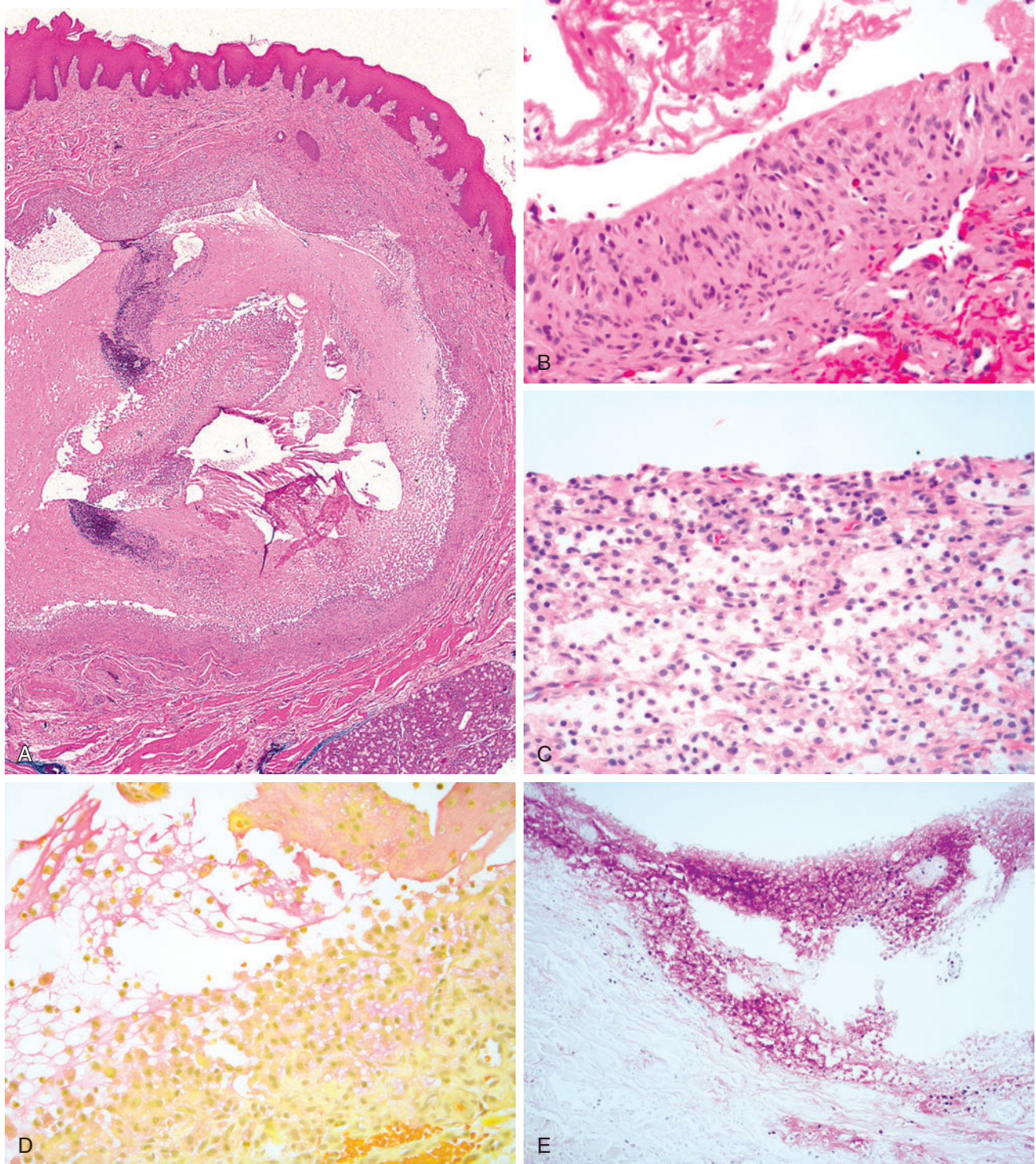


Fig. 19-14. Mucus extravasation phenomenon.

A, Mucus extravasation phenomenon characterized by a well-circumscribed submucosal mucin-filled cystic lesion. Cyst lining includes **(B)** granulation tissue and/or **(C)** inflammatory cells; intraluminal and intramural mucinous material is positive for **(D)** mucicarmine (weakly) and **(E)** PAS with diastase.

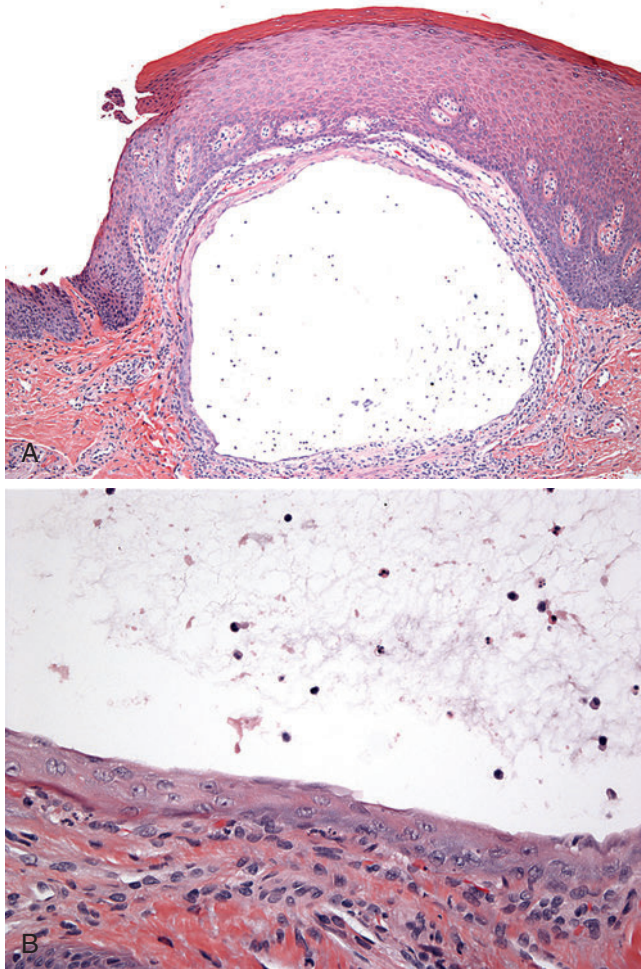


Fig. 19-15. Mucus retention cyst.

A, Unilocular mucin-filled submucosal cyst. **B**, Cyst has an epithelial lining composed of a uniform layer of cuboidal nonkeratinizing squamous epithelium.

- Cyst filled with eosinophilic material that stains with mucicarmine and PAS with diastase
- Significant associated inflammatory cell infiltrate is not typically present.

Differential Diagnosis

- Diagnosis of mucus retention cyst is usually straightforward, although in any given case the differential diagnosis includes a salivary gland neoplasm such as a mucoepidermoid carcinoma.
 - Absence of identifying the cellular components of mucoepidermoid carcinoma (i.e., mucous cells, epidermoid cells and intermediate cells) plus the absence of invasive growth exclude this diagnostic consideration.

Treatment and Prognosis

- Surgical excision is curative.

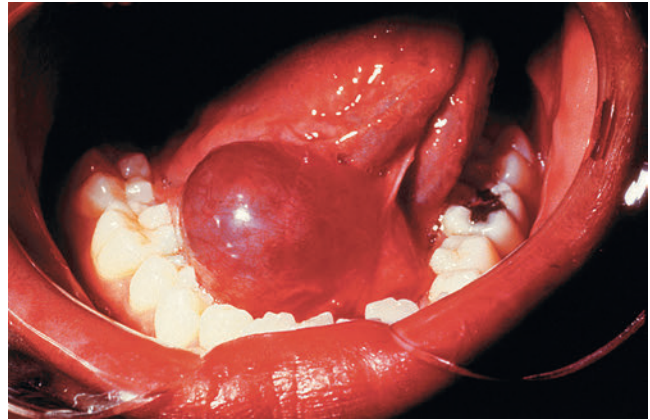


Fig. 19-16. Simple ranula.

Simple ranula identified as a large, fluid-filled mass in the lateral aspect of the floor of the mouth.

Ranula (Fig. 19-16)

Definition: Form of mucus retention cyst or mucus extravasation phenomenon specifically occurring in the floor of the mouth in association with the ducts of the sublingual or submaxillary gland.

- In Latin, ranula means “frog-like” and is so named due to its bluish appearance, likened to a frog’s belly.

Clinical

- Rare as compared with the mucus escape phenomenon (extravasation mucocele)
- No gender predilection; may affect any age group
- Most commonly a unilateral lesion but may be bilateral
- Cause considered similar to usual mucocele.
- Ranulas are divided into two types:
 - Simple ranula:
 - Considered a true cyst based on the presence of an epithelial lining
 - Plunging ranula:
 - Considered a pseudocyst based on absence of an associated epithelial lining

Simple Ranula (Sublingual Ranula)

- Occurs in lateral aspect of the floor of the mouth
- Most frequently associated with sublingual gland:
 - Occasionally may be associated with submandibular gland
- Presenting symptoms include loud snoring and a painless mass; if large, deviation of the tongue may occur.

Pathology

Gross

- Fluctuant masses measuring up to several centimeters

- Superficial lesions may impart a bluish color; more commonly, the lesions are deep-seated with the color of the overlying intact mucosa.

Histology

- May be a unilocular or multilocular cystic lesion
- Often associated with an epithelial lining; the latter including squamous, cuboidal, or columnar cells
- Cysts contain amorphous eosinophilic material.

Differential Diagnosis

- Epidermoid cyst
- Pleomorphic adenoma
- Lipoma

NOTE: The histologic findings relative to all of the above-listed lesions readily differentiate these entities from a simple ranula.

Treatment and Prognosis

- Surgical excision, including removal of the entire associated salivary gland, is the treatment of choice; some authorities prefer to simply unroof the lesion (marsupialization of the cyst wall) rather than performing total excision.
- Inadequate excision occasionally results in recurrence.

Plunging Ranula (Deep Ranula)

(Figs. 19-17 and 19-18)

- Extends beyond mucous membranes with herniation through the mylohyoid muscle into the neck resulting from mucus extravasation
- Clinical presentation is that of a painless neck mass in the submental or submandibular triangle with or without an associated lesion in the floor of the mouth.

Pathology

Histology

- Appear as pools of mucus surrounded by fibrous tissue, chronic inflammatory cells, including histiocytes
- Associated epithelial lining is not seen.
- Mucicarmine and PAS with diastase staining helpful in identifying extravasated material as mucus

Differential Diagnosis

- Epidermoid cyst
- Thyroglossal duct cyst
- Cystic hygroma
- Branchial cleft cysts

NOTE: The histologic findings and anatomic localization relative to all of the above-listed lesions readily differentiates these entities from a plunging ranula.



Fig. 19-17. Plunging ranula.

Plunging ranula in which there is herniation from the floor of the mouth through the mylohyoid muscle with a painless mass in (A) the submandibular area and (B) in the submental area.

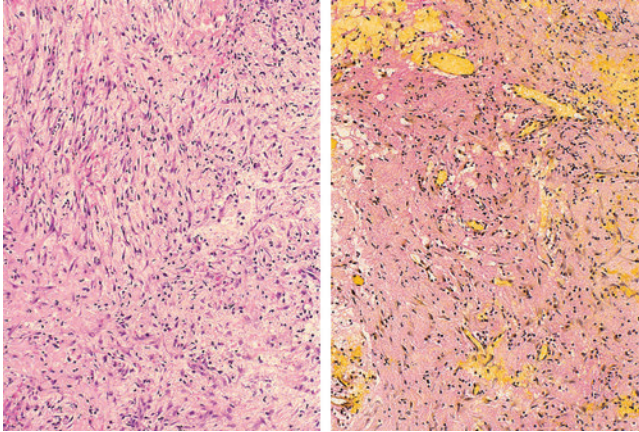


Fig. 19-18. Plunging ranula.

Left, Histologically, plunging ranulas appear as mucinous material surrounded by fibrous tissue, chronic inflammatory cells including histiocytes without an associated epithelial lining. *Right*, Mucicarmine staining shows the presence of weakly positive mucin material within the fibroinflammatory tissue.

Treatment and Prognosis

- Meticulous excision of the lesion including excision of the associated salivary gland of origin is the preferred treatment.
- Failure to include resection of the salivary gland results in recurrence.

INFECTIOUS, INFLAMMATORY, AUTOIMMUNE LESIONS OF SALIVARY GLANDS

Sialadenitis

Definition: Acute, subacute, or chronic inflammation of salivary glands due to a variety of causes including infectious disease, inflammatory condition, part of a systemic or localized autoimmune disease, secondary to trauma or secondary to stone formation.

- Sialadenitis may be acute or chronic and result from obstructive or nonobstructive causes.
- Nonobstructive sialadenitides are generally caused by an infectious agent and are divided into acute and chronic forms.

Acute Nonobstructive (Infectious) Sialadenitis

Clinical

- Infections of salivary glands may occur in a previously healthy gland or may result from a decrease in

the function of the gland secondary to physiologic dysfunction or to an anatomic barrier.

- Microorganisms may gain access to the gland via retrograde extension through the ductal system, lymphatic spread to intraglandular lymph nodes, or by hematogenous routes.
- Acute sialadenitis most commonly affects the parotid and submandibular glands.
- Acute sialadenitis may be bacterial or viral in origin:
 - *Staphylococcus aureus* and *Streptococcus viridans* are the most commonly cultured bacteria, but anaerobic bacteria have also been implicated in a significant number of cases.
 - Most common viral illness infecting the salivary glands is epidemic parotitis, also referred to as mumps, the causative organism being an RNA virus in the Paramyxovirus group:
 - Patients who are serologically negative for mumps may have infection caused by other viruses including Cocksackie A, ECHO, Epstein-Barr virus, cytomegalovirus, parainfluenza virus type C, and lymphocytic choriomeningitis virus.
 - In addition, the salivary glands represent a site of involvement for human immune virus (HIV) infection with subsequent development of HIV-associated salivary gland disease.
 - Opportunistic infections such as cytomegalovirus, adenovirus, cryptococcus, and histoplasmosis may secondarily infect the salivary glands of immunocompromised patients:
 - CMV sialadenitis may occur in the immune-competent patient, too.

Mumps (Fig. 19-19)

Definition: Self-limiting illness caused by an RNA virus in the Paramyxoviridae family that affects salivary glands.

Synonym: Epidemic parotitis

Clinical

- Acute illness of school-aged children and teenagers; uncommon in people 20 years of age and older
- Due to immunization programs that include measles, mumps, and rubella, mumps is uncommon in the United States.
- Highly contagious; transmitted by droplet spread of upper respiratory secretions
- After an incubation period of around 16 to 18 days, disease onset includes a prodrome of fever, headache, malaise, and nausea followed by painful, rapid swelling of one or both parotid glands over a 1- to 3-day period:
 - Pain is potentiated by foods that stimulate salivation, including citrus fruits or other sour liquids.



Fig. 19-19. Mumps.

This child had rapid and painful enlargement of both parotid glands over days.

- Other glands may be affected, including the lacrimal gland, thyroid gland.
- Systemic manifestations due to viremia may include:
 - Hepatosplenomegaly, pancreatitis, abdominal pain, lymphadenopathy, polyarthritides, (aseptic) meningitis, and encephalitis:
 - Systemic manifestations are more likely to occur in adults.
 - Orchitis and epididymitis can occur in approximately one third of postpubescent males.
 - Swelling and systemic symptoms gradually subside in 3 to 7 days.
- Diagnosis usually made on clinical grounds, which may include serum antibody titers and serum isoamylase fractions; surgical resection rarely occurs.
- Patients who are serologically negative for mumps may have infection caused by other viruses, including Coxsackie A, ECHO, Epstein-Barr virus, cytomegalovirus, parainfluenza virus type C, and lymphocytic choriomeningitis virus.

Pathology

- Histologic findings include presence of a marked lymphoplasmacytic cell infiltrate in periductal and periacinar tissues, as well as hemorrhage and necrosis.
- Viral inclusions are not identified.

Treatment and Prognosis

- Self-limiting infection and treatment is symptomatic.



Fig. 19-20. HIV salivary gland disease.

This HIV-infected patient has enlargement of his right parotid gland area, which represents the clinical presentation of HIV salivary gland disease. Note the scar of the left neck representing prior resection of an enlarged left parotid gland, which also shows HIV-related changes.

- Complications of infection are rare and include:
 - Sterility in men secondary to testicular atrophy after orchitis
 - Deafness as a sequelae to encephalitis
- Fatalities are rare and are related to encephalitis, myocarditis, and nephritis.

Human Immunodeficiency Virus Salivary Gland Disease (HIV-SGD) (Figs. 19-20 through 19-26)

Definition: HIV-SGD is defined as those HIV-infected individuals with xerostomia, enlargement of one or more major salivary glands, or both.

Synonyms: AIDS-related parotid cyst (ARPC); cystic lymphoid hyperplasia (CLH)

Clinical

- Include HIV-infected individuals with xerostomia, enlargement of one or more major salivary glands, or both of the above
- May represent the initial manifestations of HIV infection
- Exact incidence of salivary gland enlargement in HIV-infected individuals is not known but has been considered to be about 5% of adult patients.

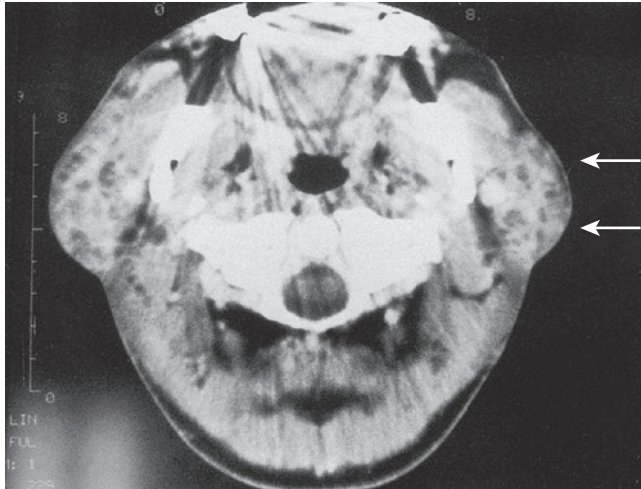


Fig. 19-21. Imaging findings in HIV-SGD.

CT scan imaging in HIV-SGD showing the presence of bilateral, multicentric, variable-sized cysts.

- Primarily affects adult men aged 20 to 60 years with greater than 90% of cases occurring in men:
 - May occur in children born of HIV-infected mothers; under these circumstances there is no gender predilection
- Symptoms include painless swelling of one or more salivary glands, xerostomia, dry eyes, and arthralgias.
- Salivary gland involvement is almost always the parotid gland (98%) and less often the submandibular gland (2%):
 - In approximately 60% of the cases there is bilateral disease.
- Salivary gland involvement typically occurs in the early stages of HIV disease prior to the development of AIDS.
- Serology evaluation will confirm HIV positivity.
 - Serologic markers that are present in Sjögren syndrome, including polyclonal hypergammaglobulinemia and production of organ-specific autoantibodies (anti-salivary duct antibodies, autoantibodies), non-organ-specific (rheumatoid factor, Anti-Nuclear Antibodies [ANA], anti-RO [SS-A], anti-LA [SS-B]) are commonly absent in HIV-SGD.
- CT scan and MRI show unilateral or bilateral multicentric cysts of varying sizes.
- Sjögren syndrome-like illness has also been identified in AIDS patients, representing additional evidence of the severely damaged immune system in these patients.
- Diffuse infiltrative lymphocytosis syndrome (DILS) and HIV-associated CD8+ lymphocytosis syndrome:

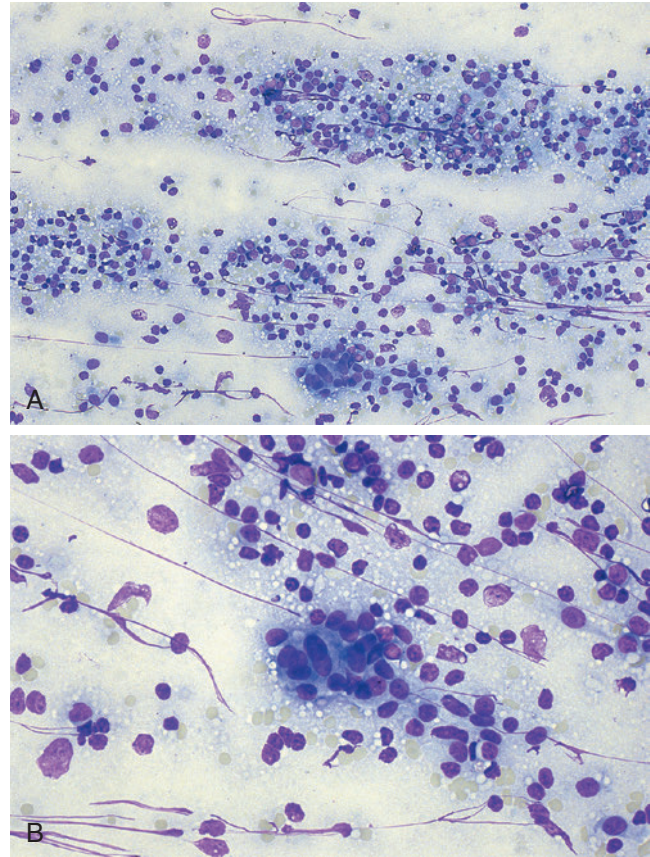


Fig. 19-22. Cytology in HIV-SGD.

Fine-needle aspiration biopsy of HIV-SGD.

A, Heterogeneous lymphoid population is present, including the presence of scattered plasma cells, macrophages, and a multinucleated giant cell (*lower*).

B, Higher magnification showing the multinucleated giant cells. In the appropriate clinical setting, these cytologic findings would be consistent with HIV infection.

- Represents an uncommon manifestation of HIV infection characterized by persistent circulating CD8+ lymphocytosis accompanied by visceral lymphocytic infiltration
 - Primarily characterized by parotid gland enlargement, sicca symptoms, and pulmonary involvement occurs in HIV infection
 - Appears to be an antigen (viral)-driven response
 - Associated with CD8 lymphocytosis and the presence of HLA-DR5 and appears to be a genetically determined host immune response to HIV
 - In DILS, certain HIV-infected individuals develop oligoclonal expansion of CD8+ lymphocytes characterized by a persistent circulating CD8+ lymphocytosis.
 - These cells infiltrate multiple organs, but the salivary glands and the lung constitute the major sites of involvement.

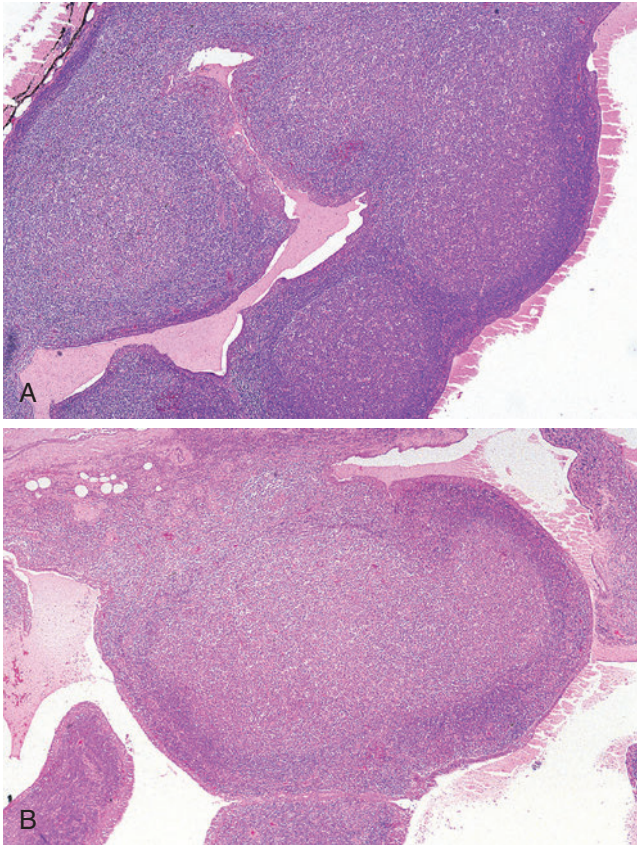


Fig. 19-23. HIV-SGD.

A, B, Multiple epithelial-lined cysts with associated lymphoid cell proliferation, including florid follicular hyperplasia with attenuated to absent mantle lymphocytes.

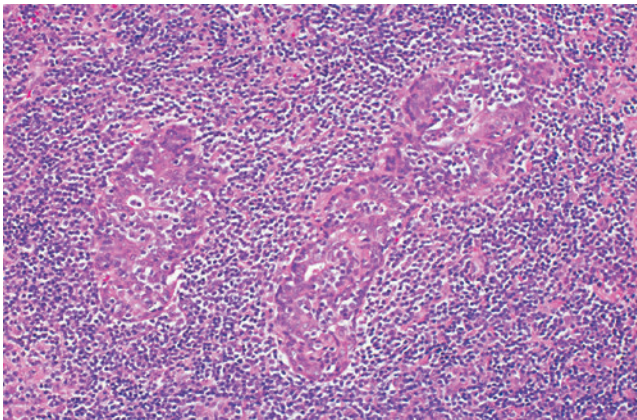


Fig. 19-24. HIV-SGD.

In addition to the epithelial-lined cysts and the lymphoid changes, the histology of HIV-SGD also includes the presence of lymphoepithelial islands (identical to those seen in lymphoepithelial sialadenitis).

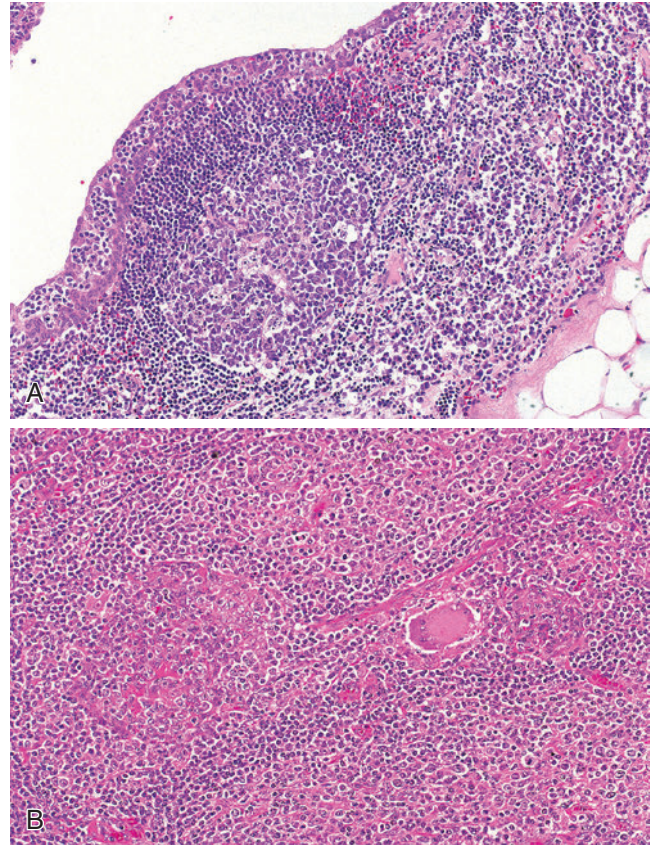


Fig. 19-25. HIV-SGD.

A, Findings include an epithelial lining infiltrated by mature lymphocytes (so-called lymphoepithelium) with a subjacent small lymphoid aggregate. **B,** Lymphoepithelial lesion (left of center) within the cyst wall. Such features in conjunction with other findings, the presence of multinucleated giant cells (right of center) would support the diagnostic consideration of HIV-SGD but requires clinical and serologic correlation.

- This infiltrative process resembles in many aspects a Sjögren-like syndrome, owing to the visceral lymphocytic infiltration.
- Pulmonary process associated with DILS may mimic clinically and radiographically the pneumonic process caused by *Pneumocystis jiroveci* (formerly *carinii*).
- Other manifestations of DILS to consider include a severe form of peripheral neuropathy, lymphocytic infiltration of the liver, evident as hepatitis, myositis, and lymphocytic interstitial nephritis.
- DILS may progress to development of parotid cysts.
- DILS in HIV has similarities to classic Sjögren syndrome, manifested by distinctive clinical, serologic, immunologic, and immunogenetic characteristics:

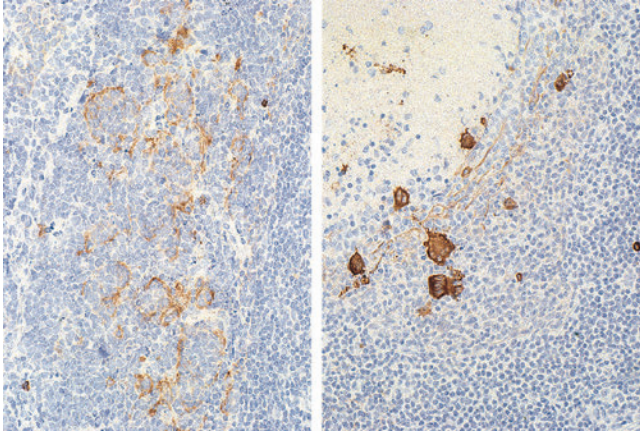


Fig. 19-26. p24 immunoreactivity.

Immunohistochemical staining against HIV p24 core antigen is confirmatory of HIV infection with reactivity (*left*) within the follicular dendritic cells of the germinal center and (*right*) multinucleated giant cells representing the reservoirs for the virus and/or antigen processing cells.

- In contrast to Sjögren syndrome, the greater degree of salivary gland enlargement and extraglandular disease, including pulmonary, renal, gastrointestinal, breast, and muscle, as well as the low frequency of autoantibodies and differing HLA associations seen in DILS, serve to distinguish DILS from classic Sjögren syndrome.
- Primary treatment anti-HIV therapy

Pathology

Cytology (Fine-Needle Aspiration Biopsy [FNAB])

- Simple and cost-effective procedure for the diagnosis
- Diagnosis of HIV-SGD can be considered in cystic parotid gland lesion(s) showing a combination of:
 - Heterogeneous lymphoid population
 - Scattered single and/or clustered foamy macrophages
 - Numerous multinucleated giant cells
 - Superficial and/or anucleated squamous cells

Histology

Lymphoid-Related Changes

- Histologic alterations similar to changes seen in lymph nodes in early phases of HIV infection, including florid follicular hyperplasia, attenuated to absent mantle lymphocytes, disruption of the germinal centers (follicle lysis), and the presence of multinucleated giant cells (MGCs) localized to interfollicular, intrafollicular, and periepithelial areas
- Monomorphic round cells with clear cytoplasm (monocytoid B-cells) can be found in clusters.

- Interfollicular mixed (benign) inflammatory-cell infiltrate with mature lymphocytes, histiocytes, neutrophils, and plasma cells are also present.

Cystic Changes

- In addition to the lymphoid changes, multiple squamous epithelial-lined cysts and lymphoepithelial lesions are present.
- Squamous epithelial-lined cysts and the lymphoepithelial lesions typically permeated by mature lymphocytes (typically monocytoid B-cells in epimyoeplithelial islands)
- Lymphoepithelial lesions formed by hyperplasia and metaplasia of ductal epithelium
- Origin of cysts appears to be from the salivary gland (parotid) epithelial structures arising in intraparotid or periparotid lymph nodes accounting for the lymphoid component:
 - Similar cysts can be found in HIV-negative patients.
- Presence of HIV-1 suggests pathogenesis of salivary gland lymphoepithelial lesions is primarily due to this virus.
- Histochemistry:
 - For the lymphoid changes and the cystic lesions, special stains for microorganisms are negative.
- Immunohistochemistry:
 - Presence of B-cell lineage (e.g., CD20, others) and T-cell lineage markers (CD3, others)
 - Epithelial markers (cytokeratins, others) delineate squamous epithelial-lined cysts and epimyoeplithelial islands.
 - Immunoreactivity with HIV p24 core antigen can be found in the germinal centers (follicular dendritic cells), scattered lymphoid cells and in the multinucleated giant cells:
 - Multinucleated giant cells may also show the presence of S100 protein and p55 (actin bundling protein).
- Cytogenetics and molecular genetics:
 - In two related settings, diffuse infiltrative lymphocytosis syndrome (DILS) and HIV-associated CD8+ lymphocytosis syndrome, monoclonal TCR gene has been reported:
 - Despite the finding of monoclonal TCR gene, there is evidence that the CD8+ expansions are reactive populations capable of mediating non-cytotoxic inhibition of HIV replication that is believed to represent an immune response to viral infection rather than a malignant disorder.

Differential Diagnosis

- Other infectious diseases
- Salivary gland lesions with morphologic changes that overlap with HIV-SGD collectively referred to

as lymphoepithelial lesion (LEL) occurring in lymphoepithelial sialadenitis (see later).

- Sjögren syndrome:
 - Serologic markers that are present in Sjögren syndrome, including polyclonal hypergammaglobulinemia and production of organ-specific autoantibodies (antisalivary duct antibodies autoantibodies), non-organ-specific (rheumatoid factor, anti-nuclear antibodies [ANA], anti-RO [SS-A], anti-LA [SS-B]) are commonly absent in HIV-SGD.
- Cystic salivary gland neoplasms:
 - In general, differentiation from salivary gland neoplasms (benign and malignant) is straightforward because the cellular components that are diagnostic for a given salivary gland neoplasm are absent in HIV-SGD.
- Malignant lymphomas:
 - Differentiation from malignant lymphoma is predicated on the presence of a heterogeneous cell population and correlating IHC reactivity for B- and T-cells, as well as the absence of a monomorphic cell population, absence of cytologically malignant cells, and absence of clonal cell population by immunohistochemical and/or molecular diagnostic modes of evaluation.

Treatment and Prognosis

- Treatment for HIV-SGD varies and includes surgical resection (parotidectomy, conservative excision, curettage), radiation, and symptomatic relief.
- Highly active antiretroviral treatment (HAART) has been shown to reduce the size of parotid swellings and even result in regression of HIV-SGD:
 - Successful outcome reflected in diminution of viral load and to some degree of immune restoration.
 - Parotid gland involvement does not appear to play any role in the course of the disease or progression to AIDS.
- Prevalence of DILS had significantly decreased in the post-HAART era, suggesting that DILS is an antigen (viral)-driven response and the primary treatment for it is anti-HIV therapy.
- HIV-SGD is benign but hematologic malignancies may occur in association with the HIV-SGD or develop subsequently:
 - Polymorphic B-cell lymphoproliferative disorders comparable morphologically and molecularly to those arising after solid organ transplantation also occur in association with HIV infection, although their biologic significance and malignant status remains unclear.

Chronic Sialadenitis

Definition: Chronic inflammation of salivary glands that may result from a variety of causes, including nonobstructive diseases and obstructive lesions.

- Causes include:
 - Mechanical obstruction, infectious disease, and autoimmune diseases
 - In many patients the cause of chronic sialadenitis is less clear and is due to a category of lesions referred to as chronic recurrent sialadenitis.

Chronic Nonobstructive Sialadenitis

- Chronic nonobstructive sialadenitis may have specific causes, including granulomatous sialadenitis (infectious and noninfectious) or irradiation.
- Sialadenitis secondary to radioactive iodine therapy for thyroid carcinoma is common.
- Granulomatous inflammation of the salivary glands most often is caused by duct obstruction (e.g., calculi, carcinoma), resulting in extravasation of the obstructed duct content into the salivary gland parenchyma causing a foreign body granulomatous inflammatory reaction.
- Granulomatous sialadenitis due to an infectious cause is less common and is caused by a number of diseases including (but not limited to) tuberculosis, actinomycosis, and cat-scratch disease.
- Sarcoidosis is yet another cause of granulomatous sialadenitis associated with chronic nonobstructive sialadenitis (see later).
- Granulomatous sialadenitis may occur as an isolated phenomenon but is more commonly seen as part of a systemic process; such a phenomenon may be seen in association with sarcoidosis, cystic fibrosis, and Crohn disease.

Sarcoidosis of Salivary Glands (Fig. 19-27)

Definition: Sarcoidosis is a multisystem chronic (noncaseating) granulomatous disease of unknown cause that affects a variety of sites, including (but not limited to) lymph nodes, lungs, mucosal sites of the upper aerodigestive tract, salivary glands, skin, spleen, and liver.

Synonym: Boeck disease

Clinical

- Worldwide sarcoidosis is most common in young to middle-aged women.
- In the United States, sarcoidosis is ten times more common in African Americans with a female

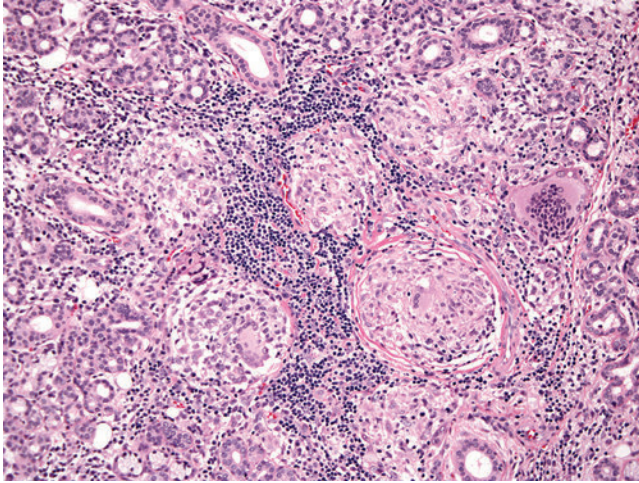


Fig. 19-27. Sarcoidosis.

Sarcoidosis in the parotid gland. Intraparenchymal noncaseating granulomas are identified. Special stains for microorganisms were negative. The patient was known to have sarcoidosis.

predominance; there is a higher prevalence among people in the southeast United States.

- Pulmonary symptoms are present in approximately 60% of cases and consist of dyspnea, cough, and nonpleuritic chest pain.
- Nonspecific symptoms may include fever, malaise, weight loss, and lymphadenopathy, the latter including (but not limited to) hilar and paratracheal lymph nodes.
- Cutaneous lesions may occur in up to one third of patients and red- or purple-appearing papules.
- In head and neck, more common sites of involvement include:
 - Cervical neck lymph nodes (anterior and posterior cervical lymph nodes), eye, salivary glands, and mucosal sites of the upper aerodigestive tract
 - Salivary gland involvement usually includes the parotid gland and submandibular gland, but minor salivary glands may be affected.
- Parotid gland involvement may occur as an isolated process or as part of a syndrome termed uveoparotid fever, also known as Heerfordt syndrome, characterized by the parotitis, xerostomia, uveitis, and facial nerve palsy.
 - Parotid gland sarcoidosis:
 - Occurs in 6% of patients with systemic sarcoidosis and may be bilateral in a majority of cases
 - May occur in association with Sjögren disease
 - May present with sicca complex (xerophthalmia and xerostomia), suggesting a clinical

diagnosis of Sjögren syndrome (see Differential Diagnosis later)

- No laboratory findings specific for or diagnostic of sarcoidosis:
 - Elevated serum levels of angiotensin-converting enzyme (ACE) are found in patients with active pulmonary sarcoidosis; however, ACE levels are elevated in other (nonsarcoid) diseases including liver disease and leprosy.
 - Cutaneous anergy to skin test (“sarcoid”) antigens referred to as the Kveim test is positive in a majority of patients with recently diagnosed (sub-acute) sarcoidosis; the Kveim test reaction may be low or absent in patients with inactive or chronic sarcoidosis.
- Although a known cause has not been elucidated to date, speculation remains that sarcoidosis is an infectious disease possibly caused by a mycobacterial infection (i.e., mycobacteria other than *M. tuberculosis* [MOTT]).

Pathology

Cytology

- Collections of epithelioid histiocytes with or without multinucleated giant cells without accompanying necrosis or acute inflammation
- Salivary gland acini with varying degrees of degenerative changes
- Efficacy, utility, and cost savings of fine-needle aspiration biopsy in the diagnosis and differential diagnosis of granulomatous sialadenitis to include sarcoidosis has been demonstrated in numerous studies.

Microscopic

- Histologic hallmark is presence of well-formed, noncaseating granulomas consisting of epithelioid histiocytes surrounded by a mixed inflammatory infiltrate and multinucleated (Langhans type) giant cells.
- Intracytoplasmic inclusions including star-shaped, referred to as asteroid bodies, and calcific laminated bodies, called Schaumann bodies, can be seen.
- No polarizable, pigmented foreign material or dissolvable material is identified.
- Histochemistry:
 - All special stains for microorganisms, including Gomori methenamine silver (GMS) and acid-fast bacilli (AFB), are negative.

Differential Diagnosis

NOTE: The noncaseating granulomas of sarcoidosis are not pathognomonic. The pathologic features of sarcoidosis are characteristic but they are not specific; the diagnosis of sarcoidosis can only be considered in the absence of identifying an infectious agent.

- Other granulomatous disease, primarily of infectious cause, such as mycobacterial infection and fungal infection:
 - Identification of microorganisms by special stains, microbiologic cultures, and/or molecular analysis allows for differentiation.
- Noncaseating granulomas unrelated to an infectious cause can be seen in association with rheumatoid arthritis (rheumatoid nodule) and as a reactive process in tissues (e.g., lymph nodes) adjacent to malignancies; detailed clinical history should allow for differentiating these lesions from sarcoidosis.
- Sjögren syndrome:
 - Patients with sarcoidosis of the salivary glands may present with sicca complex (xerophthalmia and xerostomia) suggesting a clinical diagnosis of Sjögren syndrome (SS):
 - In contrast to patients with sarcoidosis, patients with SS present more frequently with Raynaud phenomenon, more often have autoantibodies, and minor salivary gland biopsy (MSGB) shows focal sialadenitis in the majority of the patients.
 - Patients with sarcoidosis more frequently have parotid gland enlargement, mainly have pulmonary and cutaneous involvement, lack autoantibodies, and histopathologic findings of MSGB may show noncaseating granulomas.
 - In cases in which there are equivocal findings by MSGB, transbronchial lung biopsy may be required and the presence of noncaseating granulomas is diagnostic of sarcoidosis.
- For a more complete discussion, including histopathologic features and illustrations, see Section 1, Sino-nasal Tract.
- Often a nodal-based proliferation occurring as part of a generalized process involving lymph nodes; SHML involve extranodal sites independent of the lymph node status
- Head and neck region represents one of the more common extranodal areas affected by SHML:
 - Within the head and neck, there is predilection for the nasal cavity and paranasal sinuses.
 - Virtually all head and neck sites may be affected in association with or independent of nodal disease, including major salivary glands.
 - Salivary gland involvement is uncommon and may occur in association with other extranodal head and neck sites involved by SHML or occurs independent of other sites of involvement.
- Salivary gland involvement:
 - No gender predilection
 - Occurs over a wide age range
- Parotid gland and submandibular glands are most often affected; lacrimal glands may also be involved.
- Patients with salivary gland involvement present with a discrete, painless mass, which clinically may suggest a primary salivary gland tumor.
- SHML may occur in association with HIV-infected patients, Sjögren syndrome, and amyloidosis; SHML co-existing with Langerhans cell histiocytosis has also been reported.
- Salivary gland lesions are polypoid, nodular, or exophytic growths with a tan-white to yellow appearance.
- No ideal treatment:
 - Treatment protocols should mirror the clinical manifestations such that a range of therapeutic modalities may be used.
- Transformation to a high-grade lymphoma may rarely occur.

Treatment and Prognosis

- Clinical course in the majority of patients is benign, and spontaneous remission may occur within 2 years of the diagnosis.
- Treatment for systemic sarcoidosis in which there is extensive disease or disease that compromises normal function can be by corticosteroid therapy.
- Prognosis for systemic disease is generally good, with up to 70% of patients improving or remaining stable after therapy.
- Advanced multisystem disease leading to extensive pulmonary involvement and respiratory failure may occur but is seen in only a small percentage of cases.
- Less than 10% of patients die of pulmonary, cardiac, or central nervous system involvement.

Extranodal Sinus Histiocytosis with Massive Lymphadenopathy

- Idiopathic, histiocytic proliferative disorder that usually resolves spontaneously
Synonyms: Rosai-Dorfman disease, Destombes-Rosai-Dorfman syndrome

Chronic Obstructive Sialadenitis

- Most common cause of obstructive or occlusive sialadenitis is stone formation referred to as sialolithiasis (see later); less common causes of chronic obstructive sialadenitis include:
 - Stenosis, stricture
 - Congenital duct malformations
 - Ascending infections
 - Kussmaul disease (fibromucinous plugs in the collecting system of dehydrated patients)
 - Trauma
- In children, mumps (see earlier) is a common cause of sialadenitis; less common, children may also suffer from recurrent parotitis, the cause of which remains uncertain, characterized by:



Fig. 19-28. Sialolithiasis.

Oral cavity showing a white stone situated within the orifice of the parotid (Stensen) duct causing an obstructive sialadenitis.

- Recurrent, acute exacerbations of inflammation resulting in a slowly progressive destruction of the parotid gland.
- Chronic sialadenitis may or may not be associated with stone formation; however, calculi are seen in nearly two thirds of patients with chronic sialadenitis.
- Chronic sialadenitis more commonly affects the parotid gland, probably resulting from the anatomy of Stenson duct, which is long and narrow making it more susceptible to any alterations in the composition of its saliva.

Sialolithiasis (Figs. 19-28 through 19-31)

Definition: Occurrence of calcereous concretions within salivary gland ducts and/or parenchyma as a result of mineralization of debris accumulated within duct lumens.

Clinical

- Calculi may be seen in the ductal system of all salivary glands but are particularly common in the submandibular gland (Wharton duct), accounting for 80% to 90% of cases, and parotid gland (Stensen duct), accounting for 10% to 20% of cases:
 - Greater involvement of the submandibular gland is thought to be due to the higher mucin content of its saliva with more adherent properties.
 - Sublingual or minor salivary glands are rarely affected.
 - Involvement of minor salivary glands usually includes the upper lip and buccal mucosa.

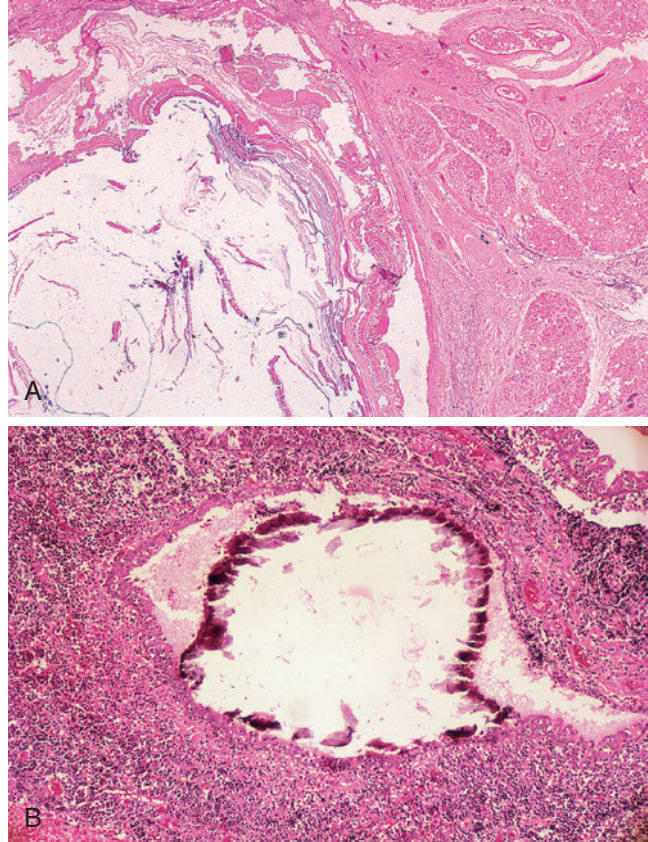


Fig. 19-29. Sialolithiasis.

A, A calculus is seen within a large duct as concentric laminations of calcification peripherally surrounded by compressed ductal epithelium and fibrotic change within adjacent salivary gland parenchyma; minimal inflammation is present. **B,** In this example a calculus is present within a duct surrounded by the presence of a marked inflammatory cell infiltrate.

- Salivary calculi occur slightly more often in men than in women; occur at any age but are most frequently seen in middle-aged adults; pediatric sialolithiasis is uncommon.
- Symptoms depend on size and location of calculi:
 - Submandibular gland calculi are:
 - Larger than those of the parotid gland, producing recurrent episodes of pain and swelling usually in association with meals
 - May be associated with sore throat or pharyngitis refractory to antibiotic therapy
 - Parotid gland calculi are:
 - Usually smaller than those of the submandibular gland
 - May function as a ball-valve effect, producing intermittent obstruction and symptoms; the latter include pain and swelling

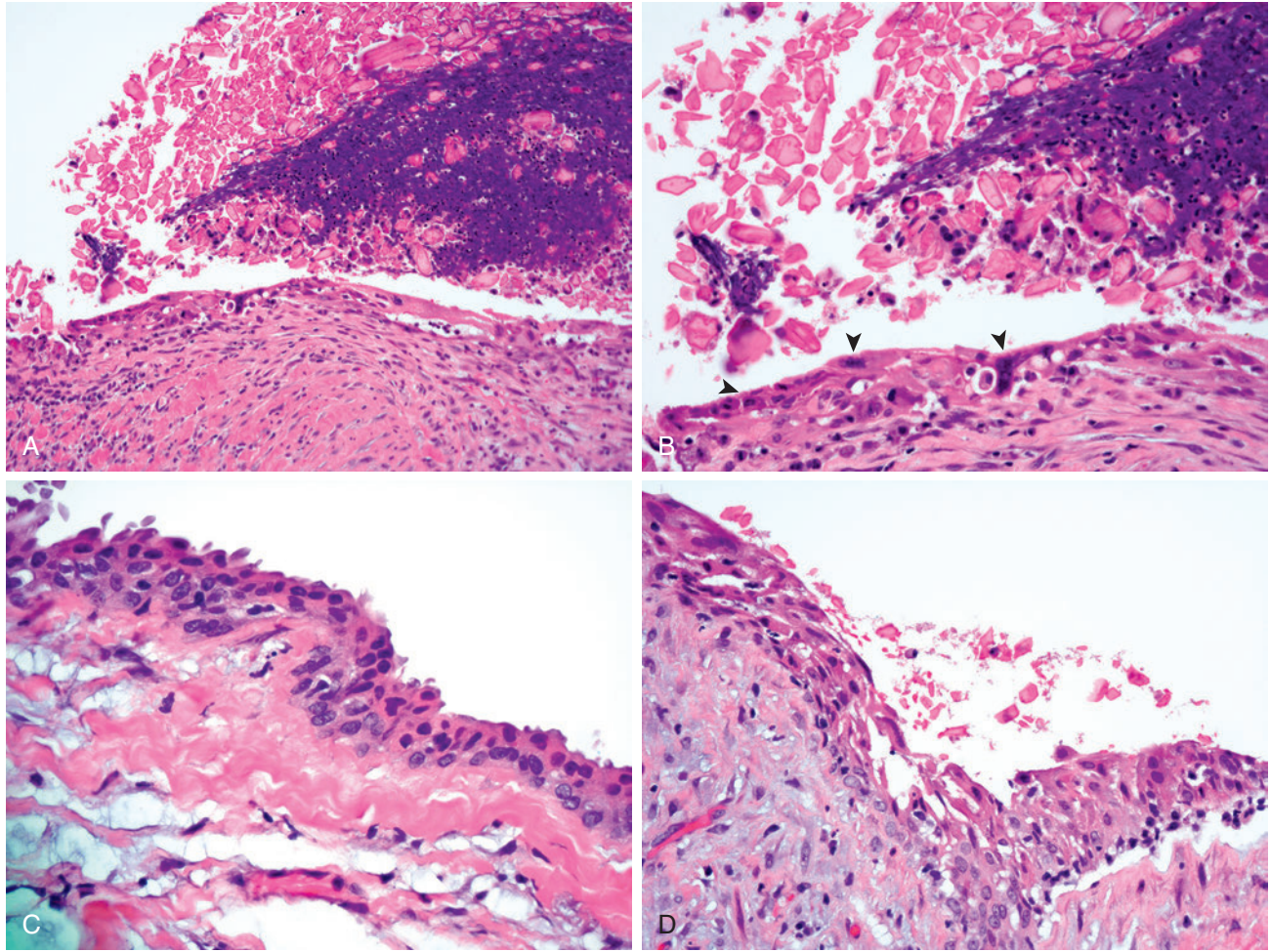


Fig. 19-30. Sialolithiasis.

A and B, Ectatic duct filled with reddish-appearing crystalline stone material with associated neutrophils and blue-appearing bacterial colonization; cyst epithelial lining is attenuated and includes scattered cells with enlarged hyperchromatic nuclei (*arrowheads*). The wall of the cyst shows fibrosis and scattered fibroblasts. The cyst lining may variably include (**C**) oncocytic cells; (**D**) squamous cells. Mucous cells may be present (not shown). **C, D,** In some cases there may be extracellular mucus extravasation (in cyst wall) that, in conjunction with squamous-appearing cells and mucocytes, may suggest a diagnosis of mucoepidermoid carcinoma (MEC). The absence of a proliferative (thickened) epithelial component, including an admixture of epidermoid cells, mucocytes, and intermediate cells as well as presence of identifiable intraductal stone material, would weigh against a diagnosis of MEC.

- If obstruction is not relieved, stasis of saliva ensues, potentially resulting in an associated bacterial infection (most often due to *Streptococcus viridans*), manifested by expression from the ducts of mucopurulent material (pus).
- Calculi may be palpated or even visualized in the distal duct system; because of its deeper anatomic location, calculi within Stenson duct are often not palpable.
- Calculi are formed by deposition of calcium phosphate and an organic matrix made up of various amino acids and carbohydrates around a central nidus thought to be either bacteria or inorganic material; stone development has no correlation to the serum calcium or phosphorus levels.
- Radiographic analysis represents the most reliable means to detect the presence of calculi:
 - Majority of calculi are radiopaque and can be visualized by routine radiography.
 - Majority of parotid gland calculi are radiolucent and may require special oblique views of the cheek for visualization.
 - Sialography may be of assistance but is often unnecessary, yielding limited additional information and being a potential source of inducing an infection.

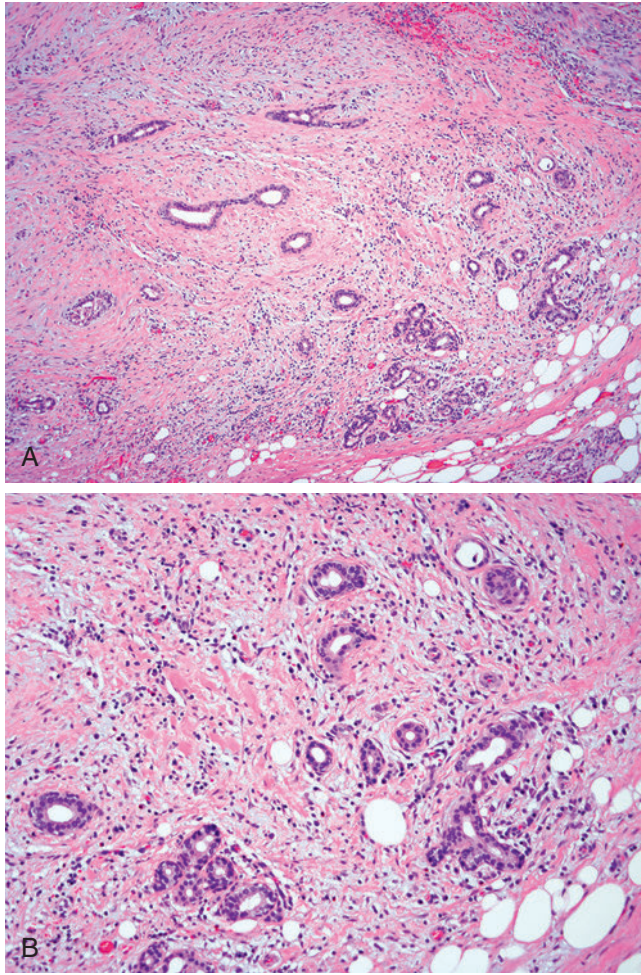


Fig. 19-31. Sialolithiasis.

A, B, Over time, the surrounding parenchymal changes in sialolithiasis may include fibrosis, parenchymal atrophy with loss of acini, chronic inflammation, and scarring.

- Cause:
 - Remains uncertain
 - Suggested correlation with smoking history, diuretic use

Pathology

Gross

- Affected gland is enlarged, firm, and nonfluctuating.
- Sialoliths are round to oval, white to yellow-brown, measuring from a few millimeters to several centimeters in diameter.

Cytology

- Abundant polyhedral, multifaceted (nontyrosine) crystalloids may be seen in the background of scanty cellular specimens composed predominantly of oncocytic cells.

- When crystalloids/stone fragments identified in aspirated material, these cases pose little diagnostic difficulty.
- When crystalloids/stone fragments not present, epithelial changes and mucus accumulation may be difficult to distinguish from low-grade mucoepidermoid carcinoma or other neoplasms.

Histology

- Calculi may be seen within the parenchyma or in the ducts as concentric laminations of calcification peripherally surrounded by compressed epithelium.
- Ductal epithelium may demonstrate mucous cell, squamous, or oncocytic metaplasia.
- With chronicity of disease, parenchymal changes may include fibrosis, parenchymal atrophy with loss of acini, chronic inflammation, ductal dilatation, and scarring.

Treatment and Prognosis

- Small stones can be treated conservatively by increased intake of fluids, moist heat, analgesics, and massage; such therapy may result in the passage of the stone with restoration of salivary flow; calculi may pass spontaneously.
- Failure by conservative means or if the stone is large necessitates surgical removal of the obstruction, which varies from excisional biopsy to shock wave lithotripsy to removal of the entire submandibular or parotid gland.
- Antibiotics are administered in those cases secondarily infected. Recurrent infections may occur if the cause of the obstruction is not removed.

Chronic Recurrent Sialadenitis (Fig. 19-32)

Definition: Represents a group of lesions primarily affecting the parotid gland characterized by recurrent attacks of swelling associated with pain involving one or both glands.

Clinical

- No gender predilection; may affect children or adults
- Clinically, characterized by recurrent attacks of swelling of affected gland with associated pain
- Primarily involves parotid gland
 - One or both parotid glands may be affected
 - Anatomically, parotid gland duct (Stensen duct) is long and narrow as compared with the shorter and wider submandibular gland duct (Wharton duct), predisposing parotid gland to abnormalities of secretions that may result in recurrent sialadenitis.

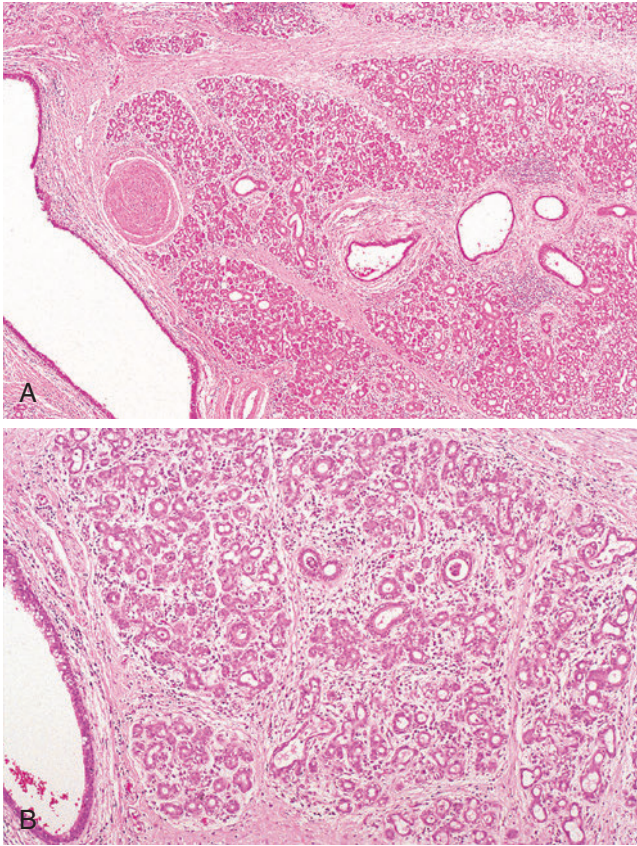


Fig. 19-32. Chronic recurrent sialadenitis.

A, B, Duct ectasia with retention of the lobular architecture of the gland; a mild inflammatory cell infiltrate (composed of mature lymphocytes and plasma cells) is present within the parenchyma.

- Cause:
 - Remains uncertain but predisposing factors associated with alterations of saliva (decreased secretion, stasis, and changes in its chemical composition) creating an environment conducive for infection with induction of ductal epithelial metaplasia resulting in obstruction and recurrent inflammation(s)
- Sialography remains the preferred investigation.
- Diagnostic sialadenoscopy may complement or even supersede sialography as the diagnostic procedure of choice, but at present more experience is needed in this technique and its use becomes more widespread.

Pathology

Histology

- In the initial stages the regular lobular architecture of the gland is retained.
- Duct ectasia surrounded by a mild inflammatory cell component composed of mature lymphocytes and plasma cells is present.

- Advanced stages characterized by a marked increase of periductal inflammatory cell infiltrate eventually resulting in near complete obliteration of the affected gland with destruction of the lobular formation and effacement of the salivary gland parenchyma.
- Lymphoid follicles may be present and in some cases lymphoepithelial islands similar in appearance to those identified in benign lymphoepithelial lesions may be present.

Treatment and Prognosis

- May spontaneously resolve with puberty; however, spontaneous resolution in the adult population is not common
- Because cause and pathogenesis remains unknown, no causal therapy is available.
- Therapy may vary from conservative treatment to surgery and a variety of therapeutic modalities have been used, including gland massage, infrared light, antibiotics, injection of a sclerosing agent (e.g., methyl violet), antiphlogistics, Trasyolol, duct occlusion, ductal ligation, ductoplasty, gland denervation, tympanic neurectomy, and radiotherapy.
- Conservative management often fails necessitating surgery (e.g., parotidectomy):
 - For patients unresponsive to conservative measures, superficial parotidectomy with preservation of the main duct is safe and effective in the treatment of chronic sialadenitis, and in some patients allows for some preservation of function.

Sialadenosis

Definition: Non-neoplastic, noninflammatory enlargement of salivary glands (in particular parotid), which is almost always associated with an underlying systemic disorder or a secretory dysfunction.

Synonym: Sialosis

Clinical

- No gender predilection; occurs most commonly in adults
- Salivary gland enlargement most often affects parotid gland:
 - Is usually bilateral
 - Is an indolent process
 - May be chronic and recurrent
 - May be associated with pain
- Almost always associated with a systemic disorder, including:
 - Diabetes, thyroid insufficiency, alcoholism, malnutrition, hepatic cirrhosis, drug reactions (e.g., antihypertensive medications), anorexia nervosa, and bulimia
 - Patients are generally afebrile.

- Pathogenesis:
 - Major loss and thinning of myofilament component of myoepithelial cells, resulting in loss of mechanical support for the acini, proposed as causative of sialadenosis:
 - Allows acinar cells to expand as secretory granules accumulate intracellularly to produce great acinar enlargement
 - Functional myoepithelial insufficiency is possibly a consequence of an autonomic neuropathy secondary to severe metabolic or hormonal disorders.

Pathology

Cytology

- Smears show clusters of swollen acini and numerous naked nuclei of acinar origin in the background and an absence of inflammatory cells.
 - Features are considered distinctive enough to enable its diagnosis on fine-needle aspiration.

Histology

- Acinar cell enlargement with absent inflammatory cell infiltrate.
 - Acinar cell enlargement may take the form of a granular-appearing cytoplasm with densely packed periodic acid Schiff positive material or honeycomb with vacuolated-appearing cytoplasm or both.
- Histologic findings demonstrate little correlation to specific underlying disorder.
- As disease persists, atrophy of parenchymal tissues are seen but the glands remain enlarged due to compensatory increase in intraglandular adipose tissue.

Differential Diagnosis

- Inflammatory and infectious disease of salivary glands:
 - A careful and detailed history should allow for the diagnosis and differentiating sialadenosis from other lesions.

Treatment and Prognosis

- Treatment directed toward treating the underlying systemic disorder
- Patients with sialadenosis secondary to systemic endocrine disorders, hepatic cirrhosis, or neurogenic abnormalities tend to be resistant to treatment.

IgG4-Related Diseases (IgG4-RD)

Definition: Multiorgan autoimmune disorder that can affect any organ, has heterogenous presentation, and is characterized by fibrous inflammation, IgG4-positive

plasma cell infiltration in affected tissues, and elevated serum concentrations of IgG4.

- Diagnosis of IgG4-RD unifies many eponymous fibroinflammatory conditions previously thought to be confined to single organs.
- Consensus on pathologic criteria for diagnosis in specific organs include:
 - Tendency to form tumefactive lesions in multiple sites
 - Characteristic histopathologic appearance, including:
 - Dense lymphoplasmacytic infiltrate
 - Storiform pattern of fibrosis
 - Obliterative phlebitis
 - Increased numbers of IgG4⁺ plasma cell
 - Often but not always elevated serum IgG4 concentrations
 - Tissue IgG4 counts and IgG4:IgG ratios are secondary in importance.
 - Pathologic findings do not supplant careful clinicopathologic correlation and sound clinical judgment.
- Recognition and diagnosis of IgG4-RD crucial owing to the fact that there is a favorable response to immunosuppression (e.g., glucocorticoids, rituximab)
- Precise mechanisms leading to disease are unknown.
- Characteristically IgG4-RD affects the pancreas, referred to as autoimmune pancreatitis (AIP), which consists of two distinct pathologic entities:
 - Type 1 AIP:
 - Manifestation of a systemic IgG4-related disease
 - Affects older patients
 - Characterized by an elevated serum IgG4 level and sites of extra-pancreatic disease
 - Characteristic features include:
 - Increased serum IgG4 levels
 - Lymphoplasmacytic sclerosing pancreatitis including:
 - Abundant infiltration of IgG4⁺ plasmacytes and lymphocytes
 - Storiform fibrosis
 - Obliterative phlebitis
 - Extra-pancreatic manifestations (e.g., sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, others)
 - Steroid responsiveness
 - Type 2 AIP
 - Not associated with elevated IgG4 levels or extra-pancreatic disease
 - Disease process confined to the pancreas
 - Affects younger patients
 - Associated with inflammatory bowel disease
 - Both subtypes can mimic malignancy, particularly pancreatic cancer.

- Possible pathogenesis:
 - IgG4-RD lesions infiltrated by T helper cells, which likely cause progressive fibrosis and organ damage
 - IgG4 antibodies are generally regarded as noninflammatory:
 - Autoreactive IgG4 antibodies are observed in IgG4-RD but there is no evidence that they are directly pathogenic.
 - Rituximab-induced B-cell depletion in IgG4-RD leads to rapid clinical and histologic improvement accompanied by swift declines in serum IgG4 concentrations.
 - Although IgG autoantibodies against various exocrine gland antigens have been described, in IgG4-RD remains unknown whether they are members of IgG4 subclass
 - Contribution of autoantibodies to IgG4-RD remains unclear.
- After the pancreatobiliary system, head and neck is next most common site for involvement by IgG4-related disease.
- Head and neck manifestations of IgG4-RD include involvement of:
 - Salivary gland(s)
 - IgG4-related sialadenitis, see later.
 - Mikulicz disease, see later.
 - Sclerosing mucoepidermoid carcinoma, see Chapter 20:
 - Suggested relationship to IgG4-RD but has not definitively been proven
 - Thyroid gland (see Section 8):
 - Conflicting information in the literature whether the fibrous variant of Hashimoto thyroiditis represents an IgG4-RD
 - Reidel thyroiditis
 - Sclerosing mucoepidermoid carcinoma:
 - Suggested relationship to IgG4-RD but has not definitively been proven
 - Sinonasal tract:
 - Eosinophilic angiocentric fibrosis
 - Other head and neck sites of involvement may include (but not necessarily limited to):
 - Ear, soft tissue, lymph nodes
 - Lacrimal gland

IgG4-Related Sialadenitis

(Figs. 19-33 and 19-34)

Definition: Chronic fibroinflammatory salivary gland disease with characteristic morphology included within the spectrum of systemic IgG4-related diseases that includes autoimmune pancreatitis and involvement of extrapancreatic organs (e.g., kidney, lung, retroperitoneum, liver, gallbladder, lymph nodes, breast, salivary glands, lacrimal glands, aorta).

- IgG4-related sialadenitis may include:
 - Chronic sclerosing sialadenitis (CSS):
 - Synonyms: Küttner tumor, punctate parotitis
 - Mikulicz disease (MD):
 - Was considered to be subtype of Sjögren syndrome (SS) based on histopathologic similarities
 - Recent studies indicated that patients with MD show high serum IgG4 concentration
 - MD considered as an IgG4-related disease distinguishable from SS
- To establish a definitive diagnosis of IgG4-related sialadenitis in the clinical and pathologic settings that correlate to CSS and MD, immunohistochemical staining should be performed to determine the number and fraction of plasma cells with IgG4:
 - Not all cases of CSS (Küttner tumor) and MD show requisite IgG4 to IgG plasma cells to establish a definitive diagnosis of IgG4-related sialadenitis.

Clinical

- Incidence of IgG4-associated sialadenitis unknown
- More common in men than in women; usually occurs from the fourth to seventh decades of life
- Primarily involves submandibular gland:
 - Typically one gland
 - Rarely multiple glands (major and minor) may be affected in a single patient
 - In Mikulicz disease (MD), in addition to salivary gland involvement, there is persistent swelling of lacrimal glands
- Symptoms include pain and swelling often associated with ingestion of food
 - Patients may present with asymptomatic swelling of affected gland.
- Disease process may be localized to salivary glands or may be associated with sclerosing lesions in extrasalivary gland tissues (i.e., systemic IgG4-related disease)
- Laboratory findings:
 - Elevated serum levels of IgG4, IgG, IgG4/IgG
 - Antibodies associated with Sjögren syndrome (e.g., anti-SSA, anti-SSB) are absent in IgG4-associated sialadenitis.
 - Serum ANCA and proteinase 3 levels are not elevated.
 - Eosinophilia, hypergammaglobulinemia, and antinuclear antibodies (ANA) may be present in systemic disease but are not typically elevated in localized disease.

Pathology

Cytology

- In combination with the clinical findings, the fine-needle aspiration biopsy (FNAB) findings can

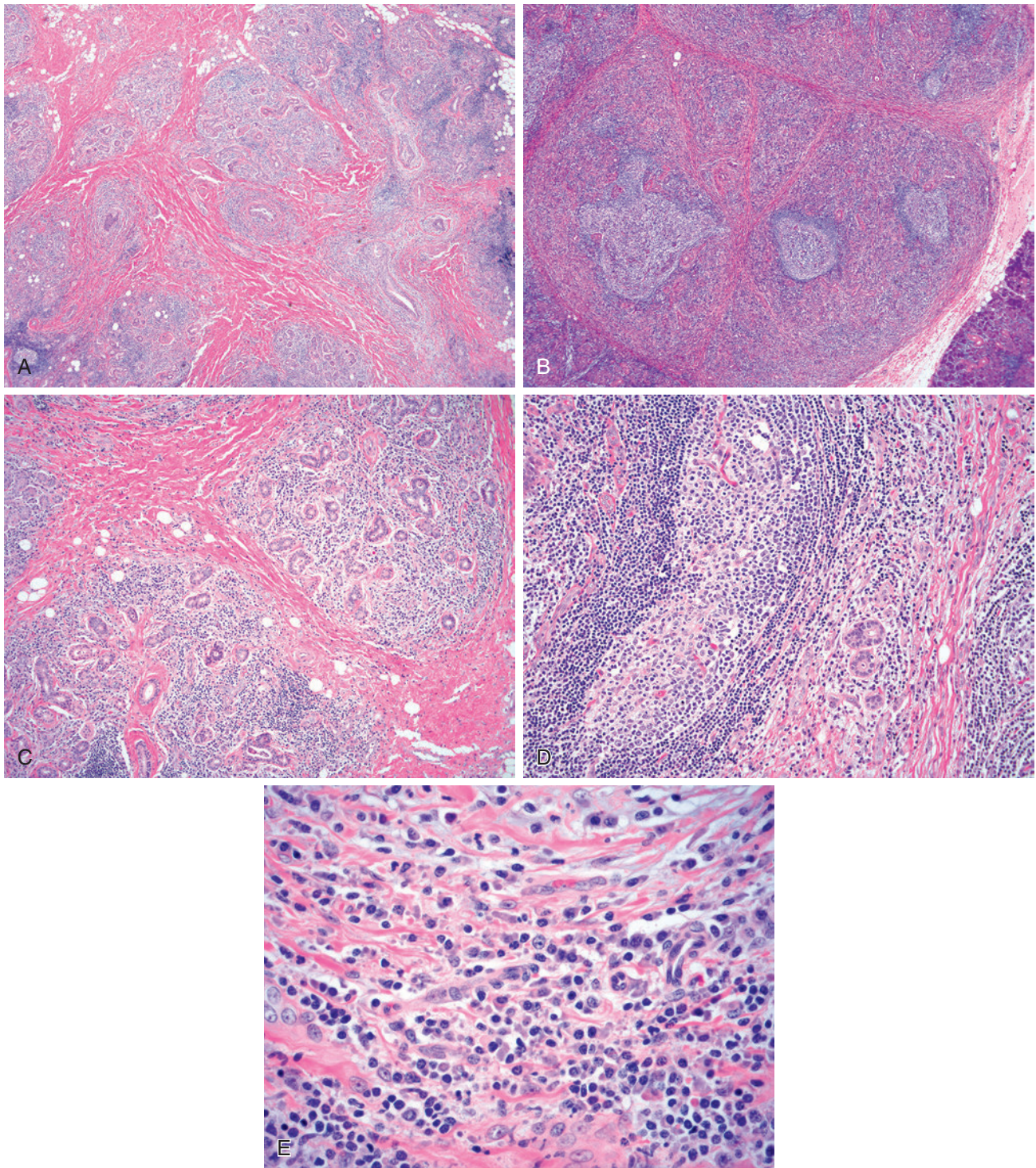


Fig. 19-33. IgG4-related sialadenitis.

IgG4-related sialadenitis of the submandibular gland. Two different cases showing varying degree of fibrosis, creating a lobular appearance including (A) storiform type and (B) nonstoriform type; irregular-shaped germinal centers are evident. Storiform-type fibrosis is less common in relationship to salivary (submandibular) glands; (C) lobular architecture is preserved with lobules separated by fibrosis; acinar atrophy is evident; (D) dense lymphoplasmacytic infiltrate within lobules and extended into fibrosis; a prominent germinal center is present; (E) sheets of mature plasma cells.

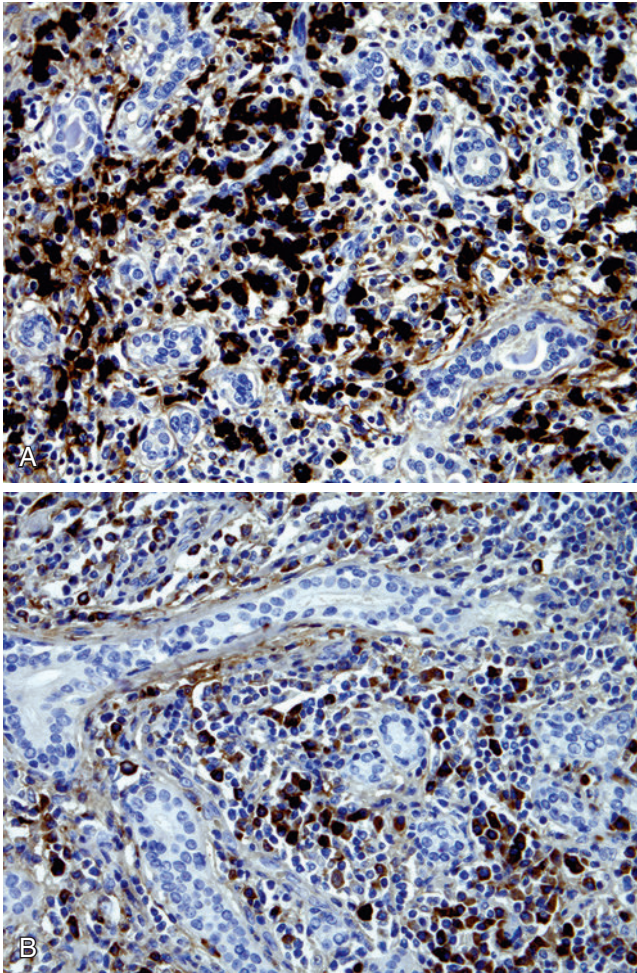


Fig. 19-34. IgG4-related sialadenitis.

Immunohistochemical staining of the plasma cells includes (A) IgG4+ plasma cells and (B) IgG+ plasma cells. There is an IgG4+/IgG+ plasma cell ratio of >40% that in conjunction with the light microscopic pathologic findings is confirmatory of the diagnosis of IgG4-related sialadenitis.

strongly suggest the diagnosis of CSS and obviate the need of surgical intervention.

- FNAB findings include paucicellular to moderately cellular aspirate characterized by the presence of scattered tubular ductal structures often enveloped by collagen bundles or lymphoplasmacytic infiltrate, isolated fragments of fibrous stroma, a background rich in lymphoid cells, and paucity or absence of acini.

Gross

- Well-defined to circumscribed lesion involving a variable proportion of affected gland or may involve entire affected gland

Histology

- Histopathologic features of IgG4-related sialadenitis include:
 - Preservation of lobular architecture
 - Lobules separated by fibrosis:
 - Typical storiform-type fibrosis seen in other organs (e.g., pancreas) may not be as frequently present in salivary glands
 - Dense lymphoplasmacytic infiltrate within lobules and extended into fibrosis
 - Large, irregular lymphoid follicles with expanded germinal centers (florid lymphoid hyperplasia)
 - Sheets of mature plasma cells
 - Acinar atrophy
 - Obliterative phlebitis may or may not be present:
 - Venous channels are obliterated by dense lymphoplasmacytic infiltrate
 - Not as frequently seen as in other organ sites (e.g., pancreas)
 - Not required for diagnosis
 - Elastic stains may assist in confirming presence of phlebitis.
- Additional findings may include:
 - Squamous metaplasia of ducts
 - Mucous metaplasia of ducts
 - May include ciliated cells and goblet cells
 - Noncaseating granulomas may be seen:
 - Likely results from mucus extravasation from ducts in association with sialolithiasis
- Immunohistochemistry:
 - IgG4 immunostaining essential test for pathological diagnosis of IgG4-related disease:
 - Particularly applies to cases without elevated concentration of serum IgG4
 - Strongly recommended even in straightforward cases as it is a simple, highly reproducible test that provides strong confirmatory evidence for the diagnosis.
 - Appropriate cutoff number of IgG4+ plasma cells varies per organ and for salivary and lacrimal glands >100 per high-power field in conjunction with light microscopic features considered highly suggestive for diagnosis
 - Abundant IgG4-bearing plasma cells virtually always present in inflamed lobules, interlobular septae, and occasionally in germinal centers
 - IgG4+ plasma cell count alone may not help to distinguish between IgG4-related disease and disorders that are not part of that disease spectrum:
 - Some inflammatory lesions not IgG4-related disease associated with high numbers of IgG4+ plasma cells per high power field (HPF) owing to abundance of plasma cells

- IgG4+/IgG+ plasma cell ratio more powerful tool than IgG4+ plasma cell counts in establishing diagnosis:
 - IgG4+/IgG+ plasma cell ratio on immunostaining widely used to assess preferential shift to IgG4 production in affected sites
 - An IgG4+/IgG+ plasma cell ratio of >40% considered cutoff value in any organ
 - In absence of other corroborative findings, a IgG4+/IgG+ plasma cell ratio of >40% in and of itself is not considered sufficient pathologic evidence of IgG4-related disease:
 - Applies particularly to cases with low overall IgG4 count per HPF, in which there may be a shift of >40% but pathologic diagnosis of IgG4-related disease is untenable in absence of classic histopathologic features and a compatible clinical picture.
 - A variety of non-IgG4-related disease entities can have IgG4+/IgG+ plasma cell ratios of >40% including conditions sometimes associated with elevated serum interleukin-6 (IL-6) concentrations (e.g., multicentric Castleman disease, rheumatoid arthritis and other immune-mediated conditions sometimes occur with abundant IgG4+ plasma cells within tissue [IgG4+/IgG+ plasma cell ratio >40%] and elevated serum IgG4 concentrations)
- Plasma cells:
 - CD138 positive
 - Polytypic kappa and lambda light chain by immunohistochemistry and/or in situ hybridization
- Additional findings:
 - CD3+ interfollicular T-cells present especially in association with ducts and acini
 - CD20+ B-cells mostly restricted to lymphoid follicles
 - Follicles express bcl6 and negative for bcl2
- Cytogenetics and molecular genetics
 - Immunoglobulin heavy chain includes polyclonal rearrangement in the majority of cases.

Differential Diagnosis

- Chronic sialadenitis, not otherwise specified
- Sialolithiasis
- Sjögren syndrome
- Lymphoepithelial sialadenitis (LESA)
- Sarcoidosis
- Malignant lymphoma

Treatment and Prognosis

- Excellent response to immunosuppression (e.g., glucocorticoids, rituximab):

- Rituximab-induced B-cell depletion in IgG4-RD leads to rapid clinical and histologic improvement accompanied by swift declines in serum IgG4 concentrations.
- Rarely, extranodal marginal zone B-cell lymphoma (MALT) of salivary gland and salivary duct carcinoma develop in background of IgG4 sialadenitis.

Lymphoepithelial Sialadenitis (LESA) (Figs. 19-35 through 19-37)

Definition: Non-neoplastic unilateral or bilateral enlargement of major or minor salivary glands, and/or lacrimal glands associated with or occurring independent of an autoimmune disease, and characterized by specific histopathologic findings.

Synonyms: Benign lymphoepithelial lesions (BLEL); myoepithelial sialadenitis (MESA); immune sialadenitis; Godwin tumor; Godwin lesion

Introduction

- Designation of benign lymphoepithelial lesion (BLEL) initially coined in 1933
- Distinctive morphologic changes associated with BLEL have been referred to by a variety of terms and clinical settings
- Morphologic changes include the presence of lymphoepithelial islands or lesions:
 - Previously referred to as epimyoeplithelial islands
 - Believed to be composed of ductal and myoepithelial cells resulting in replacement of the term BLEL with myoepithelial sialadenitis (MESA)
 - Myoepithelial component has not been affirmed; hence the change in terminology to lymphoepithelial sialadenitis (LESA) and for the characteristic cell islands to be called lymphoepithelial islands or lesions.
- Morphologic changes of LESAs are distinctive but not pathognomonic and may be identified in a variety of salivary gland non-neoplastic and neoplastic lesions (Box 19-2), arguably most common in Sjögren syndrome

BOX 19-2 Occurrence of Lymphoepithelial Lesions in Salivary Gland Diseases

- Sialolithiasis
- Sialadenitis (infectious and noninfectious)
- Lymphoepithelial sialadenitis (LESA)
- Sjögren syndrome and other connective tissue disorders
- HIV-associated disease (benign lymphoepithelial cysts)
- Lymphoma

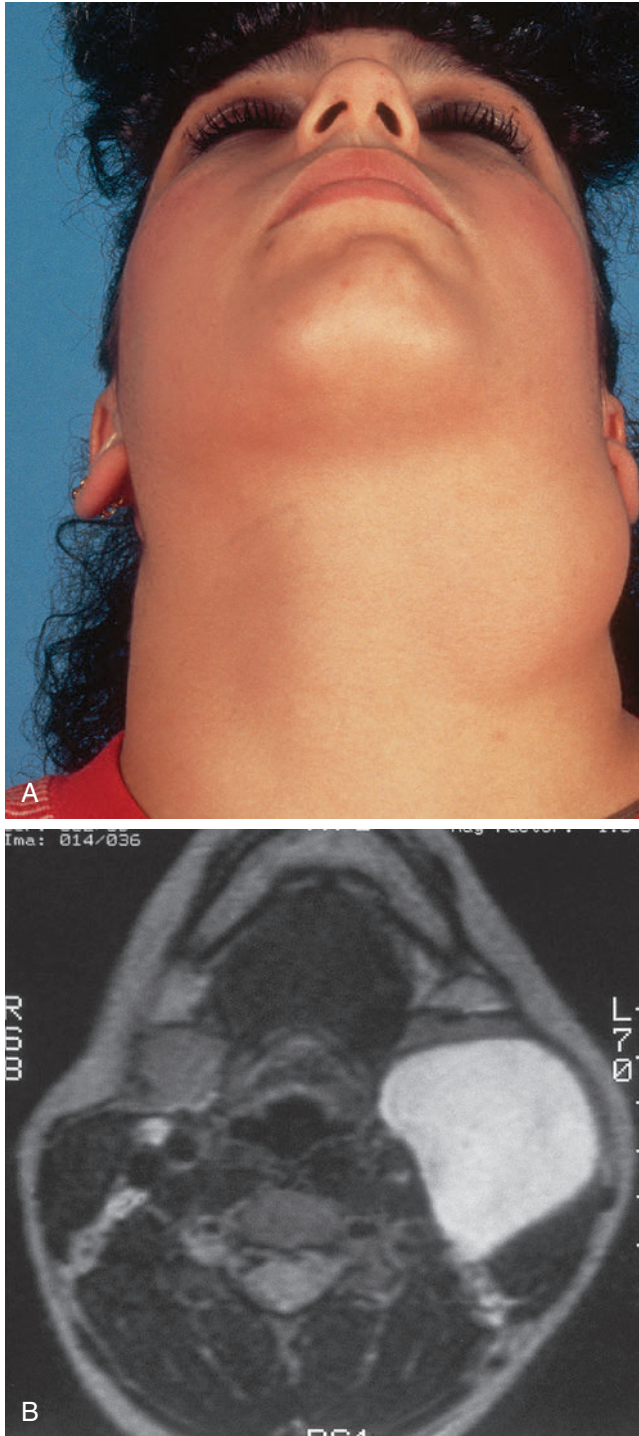


Fig. 19-35. Lymphoepithelial sialadenitis.

A, Lymphoepithelial sialadenitis (LESA) presenting as a markedly enlarged left parotid gland along the mandible and lateral neck region. **B**, Radiographic findings depict the presence of an enhancing, well-delineated, solid lesion with diffuse enlargement of the parotid gland.

Clinical

- More common in women than men (3:1); most common in the fourth to seventh decades of life
- Primarily affects parotid gland (80% to 85%) and submandibular gland (10% to 15%)
- Presentation includes unilateral diffuse and firm swelling of involved glands:
 - Approximately 20% may be bilateral
 - Pain may be present in up to 40% of cases.
- High proportion of cases (approximately 50% to 85%) have clinical and laboratory evidence of Sjögren syndrome (see later).
- Represents a risk factor for development of salivary gland lymphoma especially when associated with Sjögren syndrome or other connective tissue diseases (e.g., rheumatoid arthritis):
 - Estimated risk to be 44 fold
 - Majority (80%) are extranodal marginal zone (MALT) type

Pathology

Histology

- Lymphoid infiltrate with follicular hyperplasia surrounding and infiltrating salivary ducts with parenchymal atrophy, disorganization and proliferation of the ductal epithelial cells to form the lympho-epithelial lesions, the characteristic finding in LESA:
 - General solid, cystic alterations of lymphoepithelial lesions may occur:
 - Cysts may vary in size from small to large, the latter resulting in a prominent cystic lesion (cystic LESA).
 - Findings may simulate those seen in lympho-epithelial cyst and in HIV-related salivary gland disease.
- In early stage of disease glandular lumens of the lymphoepithelial lesions are preserved; with progression of disease there is near total or total effacement of the normal architecture with replacement of acinar tissue of the gland lobules with the lymphoid infiltrate as well as obliteration of the glandular lumens of the lymphoepithelial lesions, which appear as irregular-shaped nests of polygonal and spindle-shaped cells containing a variable amount of eosinophilic hyaline material.
- Overall lobular architecture of affected gland is preserved.
- Early changes include multiple scattered foci of periductal lymphoid proliferation.
- Germinal center formation within the lymphoid infiltrate varies from rare to extensive; reactive follicles often have irregular outlines and do not show expansion of the mantle or marginal zones.

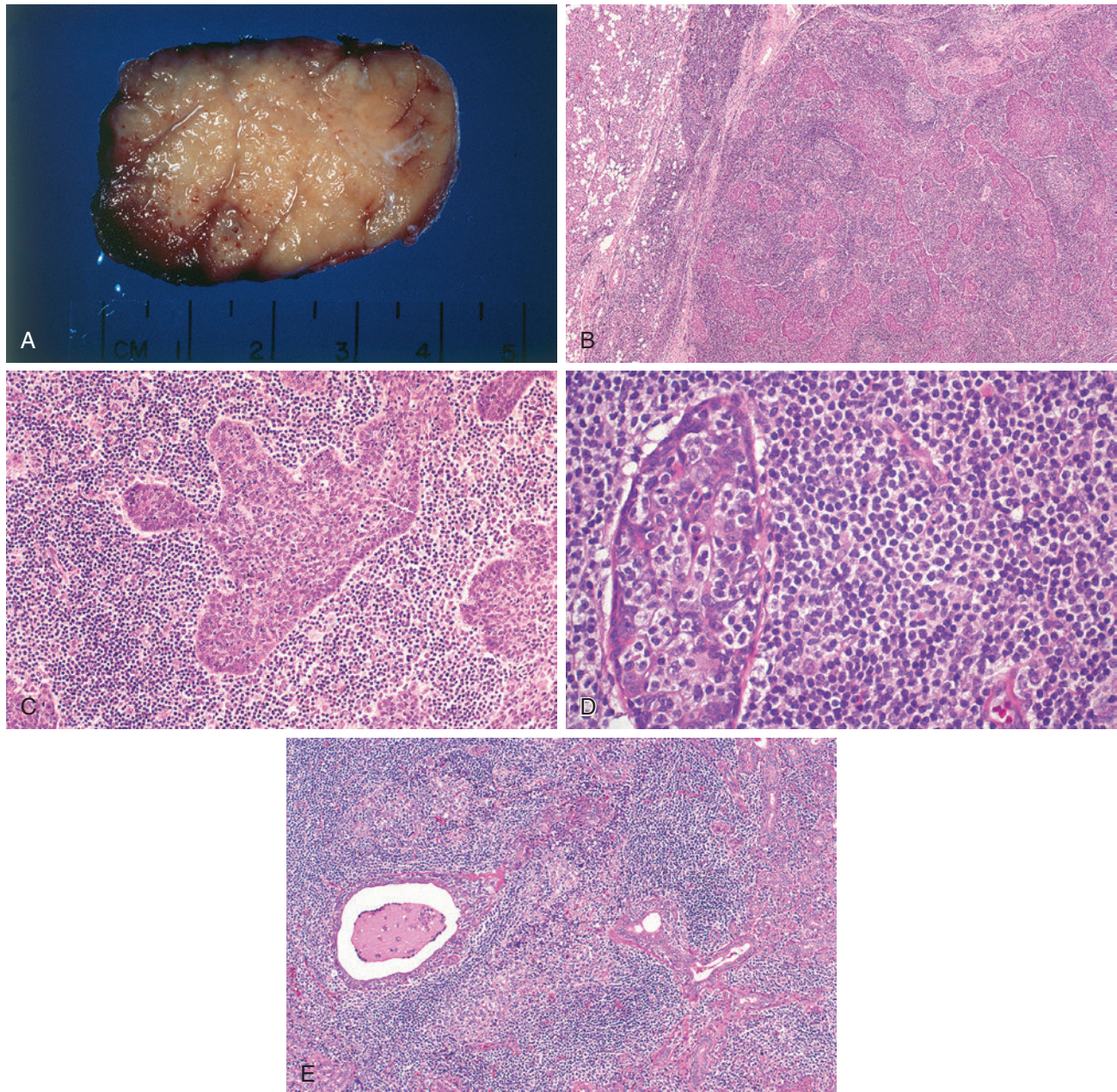


Fig. 19-36. LESA.

A, Enlarged parotid gland with diffuse nodularity and tan-white to fleshy appearance. **B**, Replacement of parotid gland parenchyma by lymphocytic infiltrate with identifiable germinal centers; the proliferation is well-demarcated from adjacent salivary gland parenchyma (*extreme left side of illustration*). **C** and **D**, Characteristic appearance of lymphoepithelial lesion (island) in which there is lymphocytic infiltration of proliferating ductal epithelium with obliteration of ductal lumina surrounded by a mixed chronic inflammatory cell infiltrate. **E**, Cystic alteration of the lymphoepithelial lesion may occur ranging from an incidental finding (as depicted here) to examples in which the cysts are markedly dilated appearing as a predominantly cystic lesion (not shown).

- Interfollicular regions show small lymphocytes, scattered immunoblasts, and variable numbers of plasma cells but not in broad sheets:
 - Polyclonal (interfollicular) lymphoid infiltrate is predominantly of T-cells.
- Lymphoepithelial lesions contain lymphoid cells of B-cell lineage:
 - Evidence of clonality has been identified in these B-cell lymphocytes but in these examples there typically is:

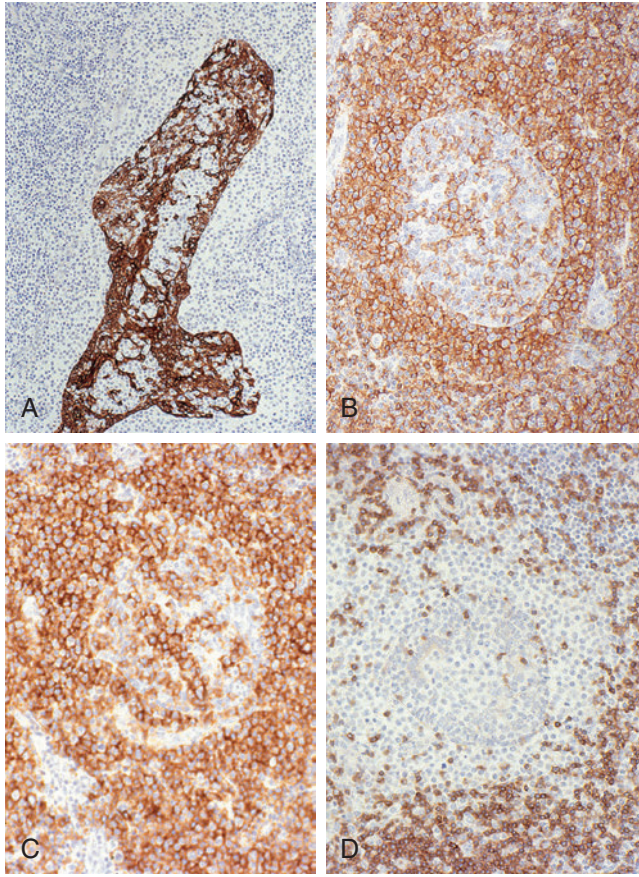


Fig. 19-37. LESA.

A, The epithelial cells of the lymphoepithelial lesions are cytokeratin positive. **B**, CD45 reactivity is present in the lymphoid component surrounding and within the lymphoepithelial lesion. **C**, Lymphoid cell infiltrate shows immunoreactivity for the B-cell marker CD20 and **(D)** T-cell marker CD3.

- Absence of additional histologic findings supportive of a malignant lymphoma
- Absence of clinical evidence supportive of a malignant lymphoma
- An overall indolent biologic course
- Some of these examples may evolve into a malignant lymphoma (extranodal marginal zone B-cell lymphoma).
- In later stages of disease, plasma cells are more conspicuous.
- Immunohistochemistry:
 - Lymphoid component:
 - Polyclonality including reactivity for B-cell and T-cell markers:
 - B-cells > T-cells
 - Lymphoid infiltrates in LESA may contain monotypic cells that have restricted immunoglobulin pattern
 - Monotypic cell population may not be invasive and may remain localized.
 - Epithelial component:
 - Cytokeratins positive
- Molecular biology:
 - Lymphoid infiltrates may reveal heavy- and light-chain Ig gene rearrangement.
 - Presence of molecular evidence of B-cell clonality may be seen in the absence of histologic features, diagnostic for a lymphoma; the meaning and importance of this finding remains controversial:
 - Most cases with monoclonal populations have an uneventful course.
 - Significance of clonality in LESA without morphologic evidence of lymphoma remains controversial.

Differential Diagnosis

- Most important differential diagnosis of LESA is malignant lymphoma:
 - Lymphomas of the major salivary glands may or may not be associated with LESA.
 - Irrespective of the setting, most lymphomas of salivary glands are B-cell non-Hodgkin lymphomas:
 - Mucosa-associated lymphoid tissue (MALT) lymphomas most common > diffuse large B-cell lymphoma and follicular lymphoma
 - See Chapter 20 for more complete coverage of salivary gland malignant lymphomas.
 - MALT lymphomas:
 - Collars of monocytoid B-cells characterized by monomorphic, medium-sized cells with abundant, pale cytoplasm and bland, uniform nuclei, and distinct cell membranes around and infiltrating within salivary ducts forming lymphoepithelial lesions:
 - Represents the strongest clue to diagnosis of MALT lymphoma
 - Normal lobular architecture is altered with replacement of acini and ducts and invasion of the neoplastic cells into surrounding structures.
 - Immunohistochemical stains show:
 - Light chain restriction
 - Diffuse sheets of CD20+ B cells
 - B-cells show aberrant coexpression of CD43
 - t(14;18) translocation with *IgH/MALT1* fusion and trisomies 3 and 18 present in a proportion of cases and assist in differentiating malignancy from benign or borderline case
 - Monocytoid B-cell lymphomas rarely have t(14;18) translocations as frequently found in MALT lymphoma of stomach and lung (as determined by immunologic studies for the bcl-2 protein)

- Lymphoepithelial cyst
- HIV-salivary gland disease

Treatment and Prognosis

- Treatment for LESA is symptomatic relief and/or directed at specific associated disease (see [Box 19-2](#)):
 - However, owing to increased risk for developing lymphoma, parotidectomy may be performed.

Sjögren Syndrome (SS)

Definition: Chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and epithelia in multiple organs with associated dry eyes (keratoconjunctivitis sicca) due to lacrimal gland involvement and dry mouth (xerostomia) due to salivary gland involvement.

Synonym: Autoimmune epithelitis

History

- Henrik Sjögren observed that many patients with a particular form of dry eyes (keratoconjunctivitis sicca) also had polyarthritis, dry mouth, and elevated ESR.
 - Clinical syndrome is now referred to as Sjögren syndrome (SS).
 - Virtually all patients who fit the clinical definition of SS have LESA; however, only 50% of patients with LESA have SS.

Clinical

- Overwhelming majority of patients are women representing from 80% to 90% of all cases.
- For women, median age is in the sixth decade; for men median age is in the fifth decade:
 - Rarely occurs in children
- Patients usually present with firm swelling of the affected gland with or without pain.
- Lesions may be unilateral, bilateral, or there may be successive enlargement of salivary and/or lacrimal glands.
- Affected gland may be diffusely or focally (nodular) enlarged.
- In order of occurrence, the parotid is primarily affected (83%), followed by the submandibular gland (11%), and then other sites (6%):
 - Minor salivary gland involvement is considered uncommon.
- Ocular manifestations (keratoconjunctivitis sicca) are quantitative and qualitative changes of tear film.
- Oral manifestations include dry, sticky oral mucosal surfaces, no or cloudy saliva, primary or recurrent dental carries, angular cheilitis, or patchy or generalized oral mucosal erythema with dorsal tongue fissuring and papillary atrophy.
- Diffuse swelling of the salivary glands that may be nontender or tender and is usually bilateral; the submandibular gland may be affected before the parotid gland.
- Extra-glandular manifestations include:
 - Raynaud phenomenon
 - Primary biliary cirrhosis
 - Diffuse interstitial lung disease
 - Interstitial nephritis
 - Atrophic gastritis
 - Hepatobiliary diseases
 - Neuropathies
 - Inflammatory vascular disease
- Symptoms may occur with or without autoimmune or connective tissue disease:
 - In relationship to connective tissue diseases, association with rheumatoid arthritis is much more common than other collagen vascular diseases, including systemic lupus erythematosus, scleroderma, polymyositis/dermatomyositis, mixed connective tissue disease, and polyarteritis nodosa.
 - Previously, patients were classified into two categories, including those with a connective tissue disease and those without connective tissue disease; the latter category referred to as sicca syndrome.
 - Primary or limited form of Sjögren syndrome occurs in the absence of another connective tissue disease.
 - Secondary or complete form of Sjögren syndrome includes the presence of another connective tissue disease.
 - Association with other diseases includes (but not limited to):
 - Autoimmune thyroiditis
 - Atrophic gastritis
 - Celiac disease
 - Inflammatory bowel disease
 - Primary biliary cirrhosis
 - Sinus histiocytosis with massive lymphadenopathy
- Despite the availability of many new imaging procedures, sialography has maintained its status as the imaging procedure of choice for evaluating SS:
 - Sialograms may show four different gradations of sialectasia, including punctate, globular, cavitary, and destructive.
 - Diagnostic accuracy of sialography is very high, with high sensitivity and specificity.

Laboratory Findings

- Most commonly used test in diagnosis is Schirmer test:
 - Measures wetting of standardized tear test strips applied between eyeball and lateral inferior eyelid

- Performed without anesthetic eye drops
- Score of ≤ 5 mm in 5 minutes considered positive test and objective evidence of ocular involvement:
 - This test may be reduced in normal subjects older than 60 years so should be excluded from the criteria or not considered for a diagnosis of SS in elderly subjects.
- Ocular staining score (OSS):
 - Sum of 0 to 6 score for fluorescein staining of cornea and 0 to 3 score for lissamine green staining of both the nasal and temporal bulbar conjunctivae, yielding a total score ranging from 0 to 12
 - OSS score of ≥ 3 considered positive test and objective evidence of ocular involvement
 - Assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years
- Laboratory evaluation includes sialochemistry with increased sodium, chloride, IgA, IgG, lactoferrin, and albumin, and decreased phosphates; mild anemia, leukopenia, eosinophilia, elevated ESR, and elevated serum immunoglobulins.
- Sjögren syndrome is characterized serologically by presence of autoantibodies against Ro/SSA and La/SSB:
 - Mechanisms by which these autoantibodies arise are not clear.
 - Most commonly detected autoantibodies are those directed against the ribonucleoproteins Ro/SSA and La/SSB, and presence of antibodies in SS is associated with early disease onset, longer disease duration, parotid gland enlargement, higher frequency of extraglandular manifestations, and more intense lymphocytic infiltration of the minor salivary glands.
 - Organ-specific autoantibodies present in SS include anti-salivary duct antibodies
 - Non-organ-specific antibodies present in SS include:
 - Rheumatoid factor (70% to 90% frequency)
 - Antinuclear antibodies (ANA)
 - Antibodies to centromere ($<5\%$)
- Antineutrophil cytoplasmic antibodies (ANCA) positivity can be found in patients with primary SS, and its detection is associated with the presence of clinical manifestations attributable to vascular involvement (cutaneous vasculitis, peripheral neuropathy, and Raynaud phenomenon).
- Patients with SS develop antibodies to three autoantigens called IFI16, KLHL12, and KLHL7:
 - These autoantigens represent family of transcription regulators.

- Antibodies to mitochondria reported in SS:
 - Found only in patients with primary biliary cirrhosis
- Plasma interleukin-6 (IL-6) elevated in primary SS:
 - Primary SS patients with celiac disease, pulmonary fibrosis or alveolitis, or peripheral nervous system symptoms had significantly higher IL-6 levels than patients without these manifestations.
 - IL-6 levels increase in parallel with the histologic grade of minor salivary gland biopsy.
 - Patients with SS have altered immunoregulation:
 - Lymphocyte-mediated destruction of exocrine glands; possibly a graft-versus host disease-like process in which the histocompatibility antigens of the ductal epithelium or lymphoid cells changes, leading to a loss of “self-recognition”

Diagnostic Criteria/Classification

- Criteria for the classification and diagnosis of SS have been suggested without universal acceptance.
- Classification criteria for SS representing a revision of the European criteria have been proposed by the American-European Consensus Group (AECG):
 - This group proposed revised international classification criteria for SS (Box 19-3) and the revised

BOX 19-3 Revised International Classification Criteria for SS

- I. Ocular symptoms
- II. Oral symptoms
- III. Ocular signs
 - a. Schirmer test (≤ 5 mm in 5 min)
 - b. Rose Bengal score or other ocular dry eye score (≥ 4 according to van Bijsterveld scoring system)
- IV. Histopathology:
 - a. Focus score of ≥ 1 (see later)
- V. Salivary gland involvement:
 - a. Unstimulated whole salivary flow (≤ 1.5 ml in 15 min)
 - b. Parotid sialography showing diffuse sialectasia (punctuate, globular, cavitory, destructive patterns)
 - c. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
- VI. Autoantibodies in serum to:
 - Ro (SSA) antigen
 - Lo (SSB) antigen
 - Both Ro (SSA) and Lo (SSB) antigens

Modified from Vitali C et al: European study group on classification criteria for Sjögren's syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group, *Ann Rheum Dis* 61:554-558, 2002, Table 2.

BOX 19-4 Revised Rules for Classification of SS**Primary SS**

1. The presence of any four of the six items listed in [Box 19-3](#) as long as either the histopathology (item IV) or serology (item VI) is positive
2. The presence of any three of the four objective criteria items (i.e., III, IV, V, VI)
3. The classification tree procedure represents a valid method for classification, although it should be more properly used in clinical-epidemiologic survey

Secondary SS

In patients with a potentially associated disease such as another well-defined connective tissue disease, the presence of items I or II (listed in [Box 19-3](#)) plus any two from among items III, IV, V (listed in [Box 19-3](#)) may be considered as indicative of secondary SS

Exclusionary Criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- AIDS
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs

Modified from Vitali C et al: European study group on classification criteria for Sjögren's syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group, *Ann Rheum Dis* 61:554-558, 2002, Table 3.

BOX 19-5 American College of Rheumatology (ACR) Proposed Classification for SS (2012)

Applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least two of the following three objective features:

1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer $\geq 1:320$)
2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm²
3. Keratoconjunctivitis sicca with ocular staining score ≥ 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

SS, Sjögren syndrome.

From Shiboski SC et al: American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort, *Arthritis Care Res (Hoboken)* 64(4):475-87, 2012, Table 7.

rules for classification, including exclusionary criteria ([Box 19-4](#)).

- In 2012 American College of Rheumatology (ACR) criteria for Sjögren syndrome (SS) proposed ([Box 19-5](#)):
 - Need for new classification criteria based on apparent lack of standardization inherent to older criteria in the field and emergence of biologic agents as potential treatments
 - Also authors felt diagnosis must rely upon well-established objective tests clearly associated with systemic/autoimmune, oral, and ocular characteristics of disease, and include alternate tests only when they are diagnostically equivalent.
- Subsequent concordant studies of AECG and ACR classification criteria yielded concordant results in majority of cases, and gene expression profiling suggests that patients meeting either set of criteria are more similar to other SS participants than to healthy controls:
 - No clear evidence for increased value of new ACR criteria over old AECG criteria from clinical or biologic perspective
 - More recent studies based exclusively on objective tests, stringency of AECG criteria, and

potential therapeutic use of biologic agents in SS showed:

- Sensitivity and specificity of ACR criteria in diagnosing SS reported to be 90.37% and 88.46%, respectively
- Sensitivity of ACR criteria in diagnosing SS patients with and without labial biopsy reported to be 88.75% and 93.67 %, respectively, with specificities of 88.89% and 88.37%, respectively
- Most sensitive item adopted in ACR criteria reported to be ocular staining score with sensitivity of 85.77%
- Most specific item was the labial salivary gland biopsy with a specificity of 88.89%.
- Sensitivity and specificity of ACR criteria in diagnosing patients with SS relatively high and may serve as the diagnosis criteria in research and clinical practice.
- ACR criteria must be validated.
- Cause
 - Remains unknown
 - Likely causes are multifactorial
 - Likely possibility is autoimmune with an abnormal response to one or more unidentified antigens:

- In support of this consideration, and as detailed previously, there are several autoimmune-related diseases (e.g., autoimmune thyroiditis, inflammatory bowel disease, primary biliary cirrhosis, others), in which there is significant involvement of salivary glands.
- Another possible cause is viral, with numerous studies suggesting a link between viral infection and SS.
- Genetic predisposition has been suggested on the basis of familial aggregation, animal models, and candidate gene association studies.

Pathology

Histology

- SS is characterized by the spectrum of histomorphologic changes associated with LESA (see above).

Labial Biopsy (Fig. 19-38)

- Minor salivary glands may demonstrate histologic alterations in patients with SS indicative of changes seen in major glands; as a result of these findings as well as ease of access a diagnostic tool in patients

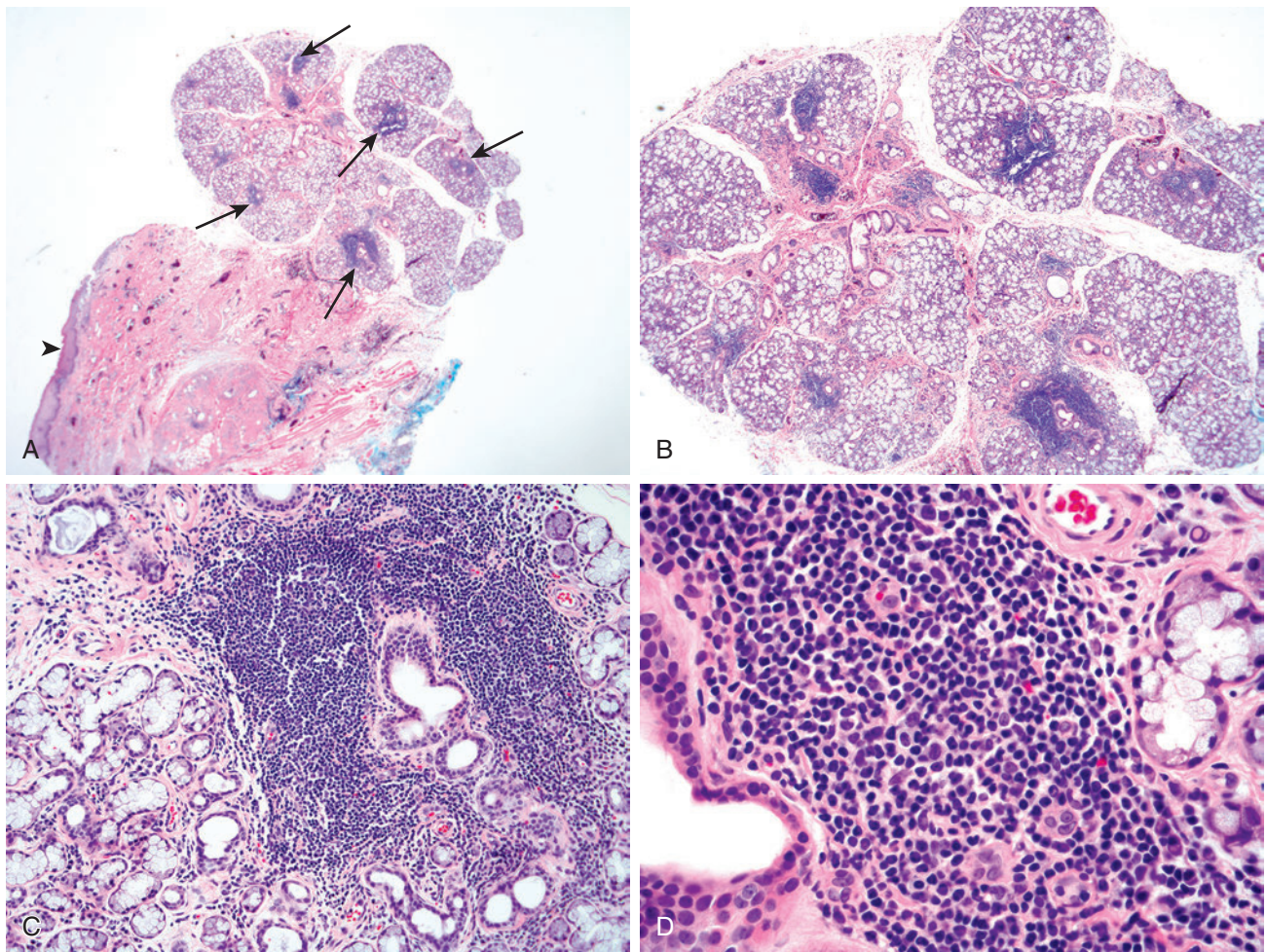


Fig. 19-38. Lip biopsy in Sjögren syndrome.

A, The biopsy includes overlying squamous mucosa (arrowhead) with greater than five lobules of minor salivary glands within the submucosa; within the minor salivary glands there are multiple lymphocytic foci (arrows). **B** and **C**, The lymphocytic cell clusters number greater than 50 lymphocytes so each cluster represents a focus score and in this example the focus score is more than 1 focus/4 mm²; note lymphocytic clusters are occurring in the background of normal-appearing minor salivary glands. **D**, The cellular components of each cluster are predominantly composed of mature lymphocytes as well as scattered plasma cells. These overall histologic findings support a diagnosis of Sjögren syndrome but are not 100% reliable, requiring additional confirmation. In this patient's case there was clinical evidence and elevated of Ro/SSA and La/SSB antibodies.

suspected of having SS is the labial salivary gland biopsy:

- “Focus Score” established in which foci containing 50 or more lymphocytes are counted
- Focus scores greater than 1 focus/4 mm² support diagnosis of the salivary component of SS.
- An adequate biopsy specimen for histologic assessment and lymphocytic infiltrate grading must include the following:
 - Specimen is taken from below clinically normal mucosa.
 - Sample includes at least five glands that are separated from their surrounding connective tissue.
 - Nonspecific chronic sialadenitis has been ruled out.
- Lacrimal gland biopsies may have more evident histopathologic findings for SS than labial salivary gland biopsies and recommendations include that labial salivary gland and lacrimal gland biopsies be performed in patients with suspected SS to reduce false-negative results and improve diagnostic accuracy.
- Comparison of labial biopsies versus parotid gland biopsies has shown that parotid gland biopsy adds very little to the minor salivary gland biopsy in the diagnosis of primary SS, but that parotid inflammatory changes may reflect disease duration and/or severity.

Treatment and Prognosis

- Treatment is symptomatic relief.
- Disease course is generally one of chronicity with long-term symptomatic treatment.
- Patients with sicca symptoms involving the eyes and the mouth usually do not progress, but development of (new) extraglandular manifestations occurs in most of SS patients over a 10- to 20-year follow-up period.
- In SS patients with immune-mediated extraglandular manifestation, the therapeutic approach is similar to systemic lupus erythematosus, although these therapies have relatively little effect on tear or saliva flow.
- Risk of developing a malignant lymphoma in patients with SS is markedly increased:
 - Estimated risk to be 44 fold
 - Majority (80%) are extranodal marginal zone (MALT) type.
 - More common in those patients with only sicca components of syndrome
 - Predisposing factor to development of lymphoma probably relates to prolonged immunologic and lymphoid hyperactivity
- Controversy surrounds role of viruses such as EBV, HHV-8, T-lymphotropic virus-1, and hepatitis C virus in lymphomatous transformation in setting of SS, but viruses have not definitively been found to play a role in lymphomatous transformation.
- Predictors for lymphoma development in SS remain to be definitively determined but may correlate to:
 - Recurrent or permanent swelling of major salivary glands
 - Lymphadenopathy, cryoglobulinemia, splenomegaly
 - Low complement levels of C4 and C3
 - Lymphopenia
 - Skin vasculitis or palpable purpura
 - M-component in serum or urine
 - Peripheral neuropathy, glomerulonephritis, and elevated beta₂-microglobulin
 - Additional factors may relate to
 - Genetic factors, CD4 lymphocytopenia, and ectopic germinal center-like structures in minor SG biopsies
- Malignant transformation of a benign lymphoepithelial lesion to a malignant epithelial neoplasm (malignant lymphoepithelial lesion) occurs much less frequently than transformation to lymphoma:
 - Although lymphoepithelial carcinomas of salivary glands are rare tumors, these carcinomas most likely develop as de novo neoplasms unrelated to other conditions (e.g., lymphoepithelial sialadenitis) (see Chapter 20).
 - Histologic setting is similar to benign lymphoepithelial lesion except for the presence of a malignant epithelial component instead of a benign epithelial component.
 - Increased incidence among Eskimos
 - More common in men than in women; most frequently occur in the fifth decade of life
 - Among Eskimos, the parotid gland is the most frequent site of occurrence; among Asians, the submandibular gland is most often involved.
 - Histologic picture of carcinomatous component ranges from low to high grade.
 - Some evidence linking Epstein-Barr virus (EBV) with this neoplasm but there is equal evidence showing an absence of EBV DNA in these neoplasms

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Neoplasms of the Salivary Glands

CLASSIFICATION OF NEOPLASMS OF SALIVARY GLANDS

Box 20-1 contains the classification of neoplasms of the salivary glands.

GENERAL CONSIDERATIONS

- Salivary gland neoplasms account for between 2% and 6.5% of all neoplasms of the head and neck.
- Demographics vary per tumor type, but in general salivary gland neoplasm are:
 - More common in women than in men
 - Occur in all age groups, including children, but with a peak incidence in sixth to seventh decades of life
- Majority of salivary gland neoplasms occur in parotid gland
- Majority of salivary gland neoplasms are of epithelial origin, representing 80% to 90% of all neoplasms
- Benign neoplasms represent approximately 75% of all salivary gland neoplasms:
 - Most common benign neoplasm is pleomorphic adenoma

BOX 20-1 Classification of Neoplasms of the Salivary Glands

Benign Neoplasms

Epithelial

Pleomorphic adenoma
Basal cell adenoma
Canalicular adenoma
Warthin tumor
Myoepithelioma
Oncocytoma
Sclerosing polycystic adenosis
Cystadenoma
Ductal papillomas:
 Sialadenoma papilliferum
 Inverted ductal papilloma
 Intraductal papilloma
Other uncommon adenomas
 Striated duct adenoma
 Intercalated duct adenoma
 Lymphadenoma (nonsebaceous)
 Keratocystoma
 Lipoadenoma
 Apocrine adenoma
 Adenofibroma
Tumors with sebaceous differentiation
 Sebaceous adenoma
 Sebaceous lymphadenoma
Salivary gland anlage tumor
Nonepithelial
Hemangioma
Neurilemmoma/neurofibroma
Lipoma
Others

Malignant Neoplasms

Epithelial

Mucoepidermoid carcinoma
Acinic cell adenocarcinoma

Mammary analogue secretory carcinoma
Adenocarcinoma, NOS
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Carcinoma ex pleomorphic adenoma
 Invasive
 Intracapsular
 Carcinosarcoma
 Metastasizing pleomorphic adenoma
Basal cell adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell adenocarcinoma; Hyalinizing clear cell carcinoma
Cystadenocarcinoma
Myoepithelial carcinoma
Salivary duct carcinoma
Intraductal carcinoma (low-grade cribriform
 cystadenocarcinoma; low-grade salivary duct carcinoma)
Squamous cell carcinoma
Adenosquamous carcinoma
Lymphoepithelial carcinoma
Neuroendocrine carcinomas
Undifferentiated (large-cell) carcinoma
Oncocytic carcinoma
Mucinous adenocarcinoma
Cribriform adenocarcinoma of minor salivary glands
 (CAMSG)
Sebaceous carcinoma/lymphadenocarcinoma
Sialoblastoma
Nonepithelial
Hematolymphoid
 Non-Hodgkin lymphoma
 Hodgkin lymphoma
Sarcomas

Secondary Neoplasms

- Among malignant tumors, mucoepidermoid carcinoma is most common:
 - True for adult and pediatric ages
- Mesenchymal neoplasms of salivary glands are rare:
 - Exception is in infants
 - Hemangioma and lymphangioma most common
 - Sialoblastoma and salivary gland anlage tumors occur almost exclusively in newborns and infants.
- As compared with neoplasms of major salivary glands, in which benign neoplasms represent the greater proportion of tumors, relative to minor salivary glands a greater proportion of neoplasms are malignant.
- Tumor types vary per gland involved
 - Some examples of tumors primarily (but not exclusively) occurring in major salivary glands include:
 - Warthin tumor
 - Basal cell adenoma
 - Oncocytoma
 - Acinic cell carcinoma
 - Mammary analogue secretory carcinoma
 - Basal cell adenocarcinoma
 - Epithelial-myoepithelial carcinoma
 - Carcinoma ex pleomorphic adenoma
 - Salivary duct carcinoma
 - Oncocytic carcinoma
 - Some examples of tumors primarily (but not exclusively) occurring in minor salivary glands include:
 - Canalicular adenoma (lip)
 - Ductal papillomas (lip, oral cavity)
 - Cystadenoma
 - Polymorphous low-grade adenocarcinoma (intraoral minor salivary glands)
 - Cribriform adenocarcinoma of minor salivary glands (tongue, oral cavity)
 - Cystadenocarcinoma
- Features associated with major versus minor salivary glands:
 - Major salivary gland neoplasms:
 - All are encapsulated.
 - Invasion beyond the capsule generally is diagnostic for malignancy.
 - Extension into the capsule does not represent invasion.
 - Invasion includes lesional cells into adjacent salivary gland parenchyma, perineural invasion, lymph-vascular invasion, invasion into connective tissues.
 - Rare exceptions to the above include:
 - ◻ Lymph-vascular permeation in pleomorphic adenomas
 - ◻ Metastatic pleomorphic adenoma
 - Several malignant salivary gland neoplasms may be encapsulated or noninvasive, including:
 - Mucoepidermoid carcinoma
 - Acinic cell carcinoma
 - Adenoid cystic carcinoma
 - Carcinoma ex pleomorphic adenoma (CEPA)
 - Epithelial-myoepithelial carcinoma
 - Mammary analogue secretory carcinoma
 - Except for CEPA, above list of malignant neoplasms has no known benign counterparts, so once requisite diagnostic criteria are established, a diagnosis can be rendered in the absence of invasion
 - Minor salivary gland neoplasms:
 - All are unencapsulated.
 - More common tumor types include pleomorphic adenoma, polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma share growth patterns, cytomorphology, cell composition and immunohistochemical reactivity such that differentiation is predicated on presence or absence of invasion (e.g., neurotropism, LVI, soft tissue, bone)
 - Generalizations relative to salivary gland neoplasms:
 - Growth patterns:
 - ALL salivary gland neoplasms are polymorphic (i.e., more than one growth pattern).
 - Polymorphic growth does not equate to any specific diagnosis (e.g., polymorphous low-grade adenocarcinoma).
 - Cytomorphology:
 - Some benign (e.g., pleomorphic adenoma) and some histologically low-grade malignant salivary gland neoplasms (e.g., polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma) may be composed of similar isomorphic cell type(s) lacking significant nuclear pleomorphism, increased mitotic activity.
 - Dual cell composition:
 - Many benign and malignant neoplasms composed of admixture of epithelial cells and myoepithelial cells as identified by:
 - ◻ Light microscopy
 - ◻ Immunohistochemical staining (cytokeratins, p63, p40, calponin, S100 protein, SMA, and/or GFAP)
 - Given above overlapping features between some benign and some malignant salivary gland neoplasms, in limited biopsies especially those including tissue fragments composed entirely or near entirely of lesional cells without surrounding tissue to evaluate for invasion, differentiation often cannot be achieved and a diagnosis of “salivary gland neoplasm, not

- further specified” is advised with the recommendation for conservative but complete excision.
- Risk factors linked to the development of salivary gland neoplasia include:
 - Radiation exposure
 - Familial or genetic predisposition
 - Tobacco use:
 - Strong association between tobacco use and the development of Warthin tumor
 - Microorganisms:
 - Epstein-Barr virus linked to lymphoepithelial carcinoma
 - Exposure to industrial chemicals
 - Similar to the thyroid gland, fine-needle aspiration biopsy (FNAB) represents the initial diagnostic modality in assessing the pathology of a salivary gland mass; FNAB is:
 - Cost effective and efficient
 - Has a sensitivity rate reported to be 81% to 98%
 - Has a specificity rate reported to be 60% to 75%
 - Has a false negative rate reported to be 5% to 10%:
 - Cytologically diagnosed as malignant but histologically proven to be benign
 - Has a false positive rate reported to be 0% to 6%:
 - Cytologically diagnosed as malignant and histologically proven to be benign
 - Those tumors in which the FNAB diagnosis is equivocal or inconclusive likely result in intraoperative consultation (i.e., frozen section analysis) to clarify and/or confirm the diagnosis (see Chapter 21 for the intraoperative diagnoses of salivary gland tumors).
 - In general, the light microscopic features of salivary gland neoplasms are distinctive so that use of immunohistochemistry is not necessarily required to arrive at a diagnosis; however, exceptions to this rule exist and immunohistochemical analysis may be required in the diagnosis and differential diagnosis of salivary gland neoplasms:
 - Immunohistochemical antigenic profile of salivary gland neoplasms often correlates to the histogenetic derivation of the tumor.
 - Tumors derived from the distal segments of the salivary duct system (intercalated ducts and acini) may take origin from a combination of epithelial and myoepithelial cells and may have different and diagnostic immunoreactivity as compared with those neoplasms that originate from more proximal segments of the duct system (striated and excretory ducts) in which myoepithelial cells are absent.
 - Some neoplasms have relatively unique markers or combination of markers, including (but not limited to):
 - DOG1 immunoreactivity in acinic cell carcinoma
 - Diffuse and strong mammaglobin and S100 protein staining in mammary analogue secretory carcinoma
 - Androgen receptor and salivary duct carcinoma
 - However, there is substantial overlap in the immunohistochemical antigenic profile among a wide variety of tumor types such that differentiating cannot be determined by immunohistochemical staining alone.
 - Immunohistochemical findings of selected salivary gland neoplasms are detailed in [Table 20-1](#).
 - SRY-related HMG-box 10 (Sox10) protein:
 - Transcription factor crucial in development of neural crest, Schwann cells, and melanocytes
 - Positive expression found in major salivary gland
 - Sox10 expression in salivary gland neoplasms reported as:
 - Positive in acinic cell carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, myoepithelial carcinoma, pleomorphic adenoma, and carcinoma ex pleomorphic adenoma:
 - Sox10 expression specific to nuclei of acini, luminal, and abluminal cells of intercalated ducts but not in other sites
 - Negative in salivary duct carcinomas, mucoepidermoid carcinomas, oncocytic carcinoma, oncocytomas, and Warthin tumor
 - In other organ sites (e.g., breast, prostate, other) the identification of two cell types (e.g., ductal and myoepithelial or basal cells) may correlate to a benign neoplasm, whereas the presence of a single cell type may correlate to an adenocarcinoma; these criteria are not necessarily applicable to salivary gland, in that there are benign neoplasms composed of only a single cell type (e.g., monomorphic adenomas) and malignant tumors composed of dual cell types (e.g., adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, others).
 - Cytogenetics and molecular genetics ([Table 20-2](#)):
 - Recent studies have identified genes correlating to specific tumor types, which can be used as adjuncts to light microscopic and immunohistochemical staining in diagnosis and differential diagnosis.
 - With increasing understanding of the biology of salivary gland neoplasms and identification of characteristic molecular signatures and genomic alterations of specific histologic subtypes, such neoplasms may be amenable to molecular targeted therapy:
 - Clinical trials exploring this approach are currently under way, and their efficacy remains to be determined.

TABLE 20-1 Immunohistochemistry* of Selective Salivary Gland Neoplasms

Tumor	PanK	LMWK	HMWK	p63	p40	S100	DOG-1	MGB	AR	GATA-3	Her-2	CD117	PLAG1
PA	+	+	+	+	+	+	–	–	–	v	–	v	+
BCA/BCAdC	+	+	+	+	+	+	–	–	–	v	–	v	v
MYO	+	+	+	+	+	+	–	–	–	v	–	v	+
MEC	+	+	+	+	+	–	–	–	–	v	–	v	–
ACC	+	+	+	–	–	–	+	–	–	–	–	–	–
MASC	+	+	+	–	–	+	–	+	–	+ (n)	–	–	–
AdCC	+	+	+	+	+	+	+ [†]	–	–	–	–	+ (lum)	–
PLGA	+	+	+	+	–	+	–	–	–	–	–	v	v
SDC	+	+	+	–	–	–	–	–	+ (n)	+ (n)	v (memb)	–	–
EMC	+	+	+	+	+	+	+ [†]	–	–	–	–	–	–
CCC/HCCC	+/+	+/+	+/+	–/+	–	–/–	–/–	–/–	–/–	–/–	–/–	–/–	–/–

*Staining characteristics vary widely among tumor types and even within the same tumor type. This table details ideal staining characteristics per tumor type, and although these staining patterns generally remain consistent, any given tumor listed may defy “convention” and show reactivity for a marker usually not associated with that tumor or may lack a marker usually associated with that tumor (e.g., p63 in myoepithelial cells).

[†]Frequently positive often showing distinctive combined apical ductal and membranous/cytoplasmic myoepithelial staining profile.

ACC, Acinic cell carcinoma; AdCC, adenoid cystic carcinoma; AR, androgen receptor; BCA, basal cell adenoma; BCAdC, basal cell adenocarcinoma; CCC, clear cell carcinoma, including hyalinizing type; DOG-1, discovered on GIST1; EMC, epithelial-myoeplithelial carcinoma; GATA-3, GATA binding protein 3; HCCC, hyalinizing clear cell carcinoma; HMWK, high molecular weight cytokeratin (e.g., CK5/6, CK14); LMWK, low molecular weight cytokeratin (e.g., CK7, CK8, CK19); lum, strong staining luminal cells; MASC, mammary analogue secretory carcinoma; MEC, mucoepidermoid carcinoma; memb, membranous; MGB, mammaglobin; MYO, myoepithelioma; n, nuclear; PA, pleomorphic adenoma; PanK, pancytokeratin (e.g., AE1/AE3; CAM5.2); PLAG1, pleomorphic adenoma gene 1; PLGA, polymorphous low-grade adenocarcinoma; SDC, salivary duct carcinoma; V, variably positive.

Specific staining characteristics:

DOG1: should be admixture of strong apical membranous, cytoplasmic and complete membranous staining

Mammaglobin: should be strong and diffuse cytoplasmic staining in MASC (same for S100 protein in this tumor)

PLAG1 immunohistochemical staining may not be confirmed by FISH analysis even for PA.

TABLE 20-2 Salivary Gland Neoplasms: Chromosomal Translocations

Tumor	Chromosomal Translocation	Gene Fusion	Percentage of Cases
Pleomorphic adenoma	Rearrangement of 8q12: t(3;8)(p21;q12) t(5;8)(p13;q12) Rearrangement of 12q13-15: t(3;12)(p14.2;q14-5) ins(9;12)(p23;q12-15)	<i>PLAG1</i> ; <i>HMG2</i>	Approximately 70%
Mucoepidermoid carcinoma	t(11;19)(q21;p13) t(11;15)(q21;q26)	<i>CRTC1-MAML2</i> <i>CRTC3-MAML2</i>	60% to 80% 6% or less
Adenoid cystic carcinoma	t(6;9)(q22-23;p23-24)	<i>MYB-NFIB</i>	80% to 90%
Mammary analogue secretory carcinoma	t(12;15)(p13;q25)	<i>ETV6-NTKR3</i>	Translocation 80% ETV6 break 99%
Hyalinizing clear cell carcinoma (HCCC) Clear cell variant of myoepithelial carcinoma (CCMC) [†]	t(12;22)(q13;q12)	<i>EWSR1-ATF1</i>	For HCCC 80% For CCMC 39% [†]
Cribriform cystadenocarcinoma of salivary glands	t(1;14)(p36.11;q12) t(X;14)(p11.4;q12)	<i>ARID1A-PRKD1</i> <i>DDX3X-PRKD1</i> Other abnormalities of <i>PRKD2</i> , <i>PRKD3</i>	To be determined but could be as high as 80%
Epithelial-myoeplithelial carcinoma	No translocation but a mutation	<i>HRAS</i> exon3, codon 61	27%*

*Chiosea SI, Miller M, Seethala RR: *HRAS* mutations in epithelial-myoeplithelial carcinoma, Head Neck Pathol 8:146-150, 2014.

[†]Includes de novo CCMC and CCMC ex pleomorphic adenoma. From Skalova A, Weinrib I, Hyrcza M, et al: Clear cell myoepithelial carcinoma of salivary glands showing EWSR1 rearrangement, Am J Surg Pathol 39:338-348, 2015.

- Prognostic factors in salivary gland tumors include:
 - Clinical staging (see below)
 - Microscopic grading:
 - Some neoplasms by definition are considered to be histologically low grade (e.g., acinic cell carcinoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, others) and other tumors are considered to be histologically high grade (e.g., salivary duct carcinoma, most cases of carcinoma ex pleomorphic adenoma, others).
 - Exceptions to the above occur such that histologically low-grade carcinomas may transform to high-grade tumors (e.g., acinic cell adenocarcinoma, others); further, there are low-grade variants of typically high-grade carcinomas, including low-grade carcinoma ex pleomorphic adenoma.
 - Some tumors such as adenocarcinoma, not otherwise specified, are histologically divided into low, intermediate, and high grade based on a variety of cytomorphologic findings.
 - Similarly, mucoepidermoid carcinoma is histologically divided into low, intermediate and high grade based on a combination of architectural and cytomorphologic findings.
 - Often but not always the histologic grade correlates to the clinical stage:
 - Low-grade tumors tend not to disseminate to regional lymph nodes and generally do not require a node dissection, whereas high-grade tumors often disseminate to regional lymph nodes, requiring a neck dissection.
- Intermediate-grade tumors may or may not disseminate to regional lymph nodes and require clinical and radiographic evaluation to determine whether there is or is not evidence of nodal metastasis; the result of this evaluation usually dictates the need for a neck dissection.
- Tumor location:
 - Some tumors occurring in a specific site have a better prognosis than the identical tumor occurring in a different location.
 - Mucoepidermoid carcinoma (MEC) of the parotid gland has an overall better prognosis than MEC of the submandibular gland.
- Facial nerve involvement:
 - Tumor involvement of the facial nerve is associated with increased morbidity (e.g., recurrence) and mortality.
- Demographics:
 - Tumors occurring in younger patients and in females are reported to have a more favorable outcome.
- Observed association salivary gland cancer and breast cancer noted for decades with recent evidence of a connection between *BRCA* gene mutations and salivary gland cancers.
- TNM classification of salivary gland carcinomas (Table 20-3)

BENIGN NEOPLASMS

PLEOMORPHIC ADENOMA (PA) (Figs. 20-1 to 20-15)

Definition: Benign neoplasm composed of cells demonstrating epithelial and myoepithelial differentiation:

- Considered a pure epithelial neoplasm with divergent differentiation that may also include mesenchymal-appearing elements (myxoid, hyaline, chondroid, and osseous areas).

Synonym: Benign mixed tumor

Clinical

- Represents most common neoplasm of salivary glands, accounting for 40% to 70% of all neoplasms of the parotid, submandibular glands, and minor salivary glands; PA of the sublingual glands is rare:
 - 80% occur in parotid gland
 - 10% occur in submandibular gland
 - 10% occur in minor salivary glands
- Slightly more common in women than men; occur over a wide age range but are most commonly seen in the third through sixth decades of life:
 - Most common salivary gland neoplasm in children and adolescents
- Most common site of occurrence is tail of the parotid gland but it may also occur in the deep lobe of the parotid, in the submandibular and sublingual glands, and in all minor salivary glands throughout the upper and lower respiratory tract:
 - PA of parotid gland occurs primarily (but not exclusively) in the superficial lobe (i.e., superficial plane to facial nerve)
 - PAs of deep lobe of parotid gland may present as a parapharyngeal space mass.
 - Involvement of minor salivary glands occurs most frequently on the palate (hard and soft), but other common sites include the upper lip and buccal mucosa.

TABLE 20-3 TNM Classification of Salivary Gland Carcinomas*

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension [†]
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension [†]
T3	Tumor more than 4 cm in greatest dimension with extraparenchymal extension [†]
T4a	Moderately advanced disease Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Anatomic Stage/Prognostic Groups	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T1N1M0
	T2N1M0
	T3N1M0
	T4aN0M0
Stage IVA	T4aN1M0
	T1N2M0
	T2N2M0
	T3N2M0
	T4aN2M0
Stage IVB	T4b AnyN M0
	Any T N3 M0
Stage IVC	Any T Any N M1

*Classification applies only to carcinoma of the major salivary glands, including parotid, submandibular and sublingual glands, and does not apply to carcinomas arising in the minor salivary glands of the upper respiratory tract.

[†]Extraparenchymal extension is clinical and macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

From Edge SB, et al: AJCC Cancer Staging Manual, ed 7, New York, 2010, Springer, p 80.

- May occur in the sinonasal tract:
 - Involve the septum (bony or cartilaginous portion) but may arise in the lateral wall
 - Tend to be myoepithelial-predominant neoplasms
- Multiple tumors or bilateral tumors are uncommon.
- Symptoms vary according to site:
 - Most are slow-growing, painless masses present for periods up to several years.
 - Other symptoms, in particular those occurring in the minor salivary glands, may include:
 - Difficulties in chewing, dysphagia, dyspnea, hoarseness, and epistaxis
 - May ulcerate overlying mucosa
- In parotid gland, the tumor typically occurs outside of the facial nerve, and facial nerve involvement typified by facial nerve paralysis is rare and, if present, should be suspicious for malignancy:
 - Infarcted PAs may uncommonly be associated with pain or facial palsy.
- Parapharyngeal space PAs:
 - Represent most common tumor of the parapharyngeal space (followed by peripheral nerve sheath tumors)
 - Usually present as an asymptomatic (cervical or intraoral) mass; other symptoms may include obstruction, unilateral conductive hearing loss, and serous otitis media

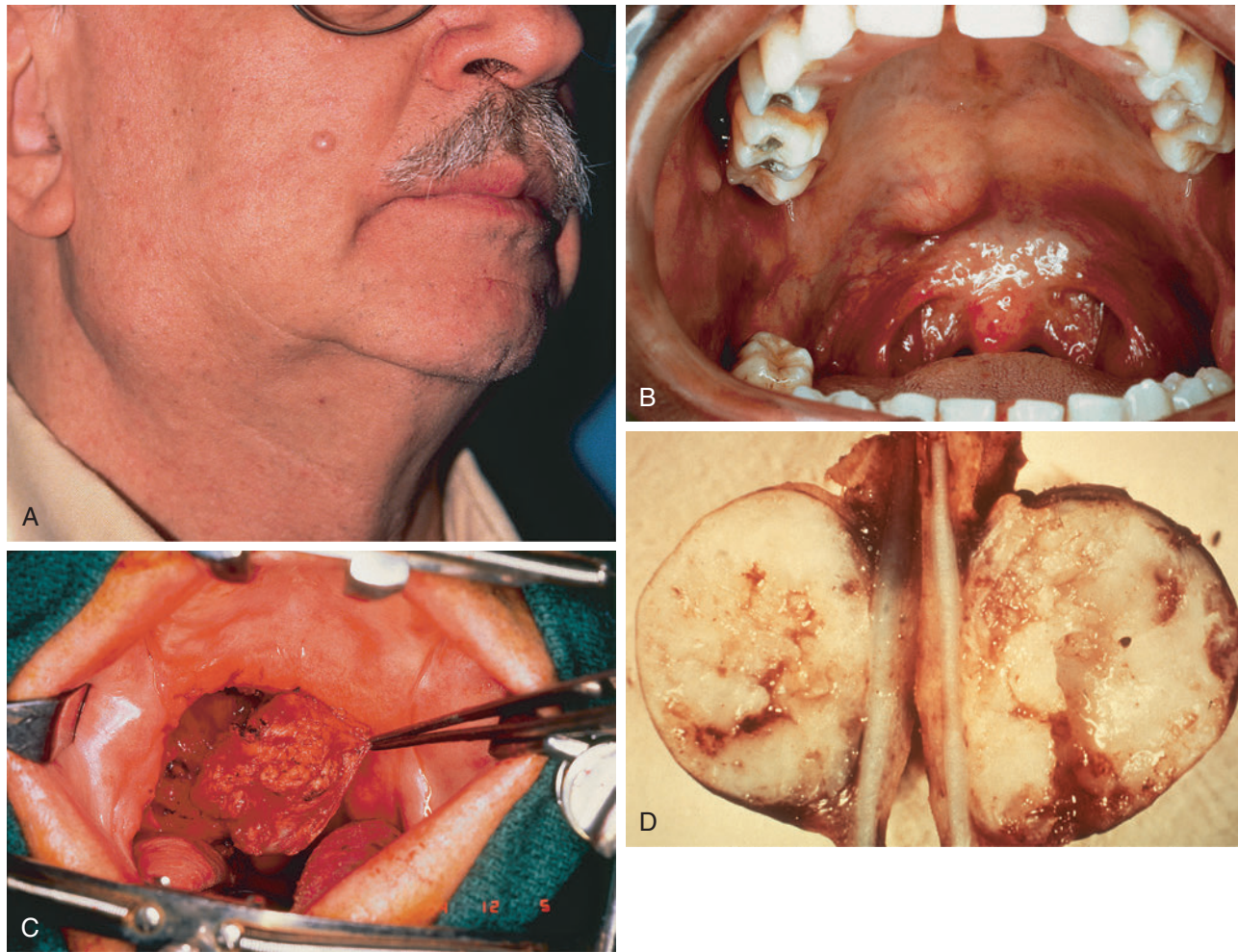


Fig. 20-1. Pleomorphic adenoma.

Pleomorphic adenomas may occur in major salivary glands, as well as minor salivary glands. **A**, Palpable parotid mass at the angle of the mandible that was firm, freely movable, and painless. **B**, Submucosal palatal swelling with intact surface epithelium. **C**, Large exophytic mass originating in the nasopharynx, hanging into the posterior oral cavity, where it was visible through the mouth. **D**, Resected large nasal septal large neoplasm (note elastic cartilage in center of image) that is circumscribed to encapsulated and on cut section appears predominantly with glistening (gelatinous) appearance.

- Parapharyngeal space is a potential space between the lateral wall of the pharynx, internal pterygoid muscle, and cervical vertebrae:
 - Other structures located within this space include cranial nerves IX through XII, great vessels of the neck, mature adipose tissue, and lymph nodes.
- Despite efforts in localization of key proteins using immunohistochemistry, the complex proteomic composition of pleomorphic adenomas (PA) has not yet been characterized.
- Matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-imaging):
 - Allows label-free and spatially resolved detection of hundreds of proteins directly from tissue sections and of histomorphologic regions by finding co-localized molecular signals
 - Spatial segmentation of MALDI-imaging data is algorithmic method for finding regions of similar proteomic composition as functionally similar regions.
 - MALDI-imaging of pleomorphic adenoma (two cases reported to date):
 - Spatial segmentation subdivided tissue in good accordance with the tissue histology
 - Numerous molecular signals co-localized with histologically defined tissue regions were found.
 - Highlighted cellular trans-differentiation within the PA

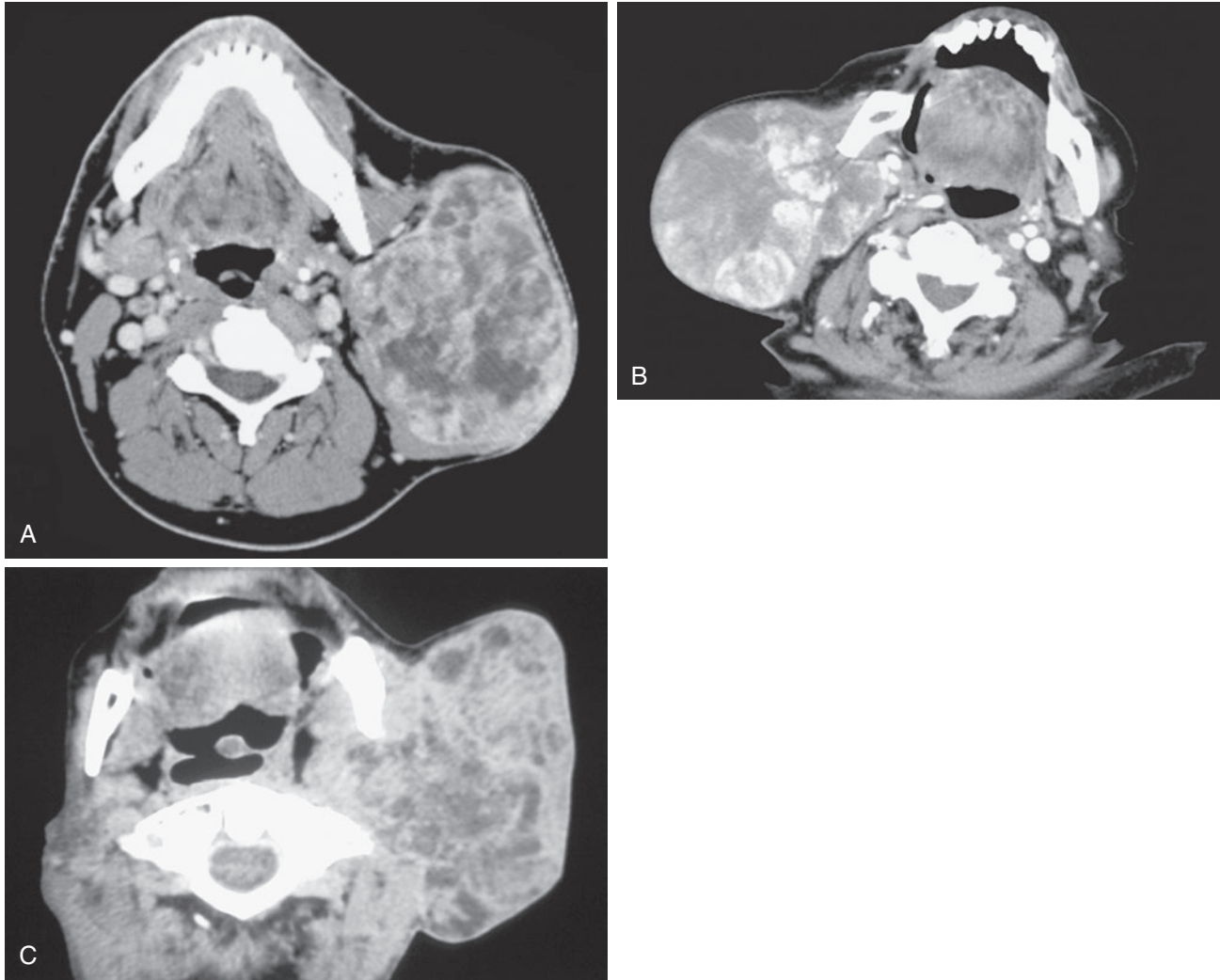


Fig. 20-2. Axial contrast-enhanced CT scans of three different patients.

In **A**, a contrast-enhanced image, there is a large, nonhomogeneous, slightly lobulated mass in the left parotid gland. There is scattered enhancement. In **B**, there is a lobulated mass in the right parotid gland with scattered areas of calcification. In **C**, there is a large, nonhomogeneous mass in the left parotid gland. All of these patients had pleomorphic adenomas. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 40-129, p 2531.)

- Spatial segmentation of MALDI-imaging data represents promising approach in emerging field of digital histologic analysis and characterization of tumors.
- Cause
 - No known etiologic factors
 - Familial occurrence rare

Pathology

Gross

- Firm, freely movable, unifocal mass:
 - Encapsulated or well-demarcated, tan-white, and solid in appearance

- May demonstrate cystic change
- Ulceration of overlying skin does not occur.
- Vary in size from a few centimeters up to large, disfiguring masses
- Minor salivary gland tumors are polypoid or lobulated, encapsulated or well-delineated, tan-white, usually measuring 1 to 2 cm but capable of attaining sizes of 7 cm or more.
- Recurrent tumors tend to be multinodular.

Fine-Needle Aspiration Biopsy

- Usually readily diagnosed by FNAB due to the presence of epithelial and stromal elements

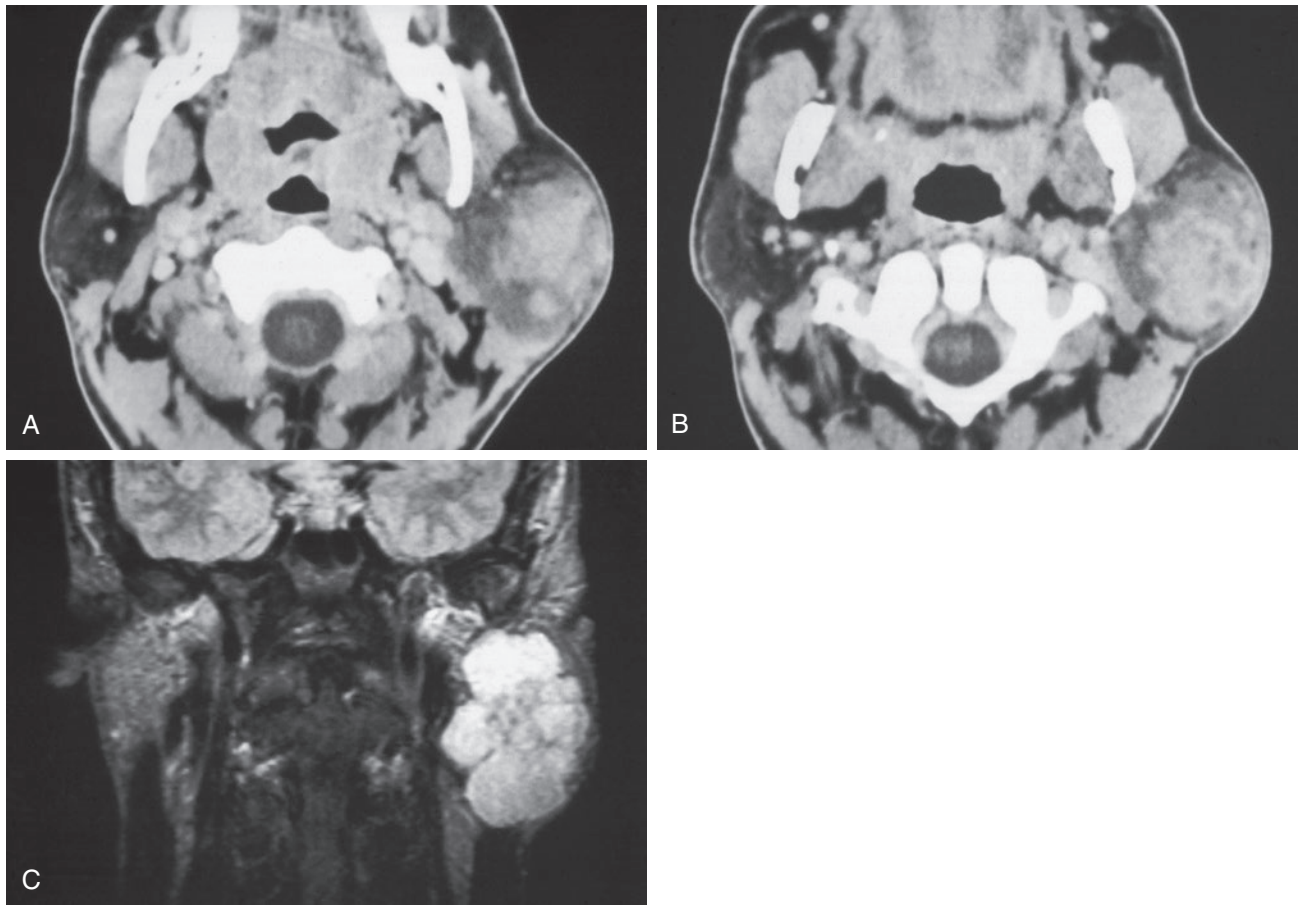


Fig. 20-3. CT and MR of pleomorphic adenoma.

A and **B**, Axial contrast-enhanced CT scans show a mass in the left parotid gland with unsharp margins. **C**, Coronal T2-weighted MR image of the same patient shows a lobulated solitary mass in the left parotid gland. The lesion is far better seen than on the CT scans. This patient had a pleomorphic adenoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 40-131, p 2532.)

- Morphologic diversity including:
 - Background filled with mucoid to fibromyxoid ground substance varying from fibrillar to myxomatous to chondroid and appearing:
 - Bright pink or magenta on Romanovsky stain
 - Bluish purple on Papanicolaou stain
 - Clusters of plasmacytoid or spindle-shaped (myoepithelial) cells:
 - Embedded in stromal matrix
 - Cohesive groups of epithelial cells with bland cytology including round to oval nuclei with fine-appearing chromatin:
 - Identified in continuity with the stromal material
- Other cellular elements and/or findings that can be seen include:
 - Squamous cells (with or without keratinization)
 - Oncocytic cells
 - Sebaceous cells
 - Tyrosine-like crystals appearing as crystalline deposits resembling the petals of a flower:
 - Not pathognomonic for pleomorphic adenoma as can be seen in nonneoplastic salivary gland lesions (e.g., parotid cysts) and in other neoplasms (e.g., polymorphous low-grade adenocarcinoma, others)
 - Intranuclear inclusions
- Degree of cellularity varies from case to case and even within the same case.
- Cellular pleomorphic adenomas:
 - Presence of cellular aspirate and relative absence of stromal component, especially if nuclear atypia is present, may present diagnostic problems in recognition as benign and in differentiating from carcinomas.
 - Cellular aspirates lacking stromal component and lacking nuclear atypia can be diagnosed as a “salivary gland neoplasm, not otherwise

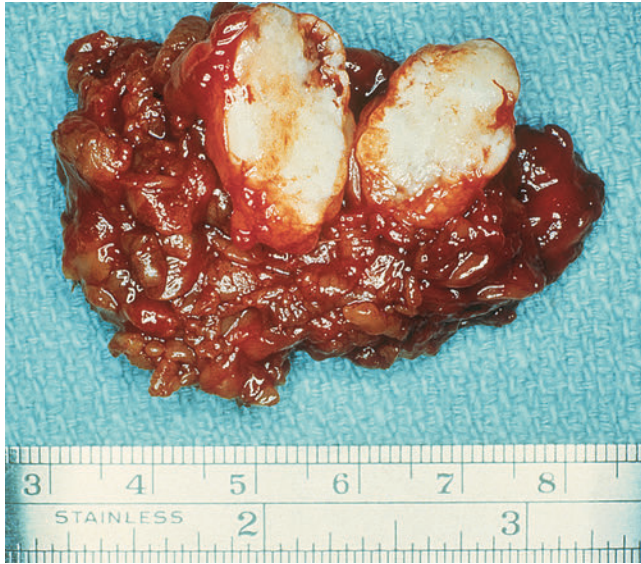


Fig. 20-4. Parotid pleomorphic adenoma.

Resected pleomorphic adenoma from the superficial lobe of the parotid gland, showing a circumscribed to encapsulated tumor that on cut section is solid with a tan-white appearance.

specified,” which would then prompt surgical removal and histologic evaluation.

Histology

Typical (Classic) PA

- In major salivary glands are encapsulated but fibrous capsule varies in thickness and may be thin or even absent:
 - Prominently myxoid tumors often have incomplete capsules and there may be juxtaposition of the tumor to adjacent normal salivary gland.
 - May be multinodular:
 - Nodules may be separate from one another.
 - Not diagnostic for malignancy
 - May have irregular growth along periphery of lesion, including lesional cells extending into capsule and/or fat:
 - Capsular extension not diagnostic for carcinoma
 - Fat may be inherent component of tumor so that lesional cells extending into fat but still within the confines of a capsule are still within the spectrum of a benign neoplasm and not diagnostic for malignancy.
- In minor salivary glands generally not encapsulated but typically circumscribed or well demarcated:
 - Extension and involvement of surface epithelium not diagnostic feature for malignancy
- Histologic appearance includes an admixture of epithelial, myoepithelial, and stromal components.

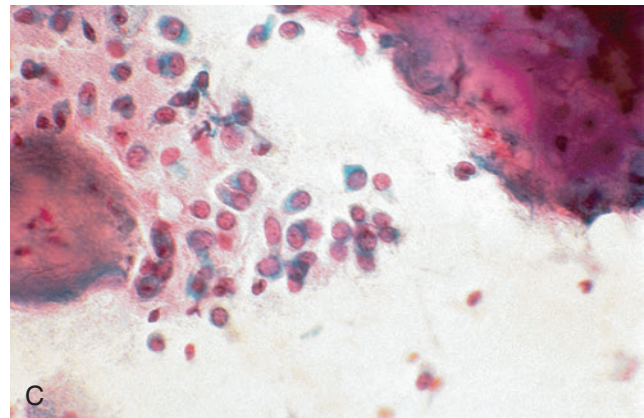
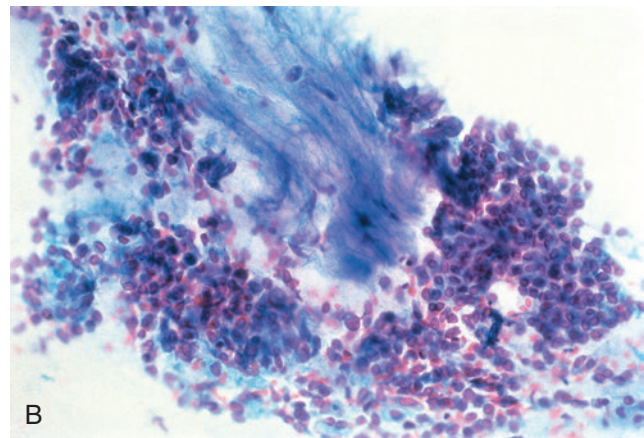
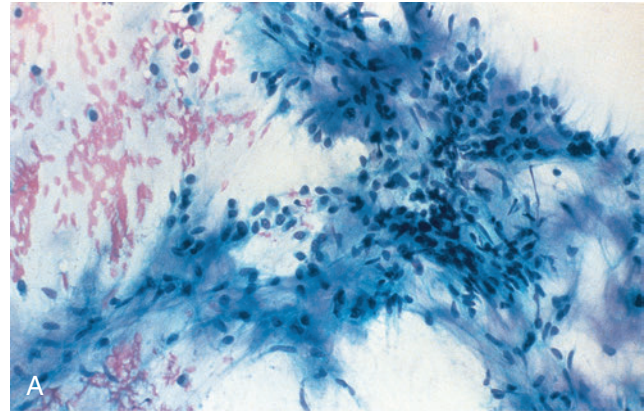


Fig. 20-5. Fine needle aspiration.

Pleomorphic adenoma, fine-needle aspiration biopsy.

A, Background is filled with mucoid to fibromyxoid ground substance appearing bluish-purple with fibrillar appearance and associated spindle (myoepithelial) cells. **B**, Cohesive groups of epithelial cells with bland cytology including round to oval nuclei with fine nuclear chromatin and associated magenta-appearing mucoid ground substance. **C**, Clusters of plasmacytoid (myoepithelial) cells with associated chondroid-appearing matrix.

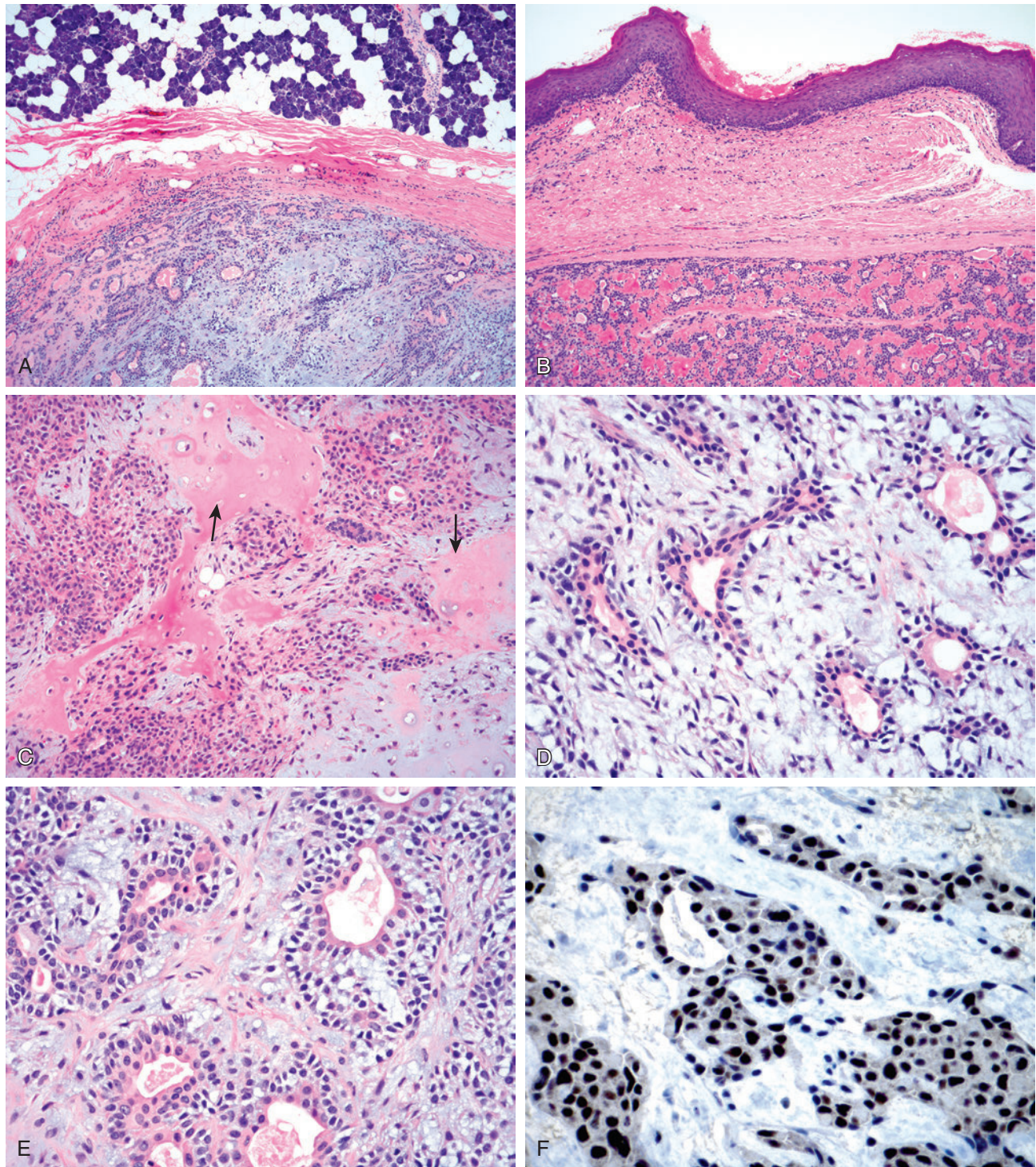


Fig. 20-6. Pleomorphic adenoma.

A, In major salivary glands, pleomorphic adenomas are encapsulated sharply demarcated from the unremarkable parotid gland parenchyma. **B**, In minor salivary glands such as seen in this palatal lesion, pleomorphic adenomas are circumscribed but not encapsulated. **C**, Characteristic components in a pleomorphic adenoma include admixture tubules/ductules and matrix stroma, the latter including hyaline (arrows) and myxoid foci. **D** and **E**, Acini or tubules are lined by ductal epithelial cells surrounded by an outer layer of modified myoepithelial cells of varying thickness. **F**, PLAG1 (nuclear) immunoreactivity.

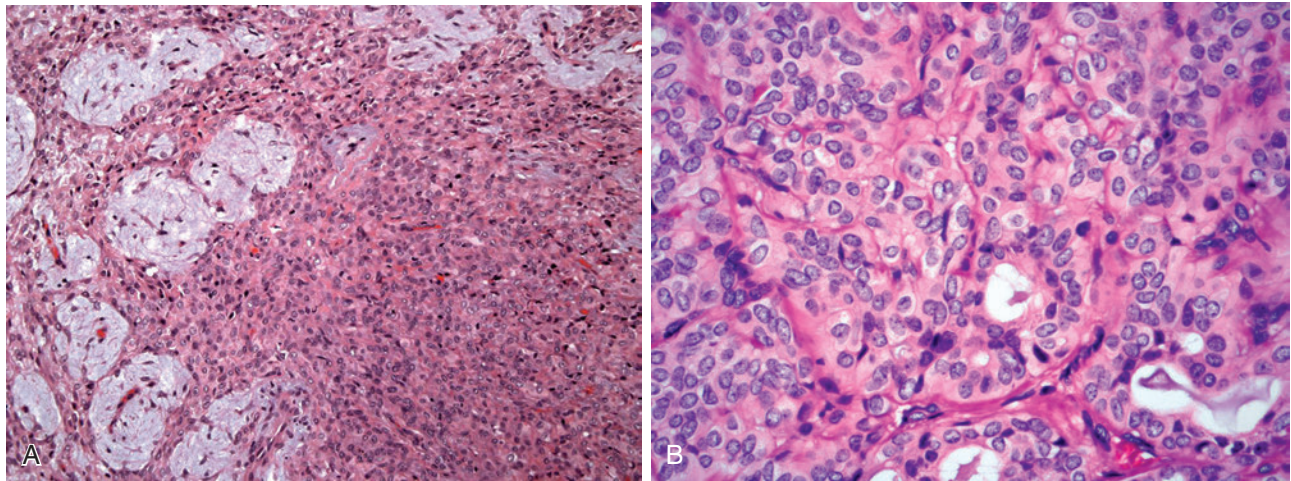


Fig. 20-7. Cellular epithelial-predominant pleomorphic adenoma.

A, At low magnification there is a cellular neoplasm with residual identifiable chondromyxoid stroma. **B,** At higher magnification, cytologically bland-appearing epithelial cells predominate lining ductules as well as in the cellular areas.

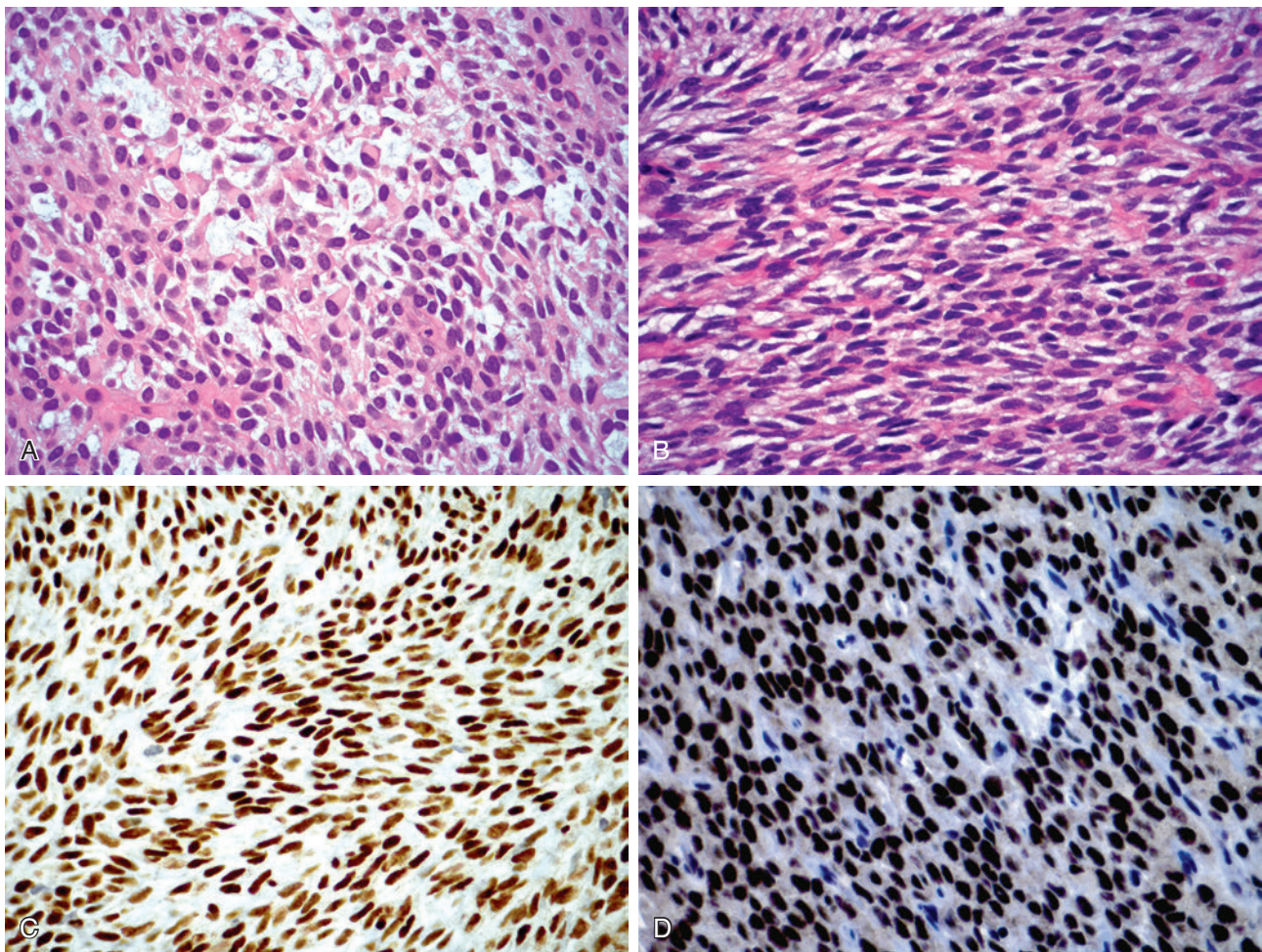
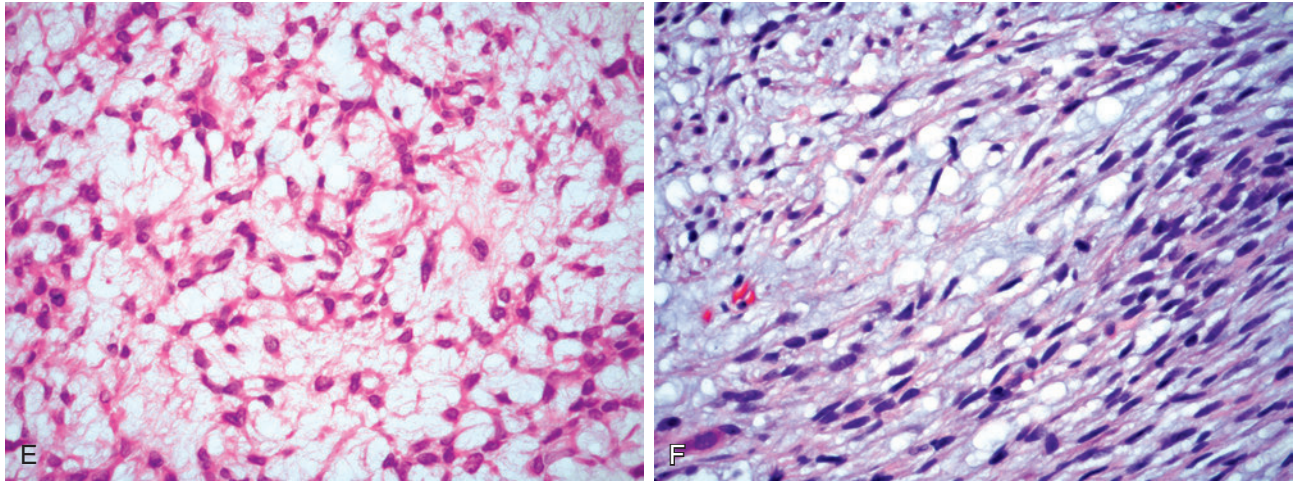
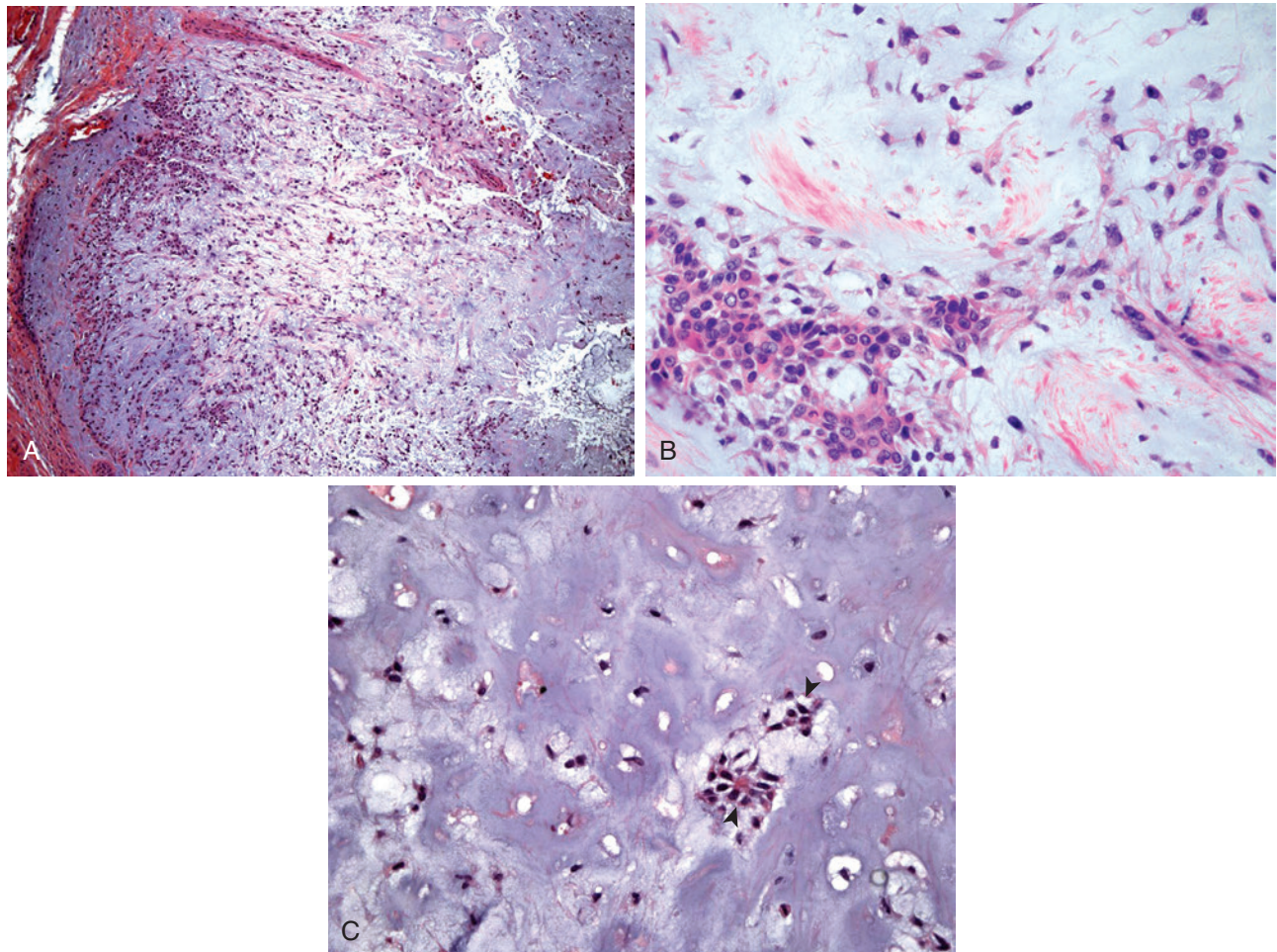


Fig. 20-8. Cellular myoepithelial-predominant pleomorphic adenoma.

The myoepithelial cells may include **(A)** solid growth composed of plasmacytoid (hyaline) and/or **(B)** fascicular pattern of growth composed of spindle shaped cells. **C,** Myoepithelial cells are strongly p63 (nuclear) positive whether appearing spindle-shaped as seen here or plasmacytoid (hyaline) (not shown). **D,** Diffuse PLAG1 (nuclear) immunoreactivity.

**Fig. 20-8, cont'd**

E, The myoepithelial cells may be arranged in a reticular or lattice-like growth pattern within myxoid stroma or show **(F)** fascicular growth (*lower right*) adjacent to lattice-like growth pattern (*upper left*).

**Fig. 20-9. Chondromyxoid predominant pleomorphic adenoma.**

A, Low magnification showing predominance of chondromyxoid matrix with variable cellularity including identifiable tubules along the periphery (*left*) of the neoplasm. **B**, At higher magnification, identifiable tubules lined by dual cell type are present extending ("melting") into the dominant chondromyxoid stroma. **C**, In some examples only very focal isolated tubules remain (*arrowheads*) in a neoplasm with predominant chondromyxoid-appearing stroma.

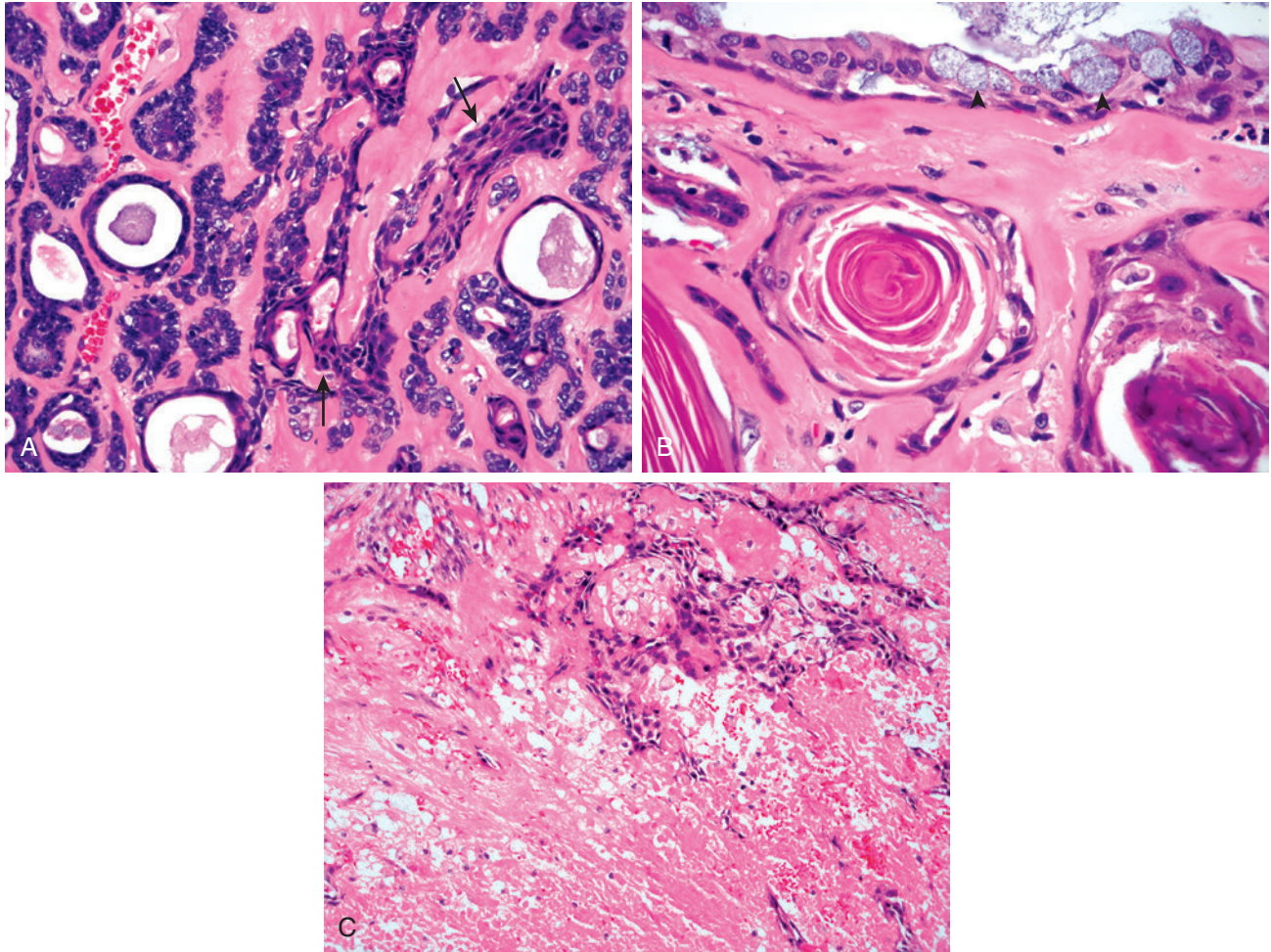


Fig. 20-10. Metaplastic and retrogressive changes following aspiration.

Post-fine-needle aspiration biopsy changes may include **(A)** squamous metaplasia (*arrows*) with keratinization and intercellular bridges; **(B)** mucous cell metaplasia (*arrowheads*) and squamous metaplasia. This combination of cell types may raise concern for a possible diagnosis of mucoepidermoid carcinoma, but the presence of keratinization and intercellular bridges are not features typically associated with mucoepidermoid carcinomas. The latter are composed of epidermoid cells lacking keratinization and intercellular bridges. **C**, Infarction (*bottom*) with squamous metaplasia.

- Morphologic variability (i.e., polymorphism) can be seen from case to case and within a single neoplasm:
 - Growth patterns may include tubular/ductular, solid, cystic, trabecular, cribriform, papillary, reticular, or lattice-like and schwannoma-like.
- Duct-lining epithelial cells form the inner layer of acini or tubules and appear flattened, cuboidal, or columnar with round to oval nuclei and a variable amount of cytoplasm appearing eosinophilic to amphophilic.
- Myoepithelial component forms the outer layer and may appear:
 - Spindle-shaped, plasmacytoid (hyaline), cuboidal, epithelioid, clear-appearing cells
 - Plasmacytoid myoepithelial cells are oval with round nuclei eccentrically located and abundant eosinophilic hyaline cytoplasm
 - Absence of perinuclear Golgi zone
- Stromal component, the product of myoepithelial cells, varies in appearance from myxoid to (hyaline) chondroid to chondromyxoid and may also appear fibrous and vascular:
 - Any one or all of these components may coexist in the same neoplasm.
 - Quantity ranges from case to case and even within a given case and may be abundant or scanty.
 - Presence of any stromal component as detailed above allows for classification as

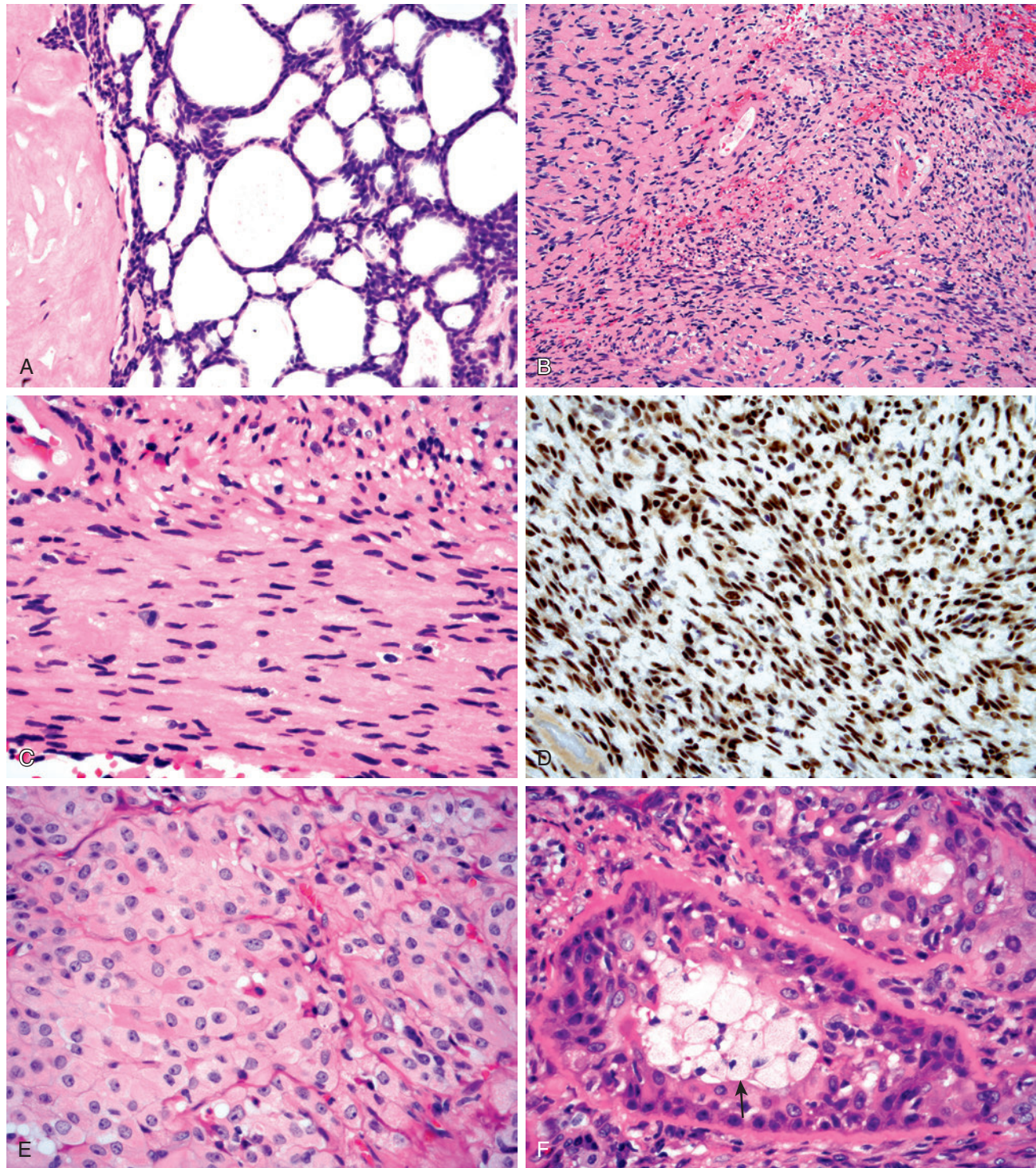


Fig. 20-11. Variant histologic findings in pleomorphic adenomas.

Other histologic findings that can be seen in association with pleomorphic adenomas may include (A) cribriform growth, which may suggest a diagnosis of adenoid cystic carcinoma, but in the setting of pleomorphic adenoma cribriform growth tends to be limited, occurring in a background of characteristic findings of pleomorphic adenoma; (B and C) schwannoma-like foci including perivascular hyalinization (B) and (C) wavy “buckled” appearing nuclei; (D) cells in schwannoma-like foci are strongly and diffusely p63 positive (nuclear), indicative of myoepithelial cells; (E) oncocytic cells focally or more extensive, the latter referred to as oncocytic type of pleomorphic adenoma; (F) sebaceous cells (arrow) within focus of squamous metaplasia;

Continued

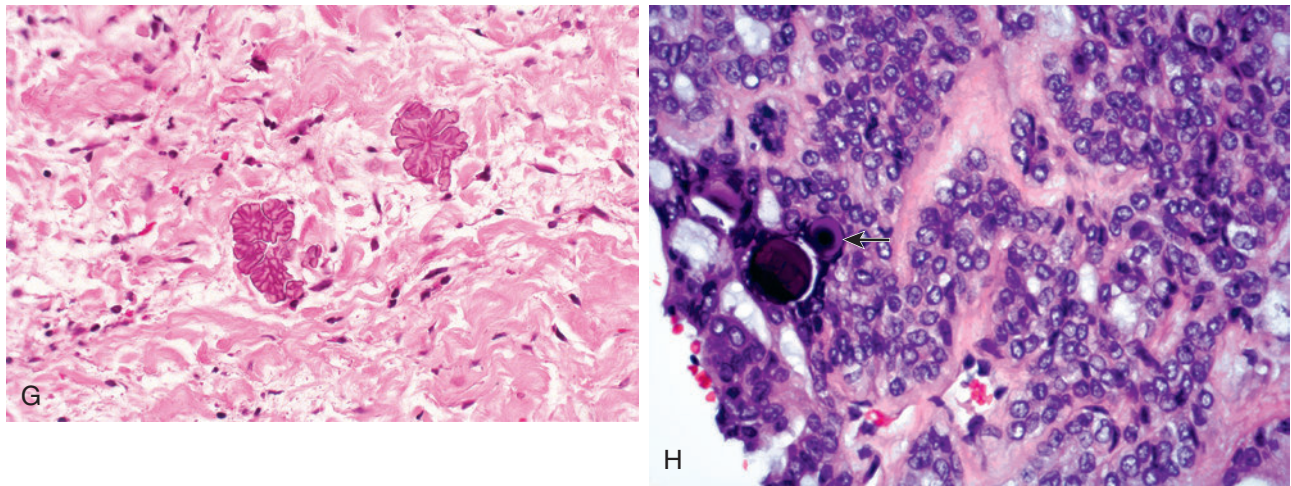


Fig. 20-11, cont'd

(G) (extracellular) tyrosine-like crystals; and (H) psammoma bodies (*arrow*).

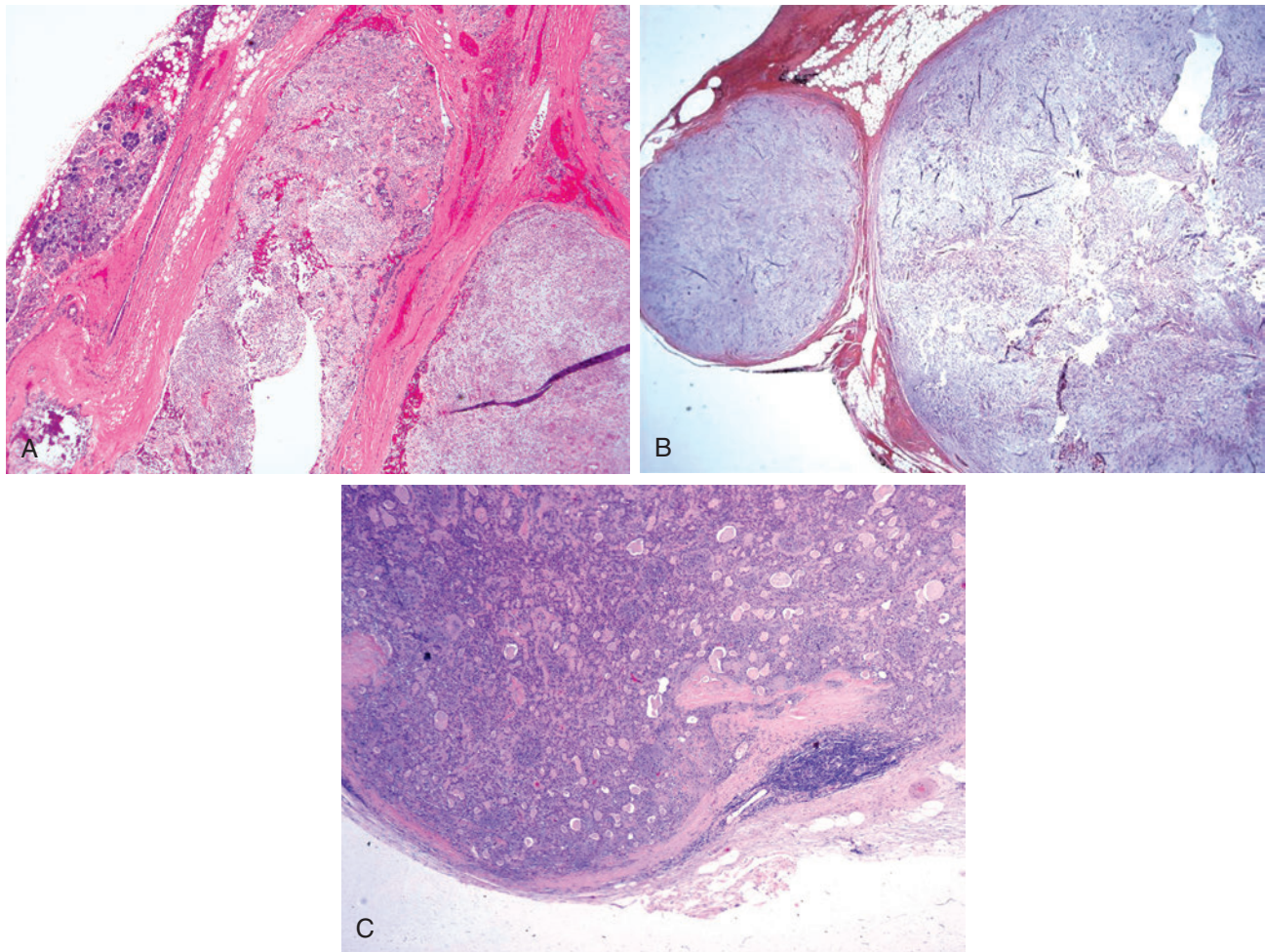
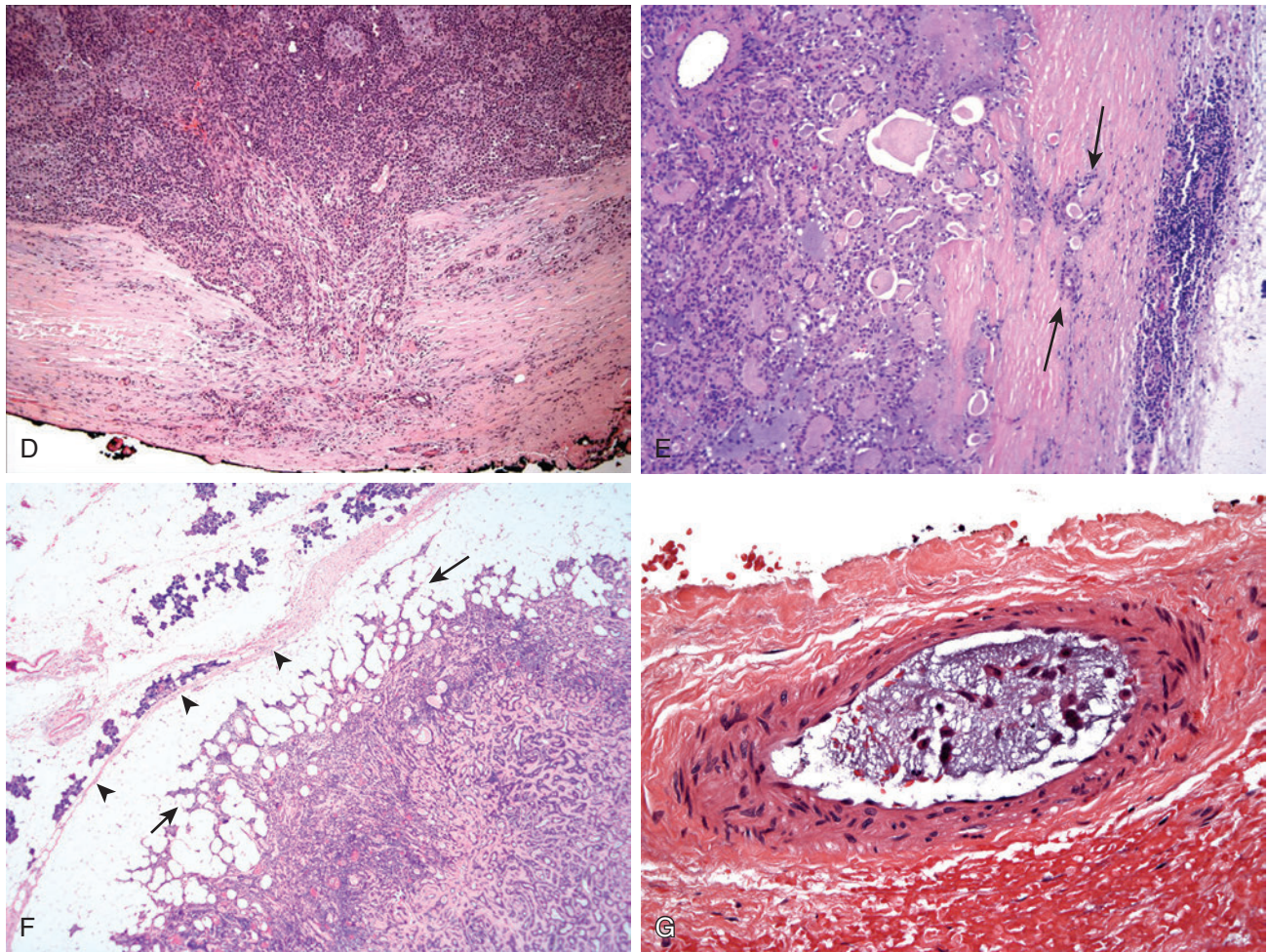


Fig. 20-12. Growth characteristics of pleomorphic adenoma.

Growth patterns that may raise concern but that are not diagnostic for carcinoma in pleomorphic adenomas may include (A and B) multinodular growth, including satellite nodules separate from the main mass; this finding is still acceptable within the spectrum of changes associated with pleomorphic adenomas; (C-E) capsular extension by (C) mushroom-like growth;

**Fig. 20-12, cont'd**

(D) protrusion into the capsule, or (E) scattered tubules (*arrows*) extending into the capsule. Such capsular extension may be a diagnostic feature for carcinoma in other organs (e.g., thyroid gland) but not in relationship to salivary gland neoplasms. Extension beyond the capsule into adjacent salivary gland parenchyma or fibroconnective tissue is considered invasive growth that generally equates to malignancy in salivary gland neoplasms. **F**, Extension into fat (*arrows*); the fat is within (part of) the neoplasm lying within the capsule (*arrowheads*) separating the tumor from the surrounding parotid gland parenchyma. **G**, Vascular permeation with tumor adherent to the vessel wall and not “floating” in the lumen as may be indicative of an artifactual change. Vascular permeation can infrequently be seen in a neoplasm with histologic features characteristic of pleomorphic adenoma and has generally been shown not to be associated with untoward behavior such as metastatic tumor.

pleomorphic adenoma rather than monomorphic adenoma.

- Extracellular crystalloids may be identified, particularly in the nonepithelial areas:
 - Crystalloids are more often present in PA than in any other salivary gland tumor but may be present in other tumor types, including polymorphous low-grade adenocarcinoma.
- Other cell components may include:
 - Squamous cells with or without keratinization
 - Mucous cells
 - Clear cells, sebaceous cells, oncocytic cells
 - Calcification and fat
- Minor salivary pleomorphic adenomas tend to be cellular and are circumscribed but unencapsulated.
 - Those occurring in the nasal cavity (particularly the septum) tend to have an increased plasmacytoid-appearing myoepithelial component.
- Multicentric pleomorphic adenomas are rare.
- Recurrent tumors are often multinodular and frequently chondromyxoid-predominant.

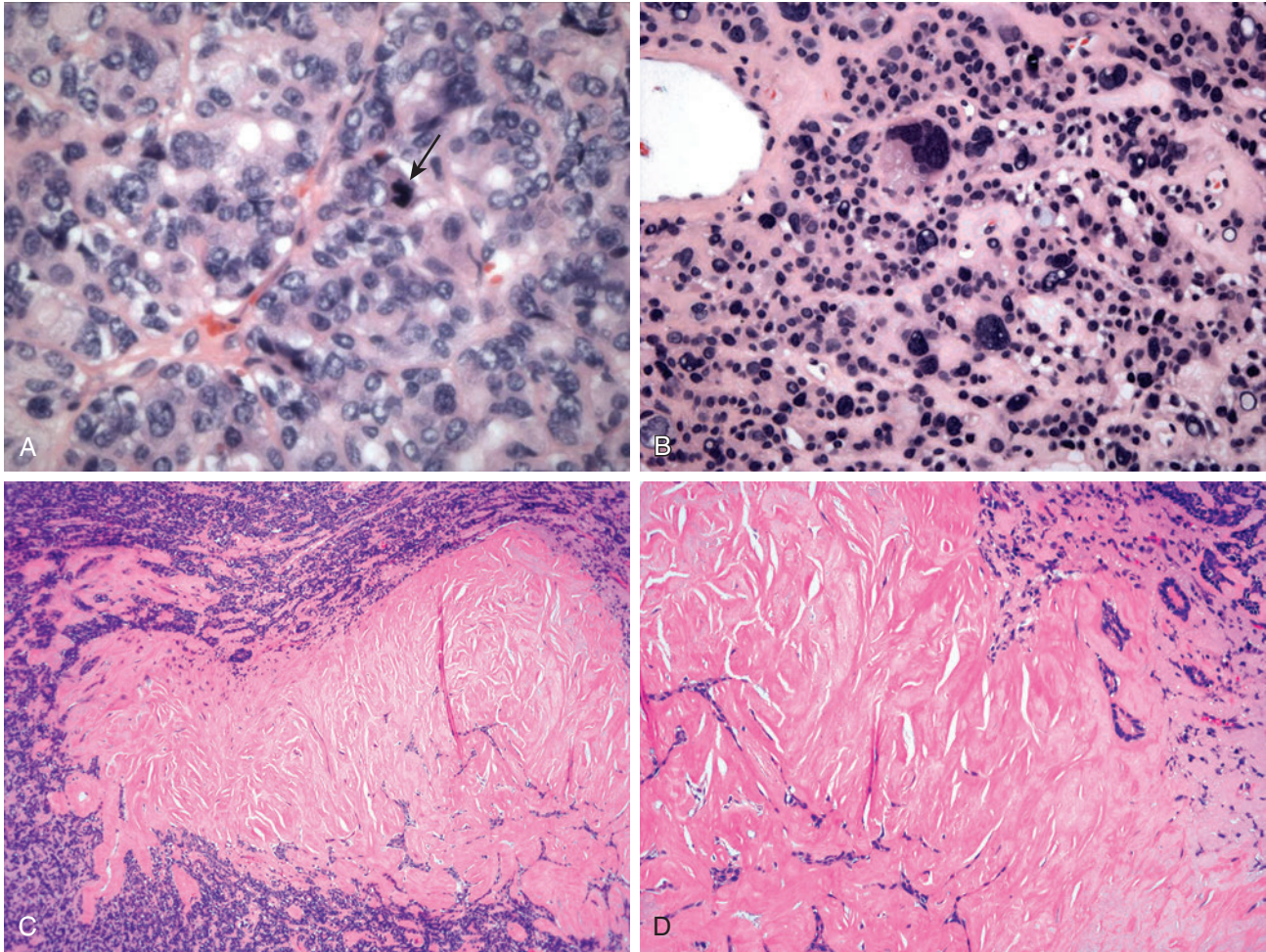


Fig. 20-13. Potential confounding findings in pleomorphic adenomas.

Cytomorphologic findings that may raise concern but that are not diagnostic for carcinoma in pleomorphic adenomas may include **(A)** presence of mitotic figures (*arrow*); numerous mitotic figures can be seen in any given pleomorphic adenoma but increased mitotic activity is not diagnostic for carcinoma. The presence of atypical mitoses (not shown) would represent a more worrisome feature for carcinoma but additional findings would still be required for a diagnosis of carcinoma. **B**, Enlarged pleomorphic and hyperchromatic bizarre-appearing (“monster”) nuclei. Generally such bizarre nuclei are focally and not diffusely identified and are thought to represent a reactive process. Diffuse nuclear atypia would represent a more worrisome feature for carcinoma but additional findings would still be required for a diagnosis of carcinoma. **C** and **D**, Broad zones of acellular hyalinization. The presence of prominent areas of acellular hyalinization is considered an atypical finding in pleomorphic adenomas that are not diagnostic for malignancy but may portend or be associated with malignant transformation (i.e., carcinoma ex pleomorphic adenoma).

- Post-fine-needle aspiration biopsy changes:
 - Secondary changes may occur following prior manipulation or fine-needle aspiration biopsy and may include:
 - Squamous metaplasia, including keratinization and/or intercellular bridges
 - Mucous cell metaplasia
 - Hemorrhage and cholesterol granuloma formation
 - Calcifications and psammomatoid concretions
 - “Pseudoinvasion” or bulging into the capsule
 - Necrosis/infarction
 - Spontaneous necrosis in a PA may occur, but the presence of necrosis/infarction in the absence of prior manipulation should raise concern for the possibility of malignancy.

Cellular Pleomorphic Adenoma

- Neoplasm showing residual foci diagnostic for pleomorphic adenoma, even if only limited in extent, but dominated by epithelial, myoepithelial, or stromal component

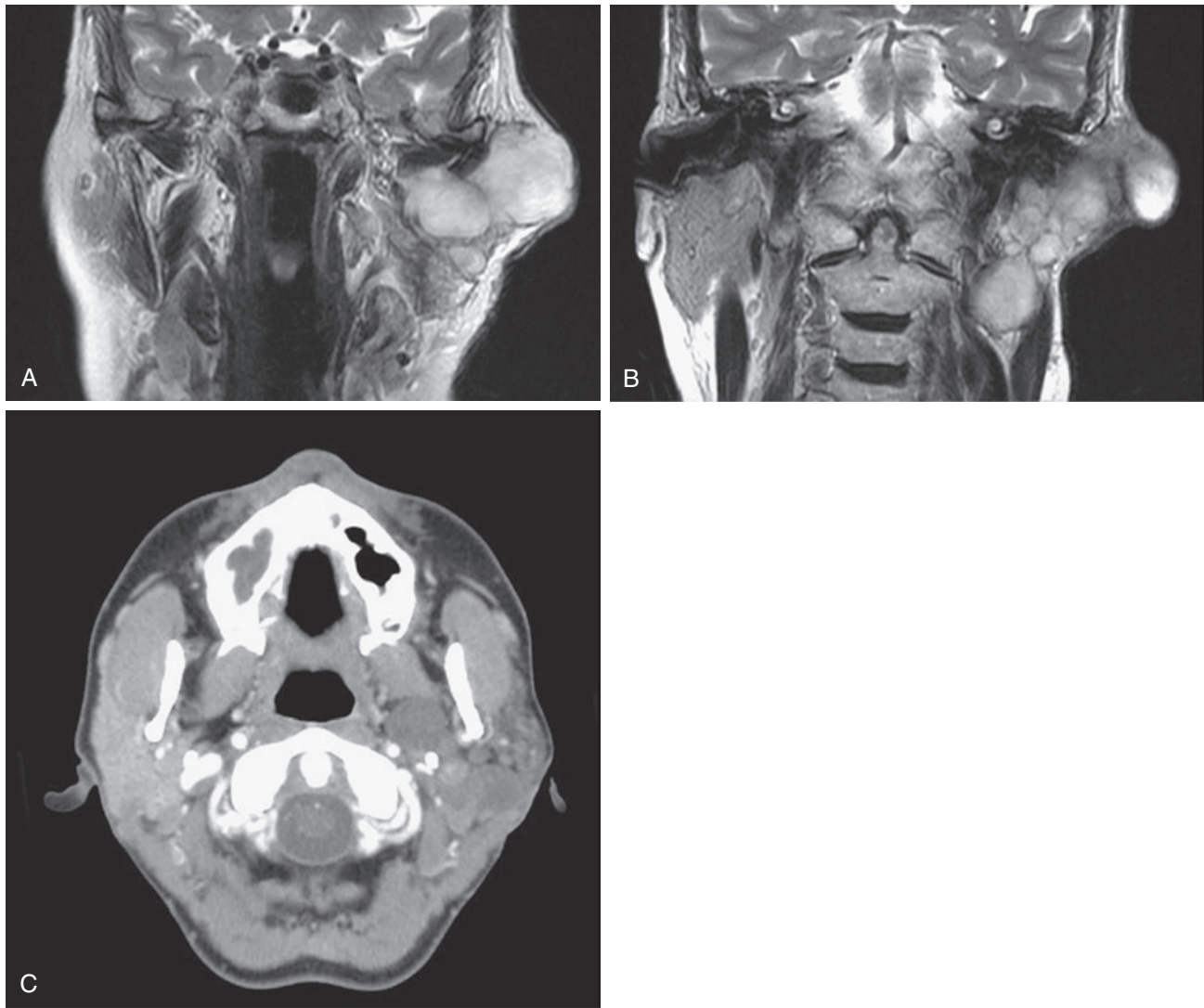


Fig. 20-14. Recurrent multinodular and multifocal pleomorphic adenoma.

A and **B**, Serial coronal T2-weighted MR images on a patient who had a prior left parotidectomy. There are multiple well-delineated masses in the left postoperative parotid bed. This patient had multiple recurrences of pleomorphic adenomas. **C**, Axial CT scan of a different patient who had a left parotidectomy. There are multiple low-attenuation well-delineated masses within the left parotid postoperative bed. This patient also had multiple recurrences of pleomorphic adenomas. These recurrences indicate that the original tumor capsule was violated at the time of the initial surgery. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 40-146, p 2541.)

- Neoplasms with overabundance of epithelial cells, myoepithelial cells, or mesenchymal component categorized respectively as:
 - Epithelial-predominant pleomorphic adenoma
 - Myoepithelial-predominant pleomorphic adenoma
 - Chondromyxoid-predominant pleomorphic adenoma
- In association with increased cellularity there may be nuclear pleomorphism, including bizarre-appearing (“monster”) cells and scattered mitotic figures, raising additional concern for possible diagnosis of malignancy:
 - Typically, bizarre cells are limited in extent and often relegated to focal areas of the tumor.
 - Mitotic figures may be identified in any given tumor but often are limited in number.
 - Increased mitotic figures can be seen in any given neoplasm and solely in the absence of other findings does not constitute a diagnostic feature for carcinoma

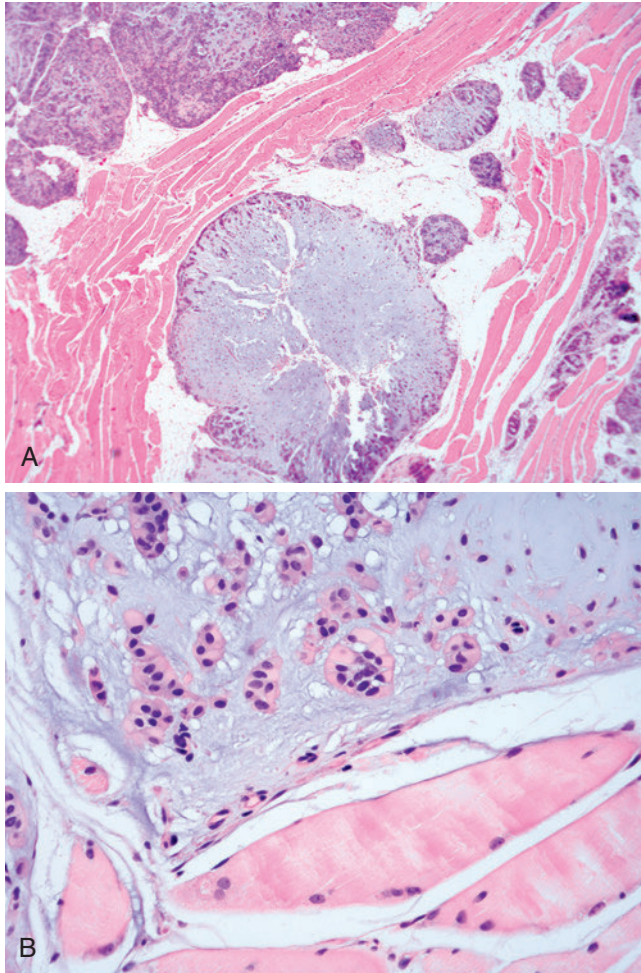


Fig. 20-15. Recurrent PA.

Recurrent pleomorphic adenomas may vary in their histologic appearance but not infrequently are chondromyxoid predominant and may include numerous nodules in soft tissue of the neck. **A**, Multiple chondromyxoid-predominant pleomorphic adenoma nodules within skeletal muscle. **B**, The nodules are composed of benign cellular features lacking malignancy cellular features. Similar to capsular extension and vascular permeation, the presence of multiple nodules of otherwise cytologically benign lesional cells is acceptable within the spectrum of changes associated with (recurrent) pleomorphic adenomas and not diagnostic for metastatic carcinoma.

- Presence of atypical mitotic figures not typically found in pleomorphic adenomas
- Rare cases may show vascular permeation but by itself this feature is not indicative of malignancy:
 - Intravascular location of neoplastic cells can be confirmed by CD31, CD34, and factor VIII-related antigen immunostains.
 - Biologic significance not completely clear but evidence supports innocuous phenomenon in a majority of cases likely related to artifactual

spillage caused by tumor injury presumably by prior fine-needle aspiration or surgery.

- Despite the presence of increased cellularity even with bizarre cells and mitoses, there is absence of features raising concern for malignancy.

Atypical Pleomorphic Adenoma

- Atypical histologic features seen in PAs that may portend transformation to a carcinoma include:
 - Diffuse nuclear atypia (anaplasia)
 - Atypical mitoses
 - Prominent zones of (acellular) hyalinization
 - Pleomorphic adenomas with prominent zones of hyalinization are more likely to develop carcinoma than pleomorphic adenomas without such hyalinization.
 - Coagulative tumor necrosis
- Presence of atypical features should prompt extensive sectioning and histologic examination of the specimen to exclude findings that may be diagnostic for malignancy.

Recurrent Pleomorphic Adenoma

- Often but not always tend to be chondromyxoid predominant
- Often multinodular and may include:
 - Innumerable variably sized, well-circumscribed nodules
 - Extensive involvement of soft tissues of the neck, including into skeletal muscle and fat
 - In spite of multinodularity retain benign cytomorphologic features

For all pleomorphic adenomas:

- Histochemistry:
 - Intraluminal epithelial mucin may be demonstrated by diastase-resistant, periodic acid Schiff-positive, and mucicarmine-positive material.
 - Stromal component is alcian blue positive but mucicarmine negative
- Immunohistochemistry (IHC):
 - Epithelial cells:
 - Cytokeratins, CEA and EMA positive
 - May be CD117 (c-kit) positive
 - Myoepithelial cells:
 - Cytokeratins, p63, p40, calponin, S100 protein, glial fibrillary acidic protein, actin and vimentin positive
 - CEA and EMA negative
 - Pleomorphic adenoma gene 1 (PLAG1) consistently positive in PAs (nuclear) in epithelial and myoepithelial cells
 - SOX10 positive (nuclear) in epithelial and myoepithelial cells
 - Low proliferation indicates by Ki67 (MIB1) staining typically less than 5%:
 - Although not definitively

- Absent to rare p53 reactivity
- Weak bcl-2 reactivity

NOTE: IHC staining characteristics of PAs variable from case to case and even within a given case and do not necessarily show consistent staining patterns reported in the literature

- Molecular biology:
 - 70% of PAs are karyotypically abnormal, including:
 - 8q12 rearrangements:
 - Translocations include t(3;8)(p21;q12) and t(5;8)(p13;q12)
 - Target gene, pleomorphic adenoma gene 1 (*PLAG1*), mapped to 8q12
 - 12q14-15 rearrangements:
 - Translocations include t(9;12)(p24;q14-15) or ins(9;12)(p24;q12q15)
 - Target gene is the high mobility group protein gene, high mobility group AT-hook 2 (*HMGA2*)

NOTE: To date, *PLAG1* and *HMGA2* not reported in any other salivary gland neoplasms (except carcinoma ex pleomorphic adenoma)

- Sporadic or clonal changes not 8q12 or 12q13-15 rearrangements
- Normal karyotype may be present.

Differential Diagnosis (Table 20-4)

- In general, diagnosis of pleomorphic adenoma does not present difficulties; however, in cellular tumors with a variety of growth patterns, particularly involving minor salivary glands (i.e., intraoral), pleomorphic adenomas may prove difficult to differentiate from other tumors including:
 - Monomorphic adenoma (MA):
 - Presence or absence of mesenchymal component differentiates PA from MA.
 - Identification of mesenchymal component in any given case can be problematic, but in such a situation decision is between two benign neoplasms so treatment and prognosis are similar.
 - Polymorphous low-grade adenocarcinoma (PLGA) of minor salivary gland origin:
 - Many overlapping findings with PAs so in limited sampling will be problematic in differentiating it from PA (see immediately below for use of p63/p40 immunostaining in the differential diagnosis)
 - Adenoid cystic carcinoma:
 - In contrast to PAs, adenoid cystic carcinomas reported to have:
 - Increased proliferation indices
 - Increase in p53 staining
 - Strong bcl-2 staining
 - Further IHC findings including pairing p63 and p40 reported to assist in differentiating PA from

polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC) include:

- PA: p63 + (68%; 21/31) and p40+ (42%; 13/31) immunophenotype
- Discordant p63+/p40– staining pattern seen only in overtly mesenchymal chondromyxoid stroma
- Cellular PA: concordant p63+/p40+ or p63–/p40– immunophenotypes
- PLGA: consistent p63+ (100%; 11/11) and p40– (100%; 11/11) immunophenotype
- AdCC: p63 + (90%; 91 of 101) and p40+ (89%; 90/101) immunophenotype
 - Single discordant p63+/p40– case was solid variant with high-grade features
- Proliferation indices (Ki67):
 - Low proliferation indices seen in association with PA, cellular PA, and PLGA typically less than 5%
 - Proliferative indices reported to be significantly higher in AdCC (up to approximately 20%)
 - Increased proliferation indices may not be present in all cases of AdCC and by itself does not unequivocally differentiate it from PA, cellular PA, and PLGA.

CAUTIONARY NOTE: Although a p63/p40 immunohistochemical panel can be a valuable tool for making distinction between PA, PLGA, and AdCC, it is not infallible and any given example may demonstrate divergence from the reported p63/p40 immunophenotype.

- Mucoepidermoid carcinoma (MEC):
 - In those examples of PA with squamous and mucinous cell metaplasia differentiation from MEC can be somewhat problematic:
 - Presence of keratinization and intercellular bridges associated with squamous metaplasia of PA contrasts to the epidermoid component of MEC typically lacking keratinization and intercellular bridges.
 - Metaplastic PAs do not harbor translocations t(11;19) and anticipated t(11;15) resulting in *CRTC1-MAML2* and *CRTC3-MAML2* fusion transcripts, respectively, and/or *MAML2* gene rearrangement found in association with MEC.
- Deep-seated dermal adnexal neoplasm
- Mesenchymal neoplasm:
 - Peripheral nerve sheath tumor
 - Smooth muscle neoplasms

Treatment and Prognosis

- Complete surgical excision is preferred treatment:
 - Parotid gland tumors usually require lobectomy with preservation of the facial nerve.

TABLE 20-4 Intraoral Minor Salivary Gland Neoplasms: Selective Differential Diagnosis

Tumor	Encapsulation	Growth Patterns	Cytomorphology	Stroma	IHC	Cytogenetic
PA	Absent but well circumscribed	Polymorphic including tubules, ribbons, sheets, cords, cysts, trabeculae	Dual cell population: ducts/glands and myoepithelial cells; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Chondromyxoid; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, p40, S100 protein, PLAG1 others; low proliferation indices	<i>PLAG1</i> <i>HMGA2</i>
CPA (E or M)	Absent but well circumscribed	Polymorphic including tubules, ribbons, sheets, cords, cysts, trabecular, fascicular, anastomosing cords	Dual cell population: ducts/glands and myoepithelial cells; for myoepithelial predominant tumors lesional cells include spindle-shaped and plasmacytoid cells but ducts/glands focally seen; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Scanty but identifiable chondromyxoid stroma; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, S100 protein, others; low proliferation indices	<i>PLAG1</i> <i>HMGA2</i>
PLGA	Absent and infiltrative	Polymorphic including tubular/ductules, cribriform, solid, linear single cell, "streaming" along periphery, papillary	Isomorphic cells with minimal pleomorphism; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Slate gray myxoid; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, S100 protein, others; p40 negative*; PLAG1 usually negative; low proliferation indices	None known although <i>PRKD2</i> rearrangement reported in a single case
AdCC tubular, cribriform	Absent and infiltrative	Polymorphic including cribriform, tubular/ductules, islands, cysts, nests, cords, solid	Basaloid cells with uniform, angulated, hyperchromatic nuclei, scanty cytoplasm; no necrosis or increased mitotic activity; intercellular hyaline material present	Myxoid-hyaline stroma	Positive for epithelial and myoepithelial markers: CK, p63, p40, S100 protein, others; PLAG1 negative; increase proliferation indices [†]	<i>MYB-NFIB</i>

*p40 not necessarily consistently negative in PLGA or positive in the other neoplasms.

[†]Increase proliferation indices may not be present in all cases of AdCC and by itself does not definitively differentiate it from PA, cellular PA and PLGA.

AdCC, Adenoid cystic carcinoma; CKs, cytokeratins; CPA, cellular pleomorphic adenoma; E, epithelial predominant; M, myoepithelial predominant; PA, pleomorphic adenoma; PLGA, polymorphous low-grade adenocarcinoma.

- Submandibular gland tumors usually necessitate complete removal.
- Minor salivary glands neoplasms require complete but conservative excision.
- Incomplete excision irrespective of site results in recurrent tumor:
- Increase risk of recurrence associated with:
 - Inadequate surgery:
 - Enucleation
 - Rupture or spillage during surgery
 - Chondromyxoid-predominant PAs:
 - Diffluent nature results in "spillage."
 - Variable capsular thickness coupled with tendency of tumor to invade capsule and/or bulge through capsule
 - Young age
- Recurrent tumors may be multifocal and in some cases may be widely distributed throughout the soft tissues of the neck, precluding surgical resection to control local disease:
 - Low-dose radiation may be used in this situation.
 - Presence of scar tissue in association with the recurrent tumor may present difficulties

relative to the facial nerve with adherence to the nerve.

- Preservation of the nerve with excision of the scar tissue and the entire parotid gland is recommended for recurrent tumor.
- Overall prognosis for PA is excellent with:
 - 5-year recurrence-free rate of 97%
 - 10-year recurrence-free rate of 94%
- Complications include malignant transformation (carcinoma ex pleomorphic adenoma) and the rare occurrence of so-called benign metastasizing pleomorphic adenoma.
- Surgical complications may include nerve damage and Frey syndrome (gustatory sweating).
- Features that may indicate a greater likelihood of malignant transformation include:
 - Occurrence in submandibular gland
 - Older patient age
 - Long-standing tumor
 - Larger tumor size
 - Prominent areas of acellular hyalinization
 - Increased mitotic activity including atypical mitoses
- Any salivary gland PA may show histologic features that raise concern for malignancy:
 - Neoplastic tissue within or extending through the fibrous capsule causes concern for malignant transformation; however, by itself capsular involvement in an otherwise unremarkable PA is acceptable and is not an indication of malignant transformation.
 - Rare cases of PA may show vascular permeation but by itself this feature is not indicative of malignancy.
 - Recurrent PA often have multiple foci of tumor within the normal salivary gland but these foci are usually discrete and circumscribed without cytologic atypia (they may show a prominent chondromyxoid stroma).
- Treatment for an atypical pleomorphic adenoma is similar to “conventional” pleomorphic adenoma albeit perhaps with more vigilant follow-up.

MONOMORPHIC ADENOMAS

Definition: Benign tumors of salivary glands characterized by a lack of the mesenchyme-like stromal component as seen in pleomorphic adenomas and composed exclusively of the epithelial component or less commonly, myoepithelial component, and arranged in a variety of morphologic patterns.

- Monomorphic adenomas encompass a whole group of neoplasms that are not pleomorphic adenomas.

WARTHIN TUMOR (WT)

(Figs. 20-16 through 20-22)

Definition: Benign salivary gland tumor characterized by its readily recognizable morphologic appearance composed of bilayered epithelium, including inner columnar oncocytic cells surrounded by smaller basoloid cells, and forming multiple cysts and papillary structures that are separate from a mature lymphocytic cell stroma.

Synonyms: Papillary cystadenoma lymphomatosum; adenolymphoma; cystadenolymphoma

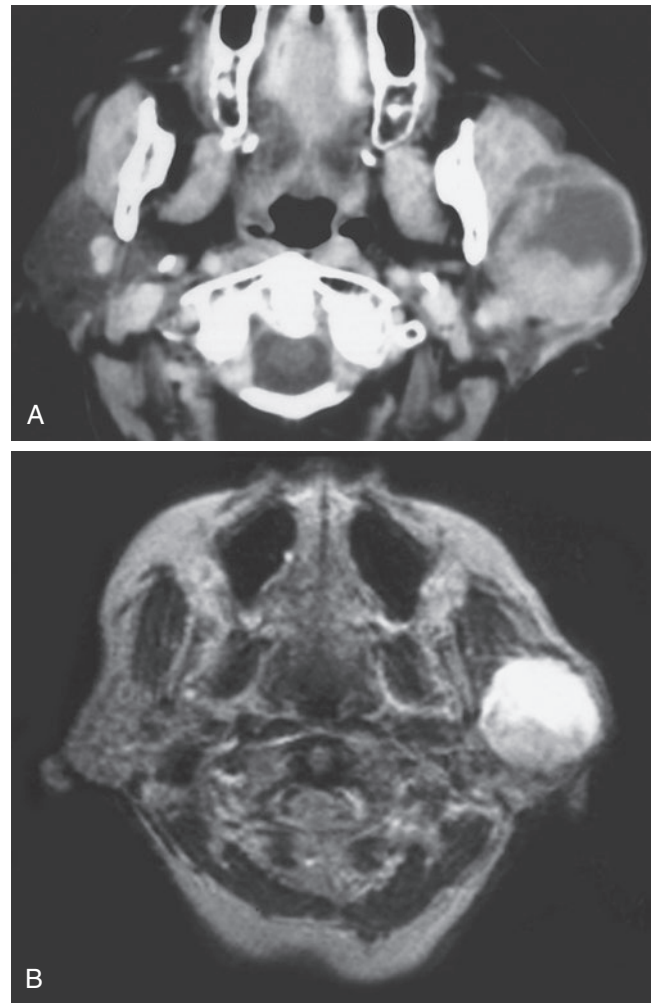


Fig. 20-16. Imaging features of Warthin tumor.

Axial contrast-enhanced CT scan (A) and T2-weighted (B) MR image show a partially cystic mass in the left parotid gland with a thick tumor nodule along the posterior wall. This patient had a Warthin tumor. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 40-157, p 2547.)

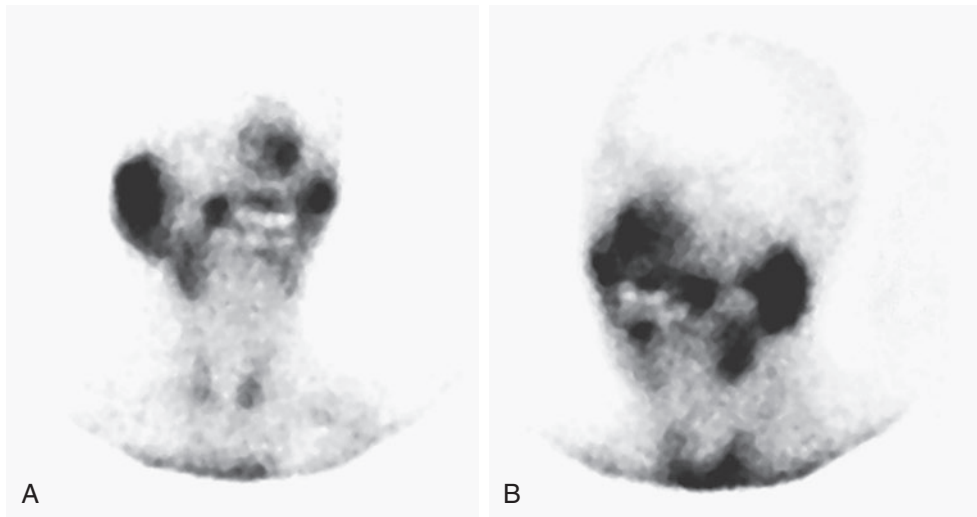


Fig. 20-17. Bilateral Warthin tumor.

Oblique frontal technetium sialograms show multiple masses with intense uptake in both parotid glands. This patient had bilateral Warthin tumors. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 40-152, p 2544.)



Fig. 20-18. Warthin tumor.

The resection specimen shows a solid and multicystic lesion; the solid areas have a nodular appearance.

Clinical

- Represents second most common benign salivary gland tumor (following pleomorphic adenoma) accounting for approximately 5% to 6% of all salivary gland tumors and up to 12% of benign parotid gland tumors
- More common in men than in women:
 - Recent evidence shows marked decline in incidence in men with increased prevalence in women.
 - These demographic changes have been linked to smoking habits with a decline in use by men and an increase of use in women.
 - Smoking has been considered as an established risk factor for the development of Warthin tumor.
- Occurs over a wide age range but is most common in the fifth through seventh decades of life; uncommon to occur in the first three decades of life
- Almost exclusively involves parotid gland, particularly in the superficial lobe along the inferior pole adjacent to the angle of the mandible; rare cases reported in submandibular gland, palate, lip, tonsil, larynx, and maxillary sinus
- Bilateral tumors can be seen in up to 10% of cases and multifocal tumors in up to 12% of cases:
 - Bilateral or multifocal tumors may occur synchronously or metachronously.
- Most common symptom is painless mass; rarely is pain an associated complaint.
- May occur synchronously or metachronously with other salivary gland tumors, including:
 - Pleomorphic adenoma (most common), monomorphous adenomas, oncocytoma, basal cell adenoma, acinic cell adenocarcinoma, ductal adenocarcinoma, and adenoid cystic carcinoma
- Radiology:
 - CT scan:
 - Well-defined area of increased density in the posteroinferior segment of the superficial lobe of the parotid

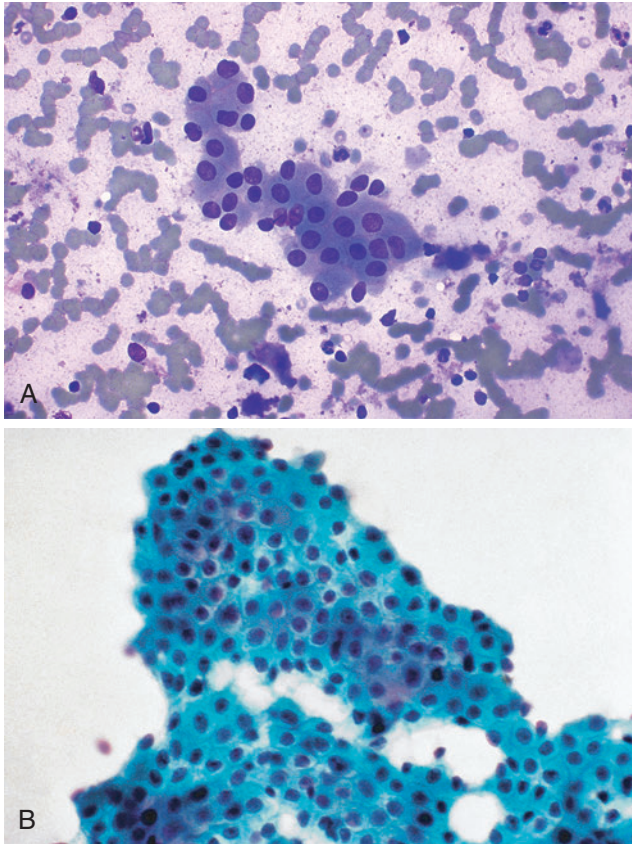


Fig. 20-19. Warthin tumor, fine-needle aspiration biopsy.

A. Cytologic features are characterized by the presence of oocytic-appearing epithelial cells and mature lymphocytes (Diff-Quik). **B.** Cohesive cluster of oocytic epithelial cells with honeycomb arrangement and scattered lymphocytes (Papanicolaou).

- Radionucleotide imaging:
 - Increased uptake of technetium-99m, which does not wash out following diagnostic administration; this finding plays an important role in diagnosis and is related to the presence of oncocytes and their increased mitochondrial content.
- Cause:
 - Strong link with cigarette smoking
 - Radiation exposure has been linked as a tumorigenic factor.
 - Role of Epstein-Barr virus (EBV) in the development of Warthin tumor is controversial:
 - Some studies document the presence of EBV in the cytoplasm of luminal cells of WT, whereas other studies do not identify EBV in WT.
 - No substantiation that EBV plays a role in development of WT.

- Pathogenesis
 - Thought to develop from neoplastic transformation of entrapped salivary duct epithelium within intra- and periparotid lymph nodes during embryologic development; in support of this theory includes:
 - Ontogenically, parotid gland is last of the salivary glands to be encapsulated, resulting in either incorporation/entrapment of lymphoid tissue within the parotid or incorporation/entrapment of parotid ducts and acini within the periparotid lymph node epithelium
 - Identification in some cases of subcapsular sinuses, a normal feature of lymph nodes and not a normal feature of non-lymph node tissues (i.e., salivary glands)
 - Occurrence in periparotid lymph nodes
 - Presence of B- and T-cell markers in the lymphoid component of Warthin tumors

Pathology

Gross

- Encapsulated, soft and fluctuant, round to oval mass with a smooth or lobulated surface composed of tan-brown tissue with multiple cystic spaces from which a mucoid or brown exudate may be expressed; within the cystic spaces papillary projections are seen
- Solid areas can be identified and are noted for a white nodular appearance representative of lymphoid follicles.
- Measures from 1 to 8 cm in diameter

Fine-Needle Aspiration Biopsy

- Combination of oocytic-appearing epithelial cells and mature lymphocytes
- Oocytic epithelial cells appear in cohesive clusters as well as individual cells and may take on a honeycomb arrangement; these cells are characterized by the presence of:
 - Abundant granular and eosinophilic-appearing cytoplasm
 - Uniform round nuclei often centrally located with identifiable nucleoli
 - Distinct cell borders
 - Absence of lymphocytes in the epithelial cluster
- Occasionally, squamous (metaplastic) cells may be identified.
- Background of aspirate may appear “dirty” with cellular debris and associated lymphoid cells:
 - Given cystic character of Warthin tumor, FNAB may yield thick, tan-brown fluid.
 - The fluid may suggest the presence of mucus.
 - In conjunction with epithelial clusters and lymphoid cells this overall appearance may engender a diagnosis of mucoepidermoid carcinoma.

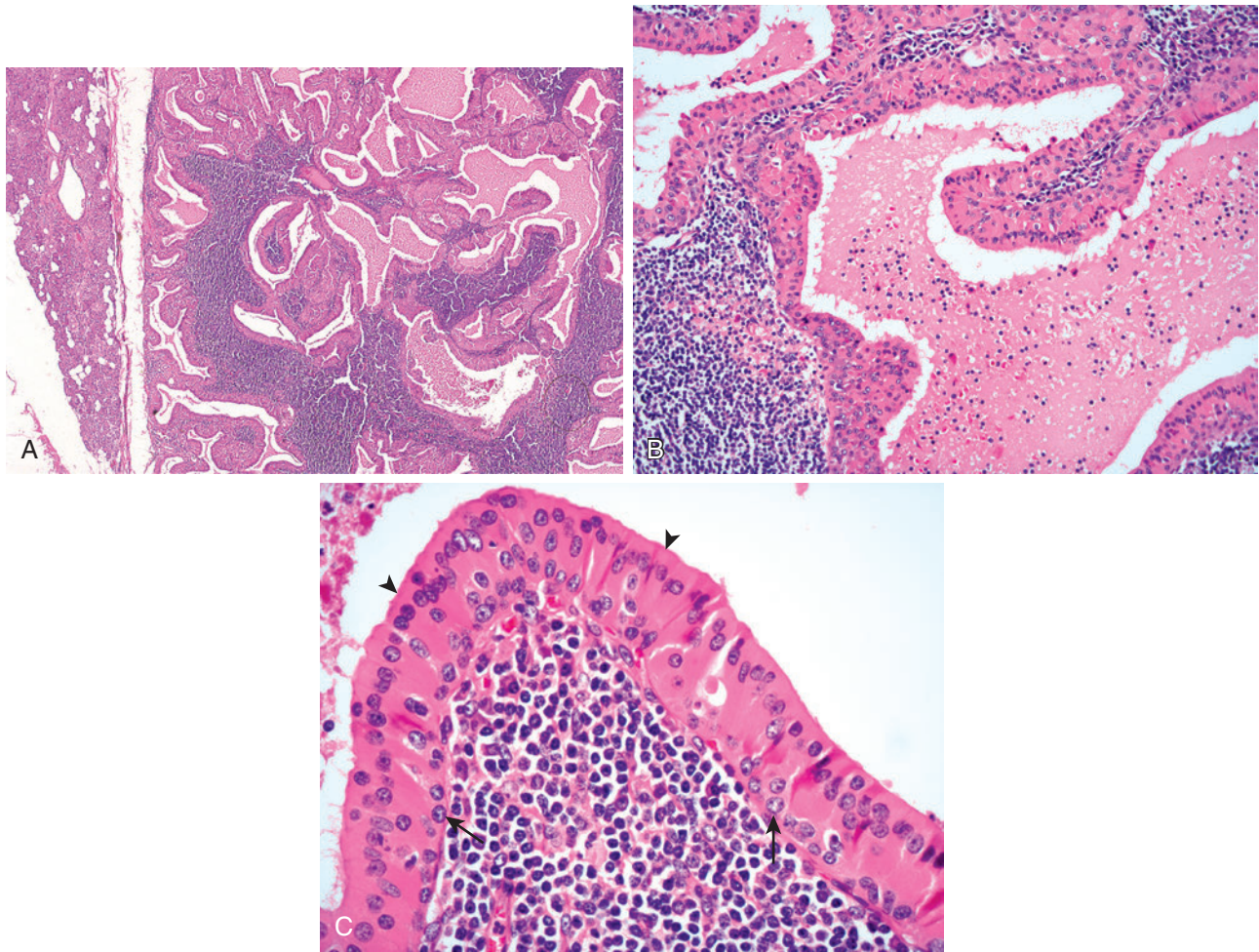


Fig. 20-20. Warthin tumor.

A, The tumor is encapsulated separated from the adjacent parotid parenchyma and characterized by cystic and papillary appearance and associated lymphoid proliferation. **B,** Slightly higher magnification shows the characterized features, including cyst formation and papillary architecture lined by oncocytic epithelial cells, which are demarcated from stromal lymphocytic cell infiltrate. **C,** At higher magnification the epithelial component lining the cystic spaces and papillary projections is composed of a double cell layer including inner (luminal) cells (*arrowheads*) composed of nonciliated, tall columnar cells with nuclei aligned toward the luminal aspect and prominent granular eosinophilic (oncocytic) cytoplasm and outer (basal) cells (*arrows*) composed of round to cuboidal cells with vesicular nuclei. The epithelial cells are sharply demarcated from the stromal lymphoid component.

Histology

- Papillary and cystic lesion composed of epithelial and lymphoid components
- Epithelial component lining the papillary projections composed of double layer of granular eosinophilic cells (referred to as oncocytic epithelia):
 - Inner or luminal cells:
 - Nonciliated, tall columnar cells with nuclei aligned toward the luminal aspect
 - Prominent oncocytic appearance of the cells is due to the presence of increased mitochondrial content.
 - Outer or basal cells:
 - Round, cuboidal, or polygonal cells with vesicular nuclei
- Lymphoid component predominantly composed of mature lymphocytes containing lymphoid follicles with germinal centers:
 - Epithelial component is sharply demarcated from the lymphoid component.
 - Other inflammatory cells that may be seen include plasma cells, histiocytes, mast cells, and occasional multinucleated (Langhans type) giant cells.

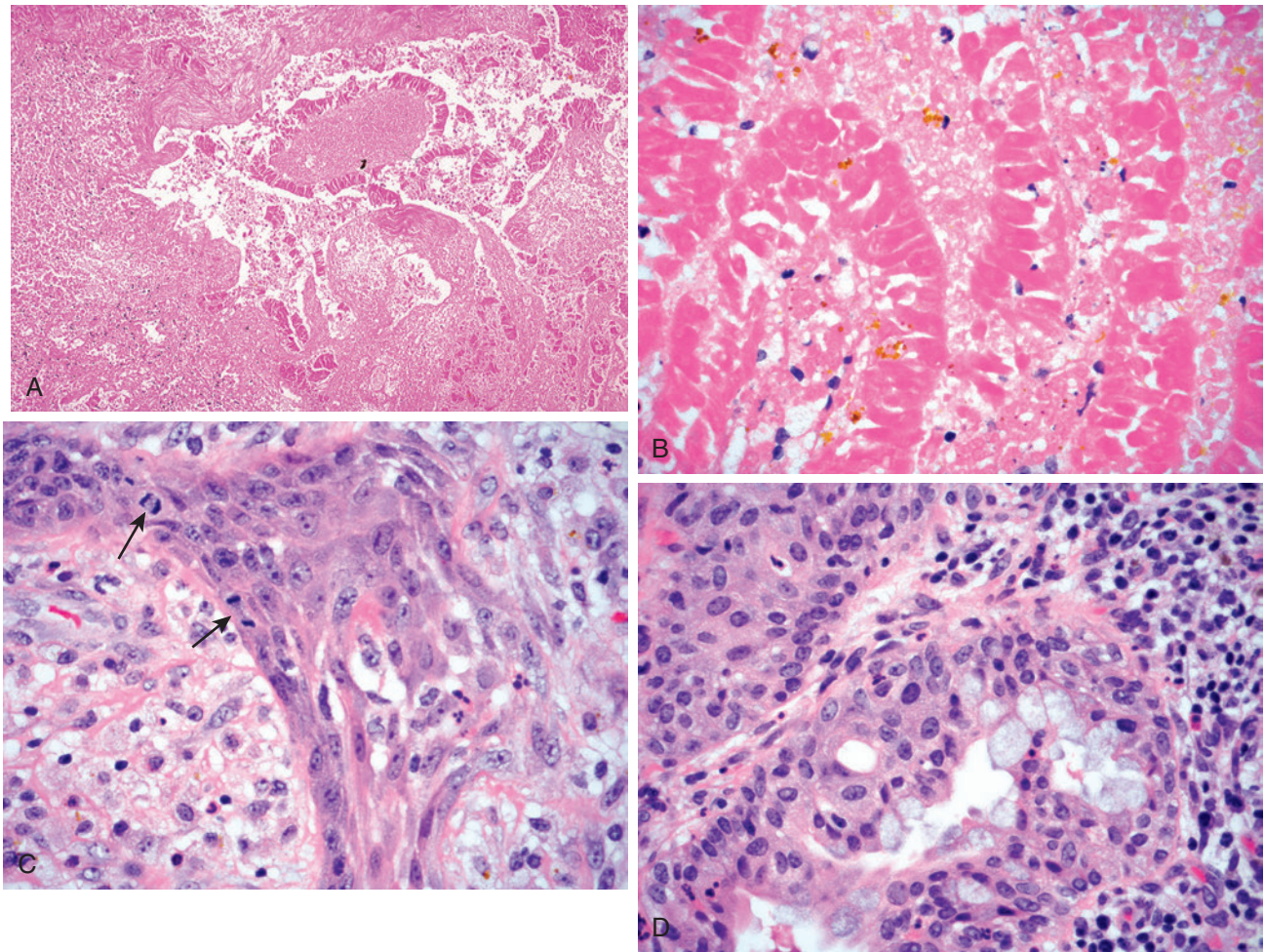


Fig. 20-21. Post needle aspiration changes in Warthin tumor.

Post-fine-needle aspiration biopsy findings in WT may include **(A)** tumor infarction retaining cystic and papillary architecture and **(B)** residual “ghost” outlines of columnar-appearing oncocytic epithelial cells; **C**, squamous metaplasia including mitotic figures (*arrows*); **D**, squamous and mucous cell metaplasia. The presence of squamous and mucous cell metaplasia may raise concern for a possible diagnosis of mucoepidermoid carcinoma but the changes are focal, occurring in the presence of other reactive and degenerative changes supporting a benign reactive (metaplastic) process rather than malignant transformation.

- Mucus-secreting (goblet) cells and sebaceous glands can be seen.
- Squamous metaplasia and focal necrosis may be seen in association with secondary inflammation.
- Lumens of the cysts may contain thick secretions, cholesterol crystals, cellular debris, or corpora amylacea-like laminated bodies.
- Post-fine-needle aspiration biopsy changes:
 - As is true of other tumors with prominent oncocytic cells, these tumors are subject to degenerative alterations either spontaneously or following needle aspiration (or biopsy), including:
 - Infarction and necrosis
 - Cytologic atypia
 - Metaplasia (squamous cell, mucous cell)
 - Granulation tissue
 - Acute and chronic inflammation
 - Fibrosis
 - Hemorrhage (recent and remote)
 - Pseudoinfiltrative pattern
- Metaplastic or infarcted variant of Warthin tumor:
 - Accounts for less than 10% of all Warthin tumors
 - Most likely develops following prior manipulation (e.g., fine-needle aspiration biopsy)
 - Extensive necrosis is present with ghost-like papillary structures remaining
 - Squamous and mucous cell metaplasia may be present.
 - Cytologic atypia may be prominent.
 - Increased mitotic figures but absence of atypical mitoses

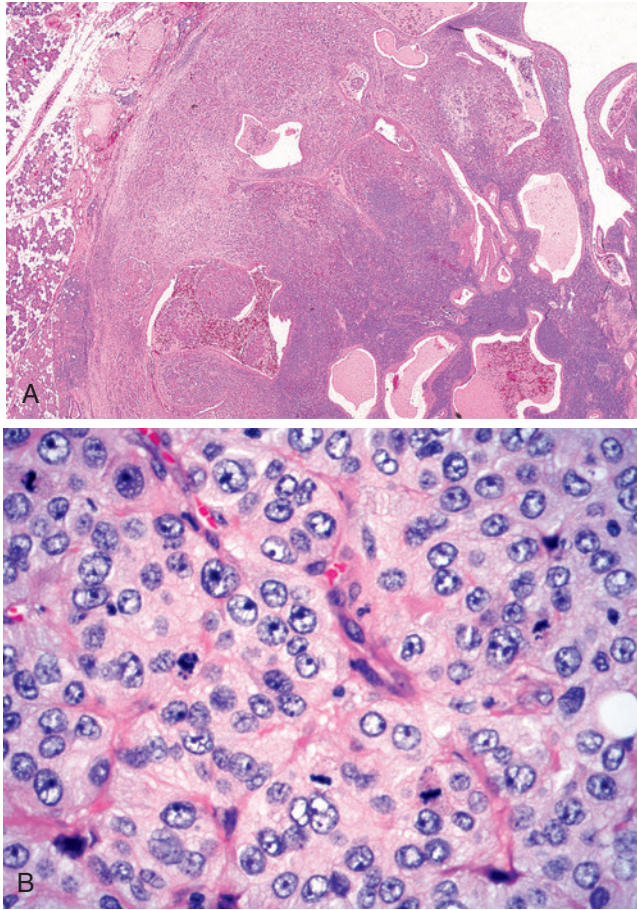


Fig. 20-22. Malignant transformation of WT.

Rare example of a Warthin tumor with malignant (carcinomatous) transformation. **A**, Warthin tumor (center and right) characterized by cystic and papillary growth with more solid areas seen along the peripheral aspect of the tumor on the left. **B**, At higher magnification the solid component is a malignant undifferentiated (large-cell) carcinoma characterized by marked nuclear pleomorphism, enlarged vesicular nuclei with prominent eosinophilic nucleoli and increased mitotic activity.

- Extensive fibrosis with dense collagen and reactive myofibroblasts are present along the periphery of the tumor.
- Mixed acute and chronic inflammation, including neutrophils, mature lymphocytes, histiocytes, and foamy macrophages may be present.
- Additional alterations may include lipogranulomas, cholesterol granulomas
- Residual noninfarcted foci of Warthin tumor may be present.
- Histochemistry:
 - Phosphotungstic acid-hematoxylin (PTAH) stains demonstrate mitochondria as seen by blue-black granules in the cytoplasm of both epithelial cell layers.

- Immunohistochemistry:
 - Epithelial cells: cytokeratins positive
 - Lymphoid cells: reactivity for B-cell (CD20) and T-cell (CD3) markers, as well as CD56, CD4 (helper cells), and CD8 (suppressor cells).
 - Sox10 negative
- Cytogenetics and molecular genetics:
 - Absence of *CRTC1-MAML2* fusion:
 - Documentation in literature of this gene fusion, commonly found in mucoepidermoid carcinoma (see below), in WT but not substantiated

Differential Diagnosis

- Histology of WT so characteristic that its diagnosis presents limited difficulty
- Cystadenoma
- Oncocytic papillary cystadenoma (for those cases identified in unusual sites)
- Salivary gland tumors/lesions with oncocytic cells either focally or a predominant component including:
 - Oncocytoma; oncocytosis; mucoepidermoid carcinoma, acinic cell carcinoma, others
- Mucoepidermoid carcinoma:
 - In those examples of WT with squamous and mucinous cell metaplasia differentiation from MEC can be somewhat problematic:
 - Metaplastic WTs do not harbor translocations t(11;19) and anticipated t(11;15) resulting in *CRTC1-MAML2* and *CRTC3-MAML2* fusion transcripts, respectively, and/or *MAML2* gene rearrangement found in association with MEC.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and should include an adequate margin of uninvolved tissue as well as preservation of facial nerve.
- Locally recurrent tumor may occur and is related to inadequate excision or to multicentrically occurring neoplasms.
- Transformation to malignant Warthin tumor is exceedingly rare with an incidence of less than 0.1% and may include the:
 - Epithelial component (carcinoma ex Warthin tumor):
 - Squamous cell carcinoma (most common), oncocytic carcinoma, adenocarcinoma not otherwise specified, undifferentiated carcinoma, mucoepidermoid carcinoma, Merkel cell carcinoma:
 - Metastasis to regional lymph nodes may occur.
 - Rarely, distant metastasis may occur.
 - Lymphoid component:
 - Malignant lymphoma, usually non-Hodgkin type

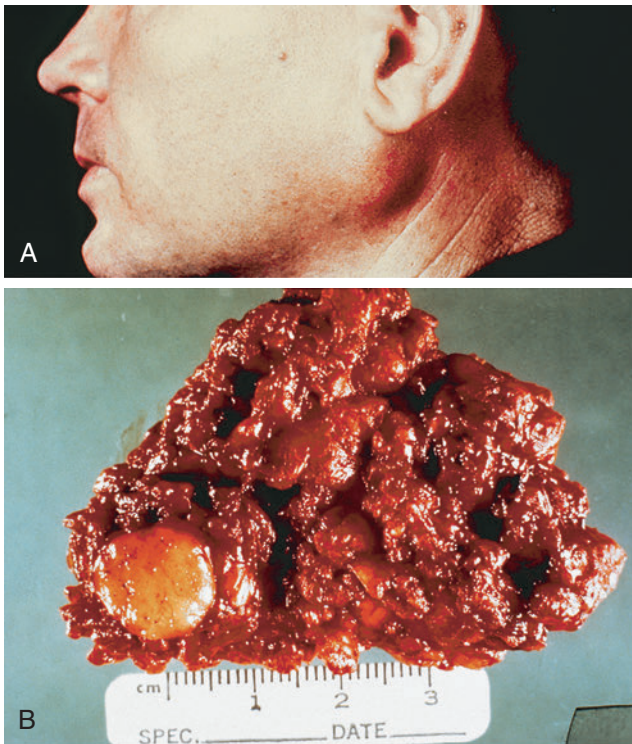


Fig. 20-23. Basal cell adenoma.

The clinical presentation and appearance of a monomorphic adenoma are similar to those of a pleomorphic adenoma and include **(A)** enlarged parotid mass at angle of mandible just inferior to the ear that was painless; **(B)** resected parotid lesion appearing circumscribed to encapsulated and solid (*lower left*).

BASAL CELL ADENOMA

(Figs. 20-23 through 20-27)

Definition: Benign neoplasm characterized by proliferation of basaloid-appearing cells and absence of mesenchyme-like stromal component seen in pleomorphic adenoma.

- Subdivided into four histologic subtypes based on morphologic pattern, including:
 - Solid
 - Trabecular
 - Tubular
 - Membranous types: only one associated with unique clinicopathologic findings (see below)

Synonym: Dermal analogue tumor is another name that has been used for the membranous type of basal cell adenoma.

Clinical

- Accounts for approximately 2% of all salivary gland tumors
- No gender predilection; occurs over a wide age range from the fourth to ninth decades of life

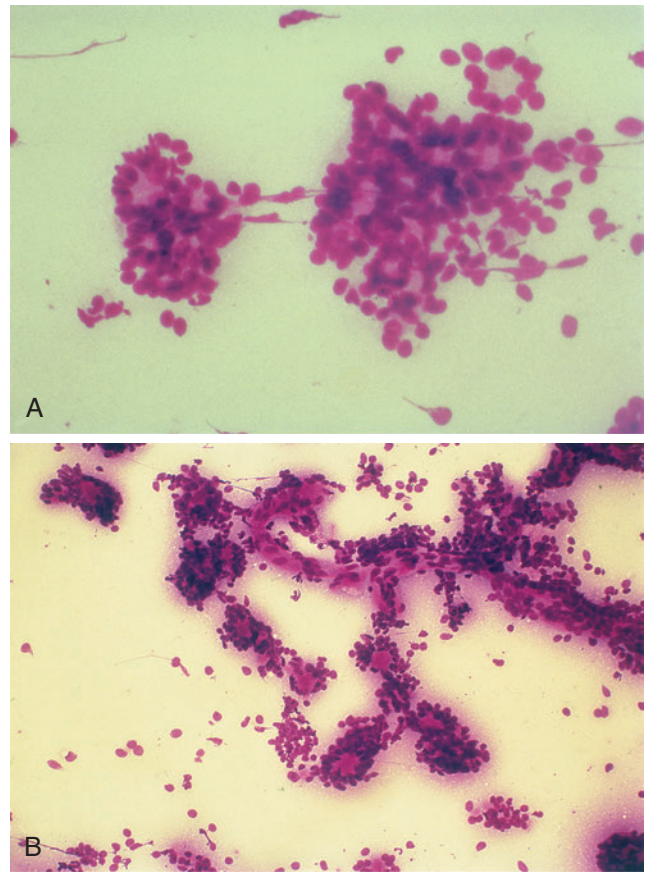


Fig. 20-24. Cytology of basal cell adenoma.

Basal cell adenoma of the parotid gland, fine-needle aspiration. **A**, Cellular aspirate including tubular structures composed of uniform basaloid cells with hyperchromatic round to oval nuclei, high nuclear-to-cytoplasmic ratio, and scanty cytoplasm. **B**, Basement membrane-like material is present, appearing as amorphous eosinophilic deposits in association with the cellular proliferation. The basement membrane material, especially seen in association with the membranous type of basal cell adenoma, may create diagnosis difficulties in differentiation with adenoid cystic carcinoma.

- Most common site of occurrence is major salivary glands particularly in the parotid gland (superficial lobe):
 - 70% occur in parotid gland
 - Up to 20% occur in the upper lip
 - Involvement of other minor salivary glands occurs but is uncommon
- Symptoms vary according to site but most frequently presents as a freely mobile, asymptomatic mass with a growth period ranging from months to several decades
 - Lip or palatal tumors may be associated with ulceration.

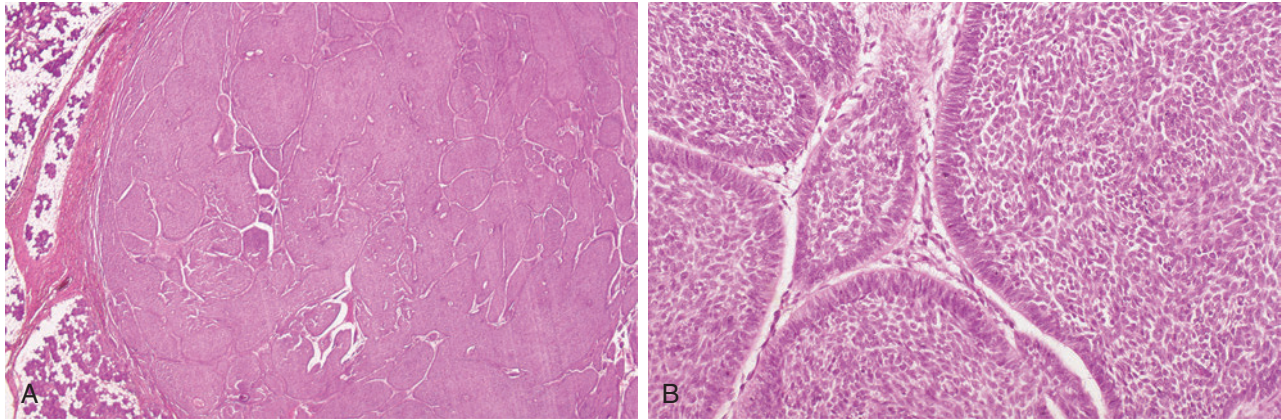


Fig. 20-25. Basal cell adenoma, solid type.

A, The tumor is encapsulated and sharply demarcated from the surrounding parotid gland parenchyma and appears solid and cellular. **B,** At higher magnification the cellular component includes basaloid cells with uniform, hyperchromatic, round to oval nuclei, indistinct cytoplasm and peripheral palisading; scant stroma is present from which the epithelial islands are sharply demarcated by an intact membrane.

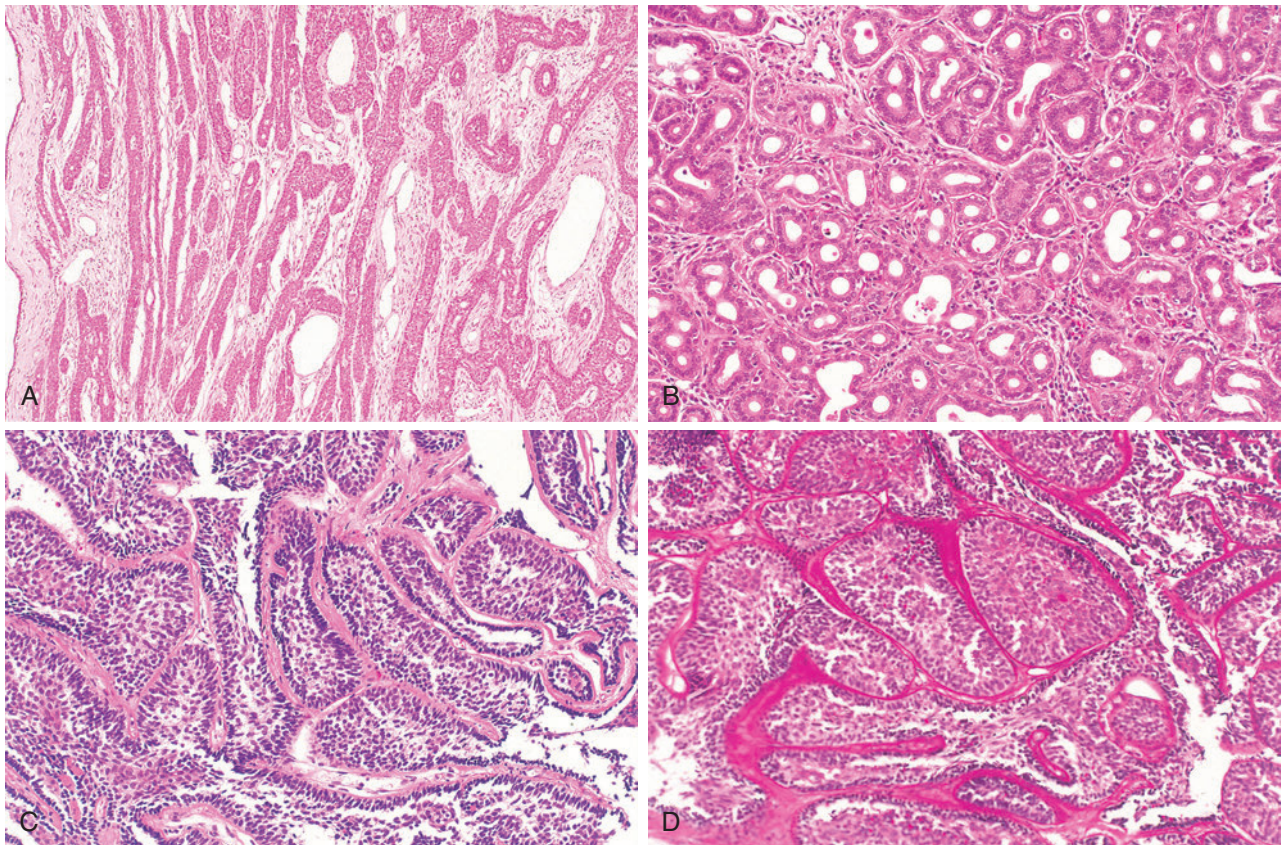


Fig. 20-26. Basal cell adenoma.

Growth patterns that can be seen in basal cell adenoma include **(A)** trabecular, characterized by the presence of elongated, ribbon-like pattern; **(B)** tubular, composed of multiple small duct-like structures; **(C)** membranous (so-called dermal analogue tumor), characterized by the presence of thick eosinophilic basement membrane-like material surrounding and separating the epithelial islands; **(D)** the eosinophilic basement membrane-like material is highlighted by periodic acid Schiff (PAS) staining.

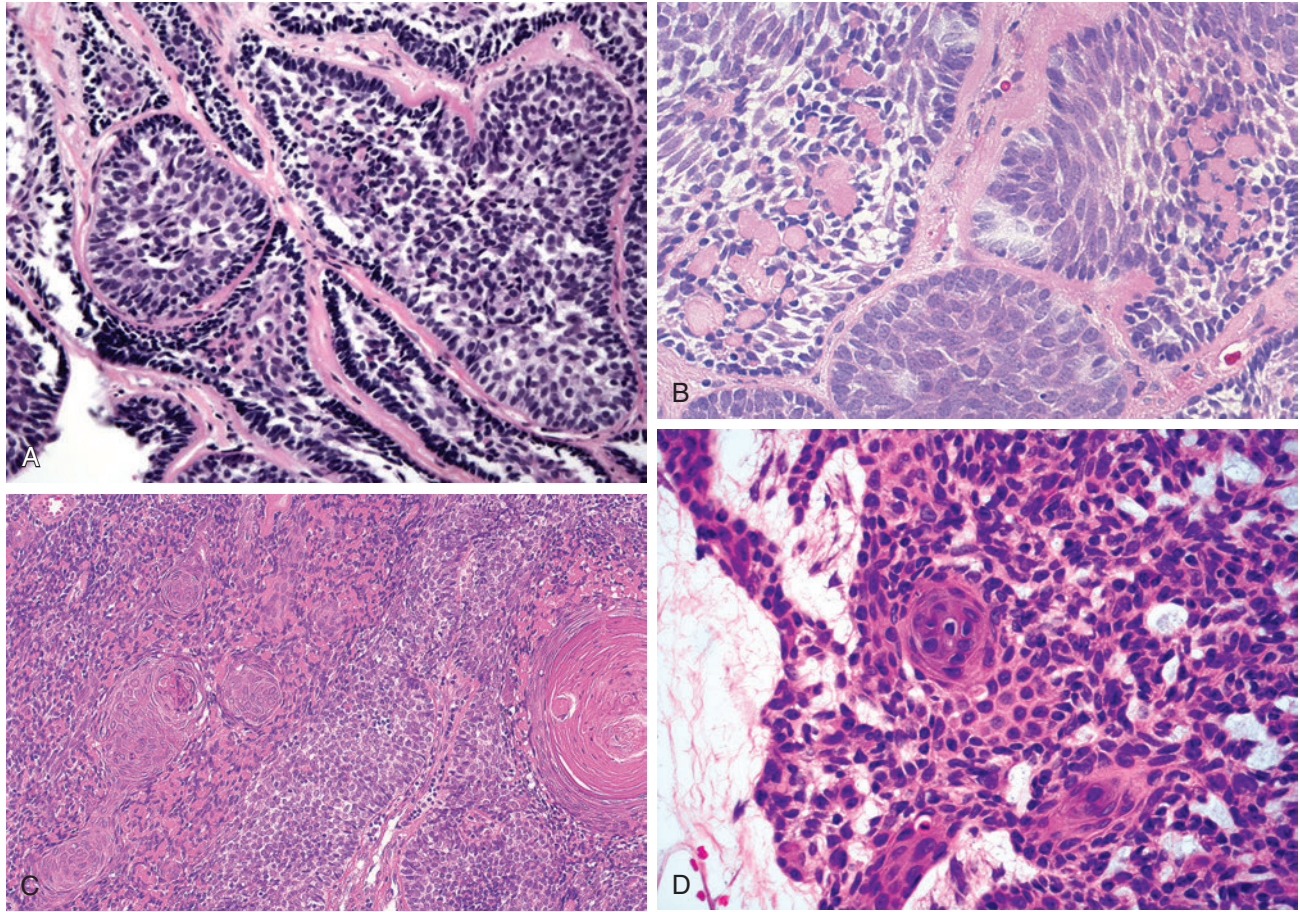


Fig. 20-27. Basal cell adenoma.

A, B, Admixture of more peripherally located smaller cells with hyperchromatic nuclei and indistinct cytoplasm and more centrally located larger polygonal-shaped cells with vesicular nuclei and more abundant cytoplasm. **B,** Reduplicated basement membrane-like material within and external to the tumor nests. **C,** Squamous eddies (“keratin pearls”) with whorled appearance as well as foci of abrupt keratinization. **D,** Higher magnification of squamous eddies, which may be very focally identified (or even absent) in basal cell adenomas. Although foci of squamous differentiation can be seen in a variety of salivary gland neoplasms, it is generally absent in adenoid cystic carcinoma, making its presence a potential useful finding in excluding adenoid cystic carcinoma.

- Cause unknown
- Membranous type of basal cell adenoma:
 - Also referred to as dermal analogue tumor
 - Distinctive variant:
 - 90% occurrence in men
 - Frequently multicentric/multifocal and unencapsulated
 - Familial cases associated with:
 - Dermal cylindroma (most common)
 - Trichoepithelioma
 - Eccrine spiradenoma
 - Milia
 - Germline mutation of cylindromatosis gene (*CYLD*), tumor suppressor gene located at chromosome 16q12-q13 implicated in familial cases

- Somatic mutations of gene found in sporadic cases

Pathology

Fine-Needle Aspiration Cytology (FNAB)

- FNAB diagnosis may be problematic given overlapping features with pleomorphic adenoma, adenoid cystic carcinoma, and basal cell adenocarcinoma.
- Cellular aspirate including sheets, trabeculae, and tubular structures composed of uniform cells with hyperchromatic round to oval nuclei and scanty cytoplasm:
 - Cells are small with high nuclear-to-cytoplasmic ratio.
- Stromal component tends to be scanty.

- Extracellular basement membrane-like material may be present, especially in the membranous type of basal cell adenoma, appearing as amorphous eosinophilic material, including spheric globules, findings that may raise the diagnosis of adenoid cystic carcinoma.
- Collagenous stroma interdigitates with adjacent tumor cells:
 - This feature has been suggested as useful in differentiating basal cell adenoma from adenoid cystic carcinoma.

Gross

- Major glands:
 - Encapsulated, tan-white to red-pink, solid mass measuring up to 4 cm in diameter
- Minor salivary glands:
 - Similar to those of major salivary glands except that, although well circumscribed, they often are unencapsulated
 - May be associated with surface ulceration

Histology

- Encapsulated neoplasm that may show variety of growth patterns allowing for subclassification into:
 - Solid
 - Trabecular
 - Tubular
 - Membranous types
 - Combination of patterns can be seen in any given case.
 - Cribriform growth may be present.
- Irrespective of growth composed of two cell types:
 - Small cells with hyperchromatic nuclei and indistinct cytoplasm usually (but not always) seen at the periphery of the cell nests:
 - These cells may be arranged in a palisading pattern around the periphery of tumor cords or islands in manner similar to cutaneous basal cell carcinomas but usually without retraction artifact from the surrounding stroma.
 - Larger polygonal-shaped cells with pale-staining nuclei, more abundant but indistinct cytoplasm usually more centrally located in cell nests
 - In addition, these cells may form squamous whorls or eddies.
- Myoepithelial rich stroma may be present in some cases characterized by:
 - Stromal spindle-shaped cells
 - S100 positive but p63 and actin negative
 - Presence of stromal myoepithelial cells assists in differentiation from adenoid cystic carcinoma, which lacks such stromal cells

- Solid basal cell adenoma:
 - Most common histologic variant
 - Solid masses of basal cells composed of small, isomorphic cells with uniform, hyperchromatic, round to oval nuclei and indistinct cytoplasm
 - Peripheral aspect of these nests are characterized by nuclear palisading
 - Scant stroma is present from which the epithelial islands are sharply demarcated by an intact membrane.
 - Squamous cells and squamous whorled eddies (“keratin pearls”) can be seen as a terminal expansion of the epithelial islands.
 - Mitoses are generally absent.
- Trabecular basal cell adenoma:
 - Basal cell proliferation growing in elongated, ribbon-like (trabecular) pattern with the cell islands separated by proliferation of a prominent vascular (capillary) stroma.
- Tubular basal cell adenoma:
 - Basal cell proliferation composed of multiple small duct-like structures lined by columnar-appearing cells with uniform, hyperchromatic, round to oval nuclei
 - Tubules are well-demarcated from the stroma by an intact membrane.
 - Stroma is noteworthy for the presence of prominent vascular pattern consisting of capillaries and venules.
 - Mitoses are generally absent.
- Tubular-trabecular adenoma:
 - Presence of tubular and trabecular patterns
 - Cellular stroma composed of myoepithelial cells
- Membranous basal cell adenoma:
 - In contrast to the other types, the membranous basal cell adenoma may be multilobular and frequently unencapsulated (present in only approximately 50% of cases).
 - Characterized by the presence of thick eosinophilic hyalin membranes surrounding and separating cell islands and creating a jigsaw puzzle appearance; this material represents reduplicated basal lamina and its appearance is similar to that of the dermal cylindroma, prompting the synonym of dermal analogue tumor.
 - Eosinophilic hyalin material can also be seen within the tumor islands and is diastase-resistant periodic acid-Schiff positive.
 - Tumor nests are often separated by normal salivary gland parenchyma, giving the appearance of multifocal growth.
 - Mitoses are generally absent.
 - Perineural invasion is not seen.

- Cribriform basal cell adenoma
 - Composed of jigsaw puzzle–like lobules with multiple cystic spaces (cribriform growth) in at least 30% of a given tumor
 - Merge with more characteristic foci of basal cell adenoma
 - Absence of invasive growth
 - May be mistaken for adenoid cystic carcinoma
- Immunohistochemistry:
 - Staining patterns support ductal and myoepithelial differentiation, including:
 - Epithelial cells:
 - Cytokeratin (low molecular weight), CEA, EMA positive
 - Myoepithelial cells:
 - p63, calponin, S100 protein, actin and vimentin positive
 - Nuclear β -catenin staining may be present.
 - bcl-2 and c-kit (CD117) reactivity may be present.
- Electron microscopy:
 - Ductal cells:
 - Microvilli, tight junctions, desmosomes
 - Myoepithelial cells:
 - Abundant microfilaments, desmosomes, junctional complexes, reduplicated basal lamina
- Cytogenetics and molecular genetics:
 - Presence of *CTNNB1* (β -catenin) gene mutation
 - Loss of heterozygosity at 16q12-13:
 - Similar finding as seen in dermal cylindroma
- Association of Basal Cell Adenoma and Intercalated Duct Lesions (IDL)
 - IDL found to coexist with salivary and nonsalivary neoplasms.
 - Among salivary tumors, basal cell adenoma appears to be associated most frequently with IDL.
 - Tubular variant most commonly associated with IDL:
 - Less frequently, nontubular variants of basal cell adenoma may harbor foci of IDL.
 - Unique hybrid lesion containing basal cell adenoma and IDL with transitional area described
 - These findings have led to the hypothesis that IDL could be a precursor of basal cell adenoma.

Differential Diagnosis

- Pleomorphic adenoma:
 - From a therapeutic and prognostic perspective there is no difference in therapy or outcome between pleomorphic and monomorphic adenomas.
- Adenoid cystic carcinoma (solid type in particular)
- Basal cell adenocarcinoma
- Ameloblastoma

Treatment and Prognosis

- Complete surgical excision is preferred treatment and is curative.
- Prognosis is excellent.
- Local recurrences are unusual but may be seen and relate to inadequate surgical excision.
- Membranous basal cell adenoma is most commonly associated with recurrence:
 - Recurrence rate of 25% reported
 - May be consequence of inadequate resection due to characteristic multifocal growth
- Malignant transformation of basal cell adenomas is exceedingly rare:
 - Gives rise to other “basal” cell carcinomas:
 - Basal cell adenocarcinoma or adenoid cystic carcinoma
 - Tumors composed of a basal cell adenoma and adenoid cystic carcinoma and have been termed *hybrid tumors*
 - Gives rise to non-“basal” cell carcinomas:
 - Adenocarcinoma, not otherwise specified
 - Salivary duct carcinoma
 - Malignant transformation highest in association with the membranous type of basal cell adenoma:
 - Reported as high as 28%

CANALICULAR ADENOMA

(Figs. 20-28 through 20-30)

Definition: Benign neoplasm with predilection for upper lip and distinct histomorphologic appearance, including branching and interconnecting cords of single and double cell thick rows of columnar epithelium and a loose stromal component.

NOTE: Originally considered to be a variant of basal cell adenoma but recognized as a distinct salivary gland neoplasm.

Clinical

- No gender predilection, although reports have varied as to male predominance and female predominance; occurs over a wide age range from the fourth to ninth decades of life but most common in seventh decade
- Almost exclusively limited to oral cavity, in particular, upper lip, which accounts for 70% to 90% of these tumors:
 - Other sites of occurrence include the buccal mucosa.
 - Infrequently, arises in parotid gland and palate
- Symptoms include gradually enlarging, nonpainful, and nonulcerated nodule/mass:
 - Symptoms may be present for long periods of time (decades).
 - Multifocal nodular growths may be seen.



Fig. 20-28. Canalicular adenoma.

Canalicular adenoma of the upper lip appearing as a subepithelial swelling.

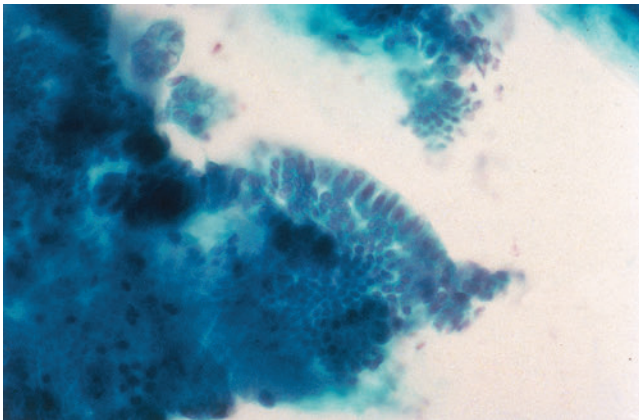


Fig. 20-29. Canalicular adenoma, fine-needle aspiration biopsy.

Cellular aspirate composed of uniform, basaloid-appearing (including a row of columnar-appearing) epithelial cells.

- Clinically, may be confused for a mucocele, sebaceous cyst, or lipoma

Pathology

Fine-Needle Aspiration

- Cellular aspirate that may include elongated, duct-like structures or tubules lined by columnar-appearing cells

Gross

- Circumscribed and/or encapsulated, tan-pink to yellow-brown, rubbery to firm nodule measuring from 0.5 to 3 cm in diameter
- Surface ulceration may be seen but is not common.
- Cystic spaces and a gelatinous mucoid material may be identified in transecting the tumor.

Histology

- Encapsulated or well-circumscribed nodules
- Not infrequently include multifocal nodules
 - Scattered nodules may be small (clinically undetectable) and may be unencapsulated.
- Consistent pattern of growth (unlike basal cell adenoma and other tumor types) and includes:
 - Double rows of columnar (basaloid) epithelial cells forming branching and interconnecting cords
 - Somewhat parallel arrangement of the rows of cells forms elongated duct-like structures resembling canals, hence the terminology of canalicular adenoma
 - Cystic dilatation of the canalicular structures may be present and may even be prominent in a given tumor.
 - Cords cut in cross-section may result in the presence of isolated tubules.
 - Alternating areas of tubules separated with closely apposed tubules is referred to as “beading,” creating an image of “beads on a string.”
- Elongated duct-like structures or tubules are lined by cuboidal to columnar cells with uniform, hyperchromatic, round to oval nuclei, variable amount of eosinophilic to amphophilic cytoplasm, and indistinct cell borders; mitoses are generally absent.
- Tubules are well demarcated from stroma by an intact membrane.
- Stroma is edematous and noteworthy for the relative absence of cellularity (scattered fibroblasts are present) and for the presence of prominent vascular pattern consisting of capillaries and venules, some with an eosinophilic cuff likely representing basal lamina and collagen.
- Histochemistry:
 - Diastase-sensitive, PAS-positive cytoplasmic granularity is seen.

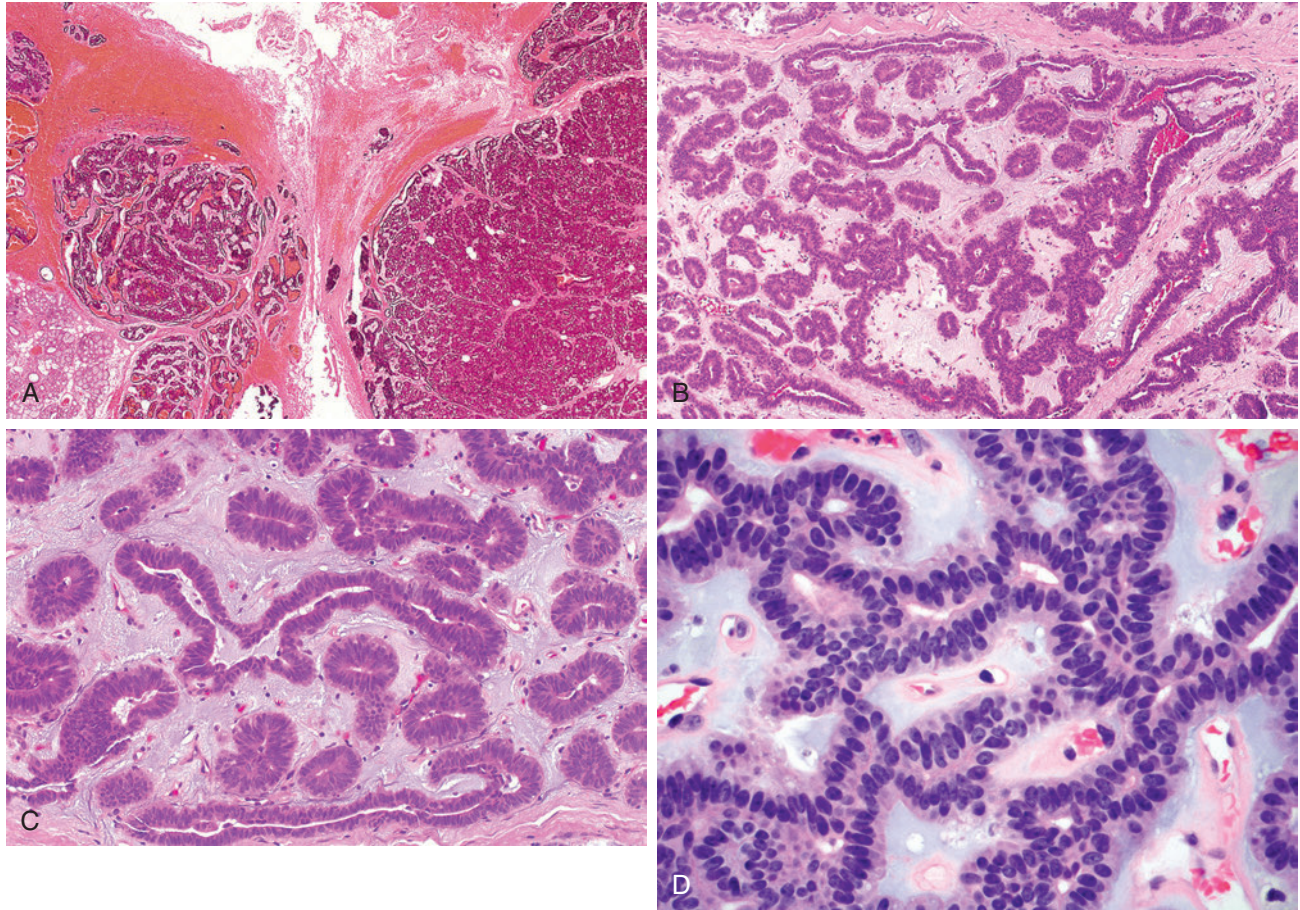


Fig. 20-30. Canalicular adenoma.

Histologically, canalicular adenoma is characterized by (A) multifocal, well-circumscribed nodules; the presence of multifocal tumor should not be misconstrued as invasion; (B and C) growth pattern that includes interconnecting cords and parallel arrangement of the rows of cells to form elongated duct-like structures resembling canals; and (D) cellular component that includes double rows of columnar (basaloid) epithelial cells with uniform, hyperchromatic, round to oval nuclei, variable amount of eosinophilic cytoplasm, and indistinct cell borders. The canals and tubules are well demarcated from the stroma.

- Immunohistochemistry:
 - Cytokeratins (pancytokeratin, CK7, CK13), S100 protein and vimentin positive
 - Variable EMA reactivity
 - Distinctive GFAP linear immunoreactive pattern among cells in proximity to connective tissue interface reported
 - Little to no myoepithelial differentiation: absence of p63, calponin, smooth muscle actin, smooth muscle myosin heavy chain
 - Recent evidence based on morphologic, immunohistochemical, and ultrastructural findings support a cell of origin demonstrating features of intercalated duct cells and striated duct luminal epithelial cells, including:
 - IHC:
 - Positive nuclear staining for S100 protein, absence of CEA and GFAP
- EM:
 - Abundant junctional complexes, including desmosomes and hemidesmosomes
 - Junctional complexes are associated with large aggregates of cytoplasmic intermediate filaments.
 - Focal microvillus projections forming intercellular lumina lined by abundant junctional complexes
 - Abundant cytoplasmic rough endoplasmic reticulum (rER) adjacent to the intercellular lumina and in apical aspects of the cells; rER is also seen near the basal lamina

Differential Diagnosis

- Basal cell adenoma
- Adenoid cystic carcinoma
- Pleomorphic adenoma

- Striated duct adenoma (SDA):
 - Has immunohistochemical similarities to canalicular adenoma, including positivity for S100 and essentially absent myoid markers and p63 staining
 - Histologic findings in SDA that are distinct from canalicular adenoma (CA) include:
 - SDA has relatively eosinophilic cytoplasm as compared with CA owing to abundance of mitochondria in the striated ductal cell cytoplasm.
 - Absence in SDA of characteristic “beading” pattern and prominent stroma present in canalicular adenoma
- Ameloblastoma
- Cutaneous basal cell carcinoma
- The multifocal growth of this neoplasm that is often devoid of a capsule can be mistaken for a carcinoma with invasion into the minor salivary gland parenchyma; awareness of this tendency reduces the likelihood of the erroneous diagnosis of carcinoma.

Treatment and Prognosis

- Conservative but complete surgical excision is the preferred treatment; enucleation is not recommended.
- Recurrence following complete excision is uncommon.

ONCOCYTOMA (Fig. 20-31)

Definition: Benign tumor of salivary gland origin exclusively composed of oncocytes, which are large epithelial cells with characteristic bright eosinophilic, granular

cytoplasm due to the presence of increased intracytoplasmic mitochondrial content and the absence of myoepithelial or basal cells.

Synonym: Oxyphilic adenoma

NOTE: Oncocytic cells in salivary glands occur in the following settings:

- Oncocytic metaplasia
- Oncocytosis (nodular or diffuse)
- Oncocytoma
- Oncocytic carcinoma
- Variety of other lesions/tumors that may have oncocytic cells (e.g., Warthin tumor, oncocytic variant of mucoepidermoid carcinoma, others)

Clinical

- Rare tumor composing less than 1% of all salivary gland neoplasms
- No gender predilection; most commonly occurs in the sixth to eighth decades of life
- Most frequently involves parotid gland but may also occur in the submandibular gland as well as in minor salivary glands throughout respiratory tract
- Symptoms vary according to the site of occurrence and most frequently present as a painless mass; other symptoms include nasal or airway obstruction.
- May occur synchronously with Warthin tumor
- Radiology:
 - Similar to Warthin tumors and as a result of the mitochondrial hyperplasia, radionuclide imaging demonstrates increased uptake of technetium-99m.
- Stimulus for induction of oncocytic change is unknown but generally considered age related, rarely seen under 50 years of age and nearly always present above 70 years old:

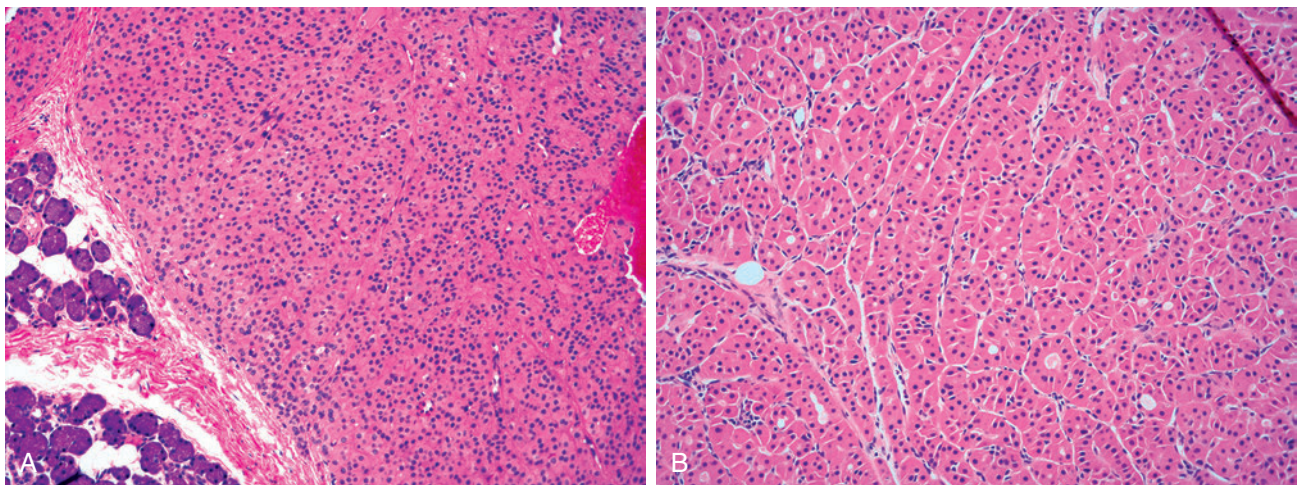
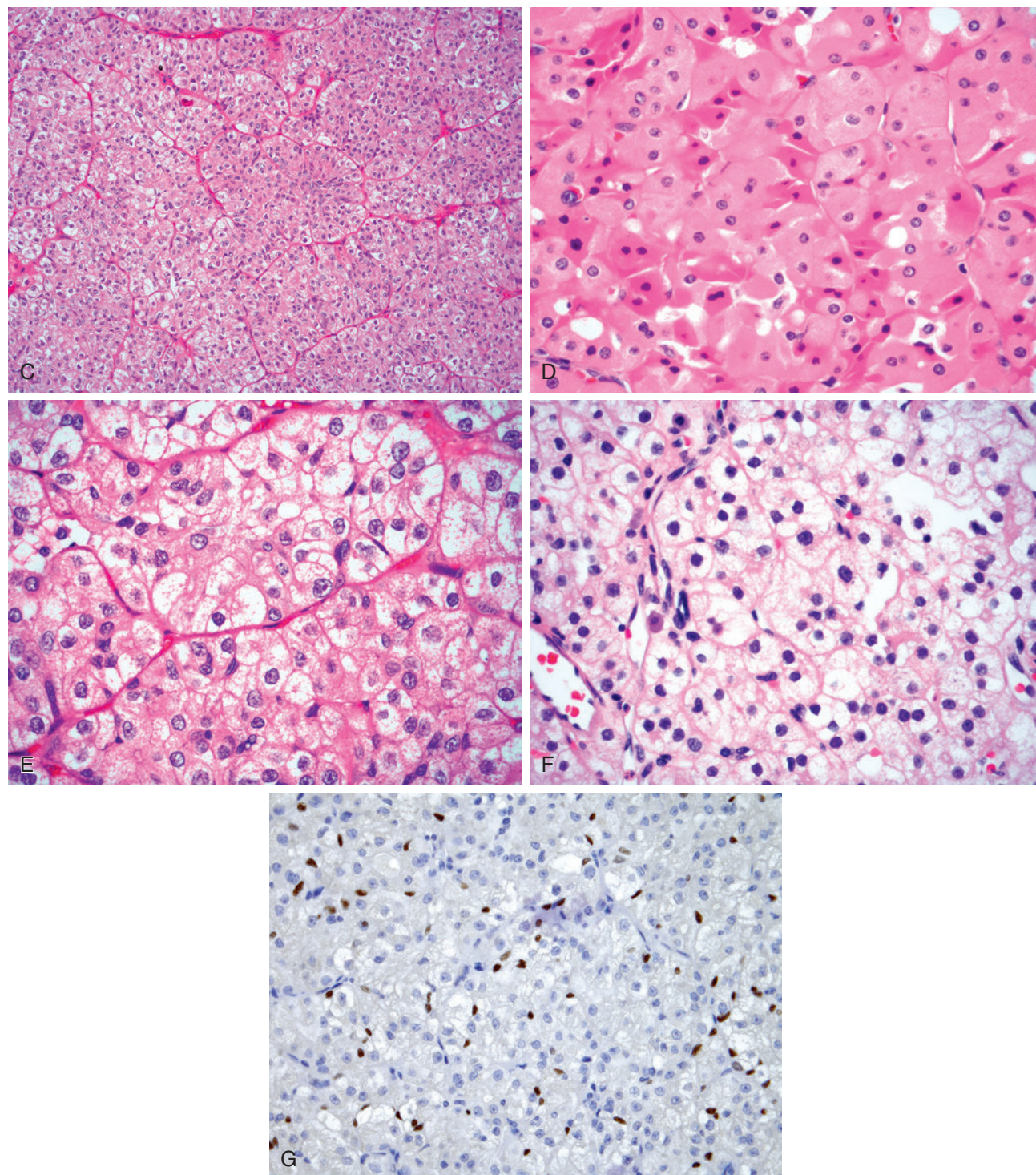


Fig. 20-31. Parotid gland oncocytoma.

A, Thinly encapsulated tumor showing solid growth exclusively composed of cells with prominent oncocytic cytoplasm; **B,** trabecular growth pattern;

**Fig. 20-31, cont'd**

C, organoid growth pattern. **D**, At high magnification the cells are polygonal, characterized by the presence of abundant granular eosinophilic cytoplasm with round to oval, vesicular-appearing nuclei with small nucleoli; overall the cells are rather bland appearing without cytomorphic features of malignancy. **E**, Many cases show an admixture of cells with oncocytic and clear-appearing cytoplasm. **F**, Clear cell variant oncocytoma in which there is partial or complete replacement of granular eosinophilic cytoplasm by cells with clear, nongranular-appearing cytoplasm; other than cytoplasmic appearance, the findings are similar to the more conventional type of oncocytoma. **G**, p63-positive cells interspersed along periphery and/or around oncocytic lesional cells represent basal cells that are not readily identifiable by light microscopy.

- Oncocytic cell changes are not limited to salivary glands but are seen in other organs, including:
 - Thyroid gland, parathyroid glands, adrenal glands, kidney, pancreas, others
- Pathogenesis remains unclear. Some theories support a neoplastic growth, whereas others suggest a hyperplastic/metaplastic phenomenon:
 - Oncocytic tumorigenesis secondary to acquired mitochondrial dysfunction has been proposed as a plausible mechanism, but few tumors harbor mtDNA alterations within the control region to support this theory.

Pathology

Fine-Needle Aspiration Biopsy

- Smears show oncocytic cells characterized by cells with granular-appearing cytoplasm.
- Oncocytic cells are arranged in sheets, papillary fragments, and as individual cells.
- Cytologic atypia is absent or focal/limited in extent.
- Typically, there is an absence of a lymphocytic cell component, but scattered lymphoid cells may be present:
 - Presence of lymphocytes in association with oncocytic cells may raise the diagnostic consideration of a Warthin tumor.

Gross

- Major salivary glands:
 - Well-circumscribed, encapsulated, lobulated, solid mass with an orange to rust-colored appearance, rarely measuring more than 5.0 cm in diameter
- Minor salivary glands:
 - Unencapsulated with less well-delineated borders with similar appearance and measurements as those of major glands; cystic change may be seen

Histology

- Encapsulated tumor with solid, trabecular, cord-like or organoid growth pattern separated by a thin fibroconnective tissue stroma; tumors involving minor salivary glands tend to be unencapsulated with an irregular growth pattern and may demonstrate invasion of adjacent structures
- Oncocytic cells represent a cytoplasmic alteration (metaplasia) of epithelial and/or myoepithelial cells with swelling of the cytoplasm by mitochondrial hyperplasia, giving the cell a characteristic granular eosinophilic appearance by light microscopy.
- Predominant/exclusive cell is enlarged and polyhedral in shape with a distinct cell membrane and characterized by an abundant granular eosinophilic cytoplasm and a centrally placed round, vesicular-appearing nucleus.

- Absence of residual normal salivary gland parenchyma such as serous acini or ductal epithelial structures within the oncocytic proliferation:
 - Contrasts to presence of such normal components in oncocytosis
- Cellular pleomorphism, mitoses, and necrosis are infrequently seen.
- Tyrosine-like crystals, appearing needle shaped or platelike, may be present in the tumor or in adjacent tissues:
 - Psammoma bodies may be identified.
- Other cell types that may be present include:
 - Sebaceous cells
 - Squamous cells
 - Mucous (goblet) cells (rare and must exclude oncocytic variant of mucoepidermoid carcinoma)
- Oncocytes are easily traumatized and prone to degenerative alterations either spontaneously or following manipulation (e.g., after fine-needle aspiration biopsy), including:
 - Infarction and necrosis
 - Cytologic atypia
 - Metaplasia (squamous cell)
 - Granulation tissue
 - Acute and chronic inflammation
 - Fibrosis
 - Hemorrhage (recent and remote)
- Clear cell oncocytoma:
 - Histologic variant of the “classic” oncocytoma composed of clear cells:
 - Partial or complete replacement of granular eosinophilic cytoplasm by cells with clear, nongranular-appearing cytoplasm
 - Transition areas of typical oncocytes to clear cells may be present.
 - Other than cytoplasmic appearance, histology and histochemical staining are similar to the more conventional type of oncocytoma.
 - Clear cytoplasm is due in part to fixation and tissue processing artifact, and to accumulation of glycogen within the cytoplasm, which displaces the mitochondria to the periphery of the cells.
 - Metastatic renal cell carcinoma must be ruled out.
- Histochemistry:
 - Phosphotungstic acid-hematoxylin (PTAH) stains demonstrate mitochondria as seen by blue-black granules in the cytoplasm; intracytoplasmic glycogen is demonstrated by diastase-sensitive, PAS-positive granules.
- Immunohistochemistry:
 - Cytokeratin, epithelial membrane antigen positive
 - S100 protein, glial fibrillary acidic protein, actin, thyroglobulin, TTF-1, CD10, renal cell marker, and Sox10 negative

- p63 and high-molecular-weight cytokeratin (CK14) positive in cells interspersed along periphery and/or around oncocytic lesional cells:
 - Represent basal or myoepithelial cells
- Low proliferation indices by Ki67 staining
- Electron microscopy:
 - Ultrastructural characteristic that defines the oncoocyte is the presence of mitochondria within the cell cytoplasm almost to the exclusion of other cell organelles
 - Other organelles can be seen as well as basement membrane and desmosomes.

Differential Diagnosis

- Oncocytic metaplasia:
 - Transformation of ductal and acinar epithelium to oncoocytes
 - Metaplastic process is an aging phenomenon and as such oncocytic metaplasia is generally not seen in patients less than 50 years of age from which time the percentage of the population with oncocytic metaplasia increases
 - In contrast to oncocytoma, oncocytic metaplasia represents non-mass-forming focal or limited changes in one or more areas within the salivary gland.
 - May be seen in tumor cells of nearly all salivary gland tumors, including most commonly in pleomorphic adenoma and mucoepidermoid carcinoma
- Oncocytosis (also referred to as oncocytic [adenomatous] hyperplasia):
 - Proliferation of oncocytic cells within the salivary gland
 - Typically appear as nodular foci referred to as nodular oncocytic hyperplasia or nodular oncocytosis
 - May represent a diffuse alteration in the affected salivary gland referred to as diffuse oncocytosis
 - In either nodular or diffuse form may present as a clinically detectable mass lesion, presenting difficulties in differentiation from oncocytoma; the differentiation of oncocytosis from oncocytoma may not be possible due to overlapping histologic features and this differentiation may be more of an academic than practical issue because treatment and prognosis are essentially similar; however, features seen in oncocytosis that may assist in differentiating it from oncocytoma include:
 - Multiple separate nodules (two or more)
 - Unencapsulation
 - Presence within the oncocytic nodules of residual nononcocytic salivary gland parenchyma, including ductular epithelium and serous acinar cells

- Warthin tumor
- Papillary oncocytic cystadenoma
- Pleomorphic adenoma
- A number of usual salivary gland carcinomas may have oncocytic cells as either a part of the tumor or as the predominant cell type; these tumors are included in the differential diagnosis of oncocytoma, including:
 - Oncocytic carcinoma
 - Mucoepidermoid carcinoma
 - Acinic cell adenocarcinoma
 - Adenoid cystic carcinoma
- Clear cell carcinoma
- Metastatic renal cell carcinoma and thyroid carcinoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
- Radiotherapy is not indicated as oncoocytes are radioresistant.
- Prognosis is excellent following removal.
- Locally recurrent tumors are uncommon.
- Transformation to an oncocytic carcinoma is rare.

MYOEPITHELIOMA

(Figs. 20-32 through 20-36)

Definition: Benign salivary gland tumor predominantly or exclusively composed of cells with myoepithelial differentiation, including spindle cells, plasmacytoid cells, epithelioid cells, or clear cells, but lacking ductal differentiation or chondroid/myxochondroid stroma. Sometimes may have abundant acellular mucoid or hyalinized stroma.

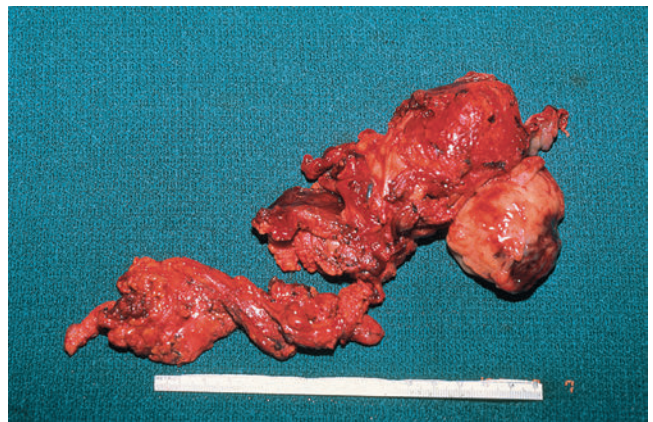


Fig. 20-32. Myoepithelioma.

Parotid gland myoepithelioma appearing as a well-demarcated, smooth, and bosselated solid lesion with a tan-yellow appearance (*right*).

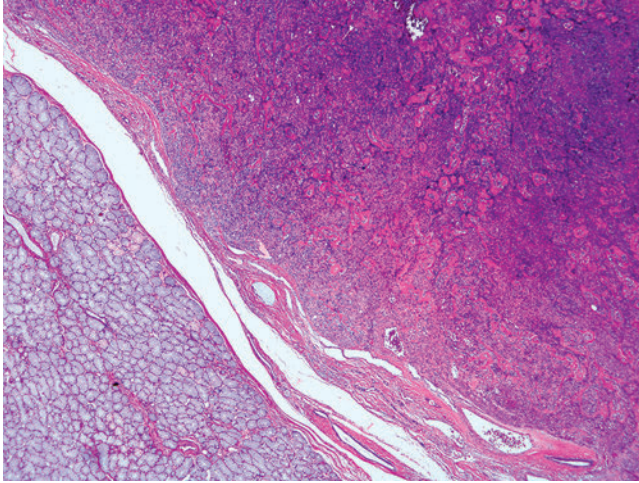


Fig. 20-33. Myoepithelioma of the palate.

The tumor is circumscribed separate from adjacent minor salivary glands and composed of a monomorphic cellular proliferation lacking ductal differentiation.

Synonyms: Myoepithelial adenoma; benign myoepithelial tumor

Clinical

- Accounts for approximately 2% of all salivary gland neoplasms
- No gender predilection; occurs over a wide age range but is most commonly seen in the third to sixth decades of life
- Although all salivary gland sites may be affected, the most common site of involvement is the parotid gland.
 - Second most common site is the palate (hard and soft palate)
 - Other sites may include the submandibular gland and oral minor salivary glands (e.g., retromolar region, upper lip).
- Most commonly present as a slow-growing, painless mass

Pathology

Fine-Needle Aspiration Biopsy

- Smears show bundles of uniform-appearing spindle-shaped, epithelioid/plasmacytoid, and stellate cells in sheets and dissociated forms:
 - Nuclear atypia is absent or limited in extent.
 - Occasionally, nuclear grooves/intranuclear inclusions may be identified.
 - Glandular/tubular structures not identified
 - By May-Grünwald-Giemsa staining most of the cells have a reddish cytoplasm.
 - Red to purple, myxoid matrix appearing as scanty fibrillar substance and as globules surrounded by tumor cells may be present and may suggest a diagnosis of adenoid cystic carcinoma.

Gross

- Well-demarcated, smooth, and bosselated solid lesion with a tan-white to tan-yellow appearance measuring up to 5 cm in diameter

Histology

- Encapsulated cellular neoplasm composed of spindle-shaped, plasmacytoid (hyaline) cells, epithelioid or clear cells:
 - Capsule varies in thickness but often is thin.
 - Tumors originating in minor salivary glands are circumscribed but not encapsulated.
- Growth patterns may include:
 - Fascicular
 - Solid
 - Trabecular
 - Reticular:
 - Uncommon pattern characterized by interconnecting cords with associated loose vascularized stroma (reticulated)
- Majority of myoepitheliomas are of spindle cell type:
 - Spindle-shaped cells have uniform, centrally located nuclei with dispersed nuclear chromatin and eosinophilic granular to fibrillar-appearing cytoplasm
 - Growth patterns include fascicular or swirling.
- Other cell types may include:
 - Plasmacytoid (hyaline) cells:
 - Polygonal with round to oval pyknotic-appearing nuclei, which may be eccentrically located as a result of the accumulation of eosinophilic hyaline material in the cytoplasm
 - A paranuclear clear zone (hof) and methyl green pyronine staining are not present.
 - Growth patterns include islands, sheets, cords, or isolated cells
 - Tumors composed predominantly of plasmacytoid myoepithelial cells occur in the palate.
 - A mucinous stroma may be seen in the plasmacytoid cell type.
 - Epithelioid cells:
 - Large polygonal cells with central nuclei and eosinophilic cytoplasm
 - Growth patterns include reticular, trabecular solid
 - Hyalinized stroma may be present and in conjunction with the tumor cells showing narrow interconnecting cords (so-called reticular pattern); confusion with the tubulotrabecular type of basal cell adenoma may arise.
 - Clear cells:
 - Abundant clear cytoplasm rich in glycogen (diastase-sensitive, PAS-positive)

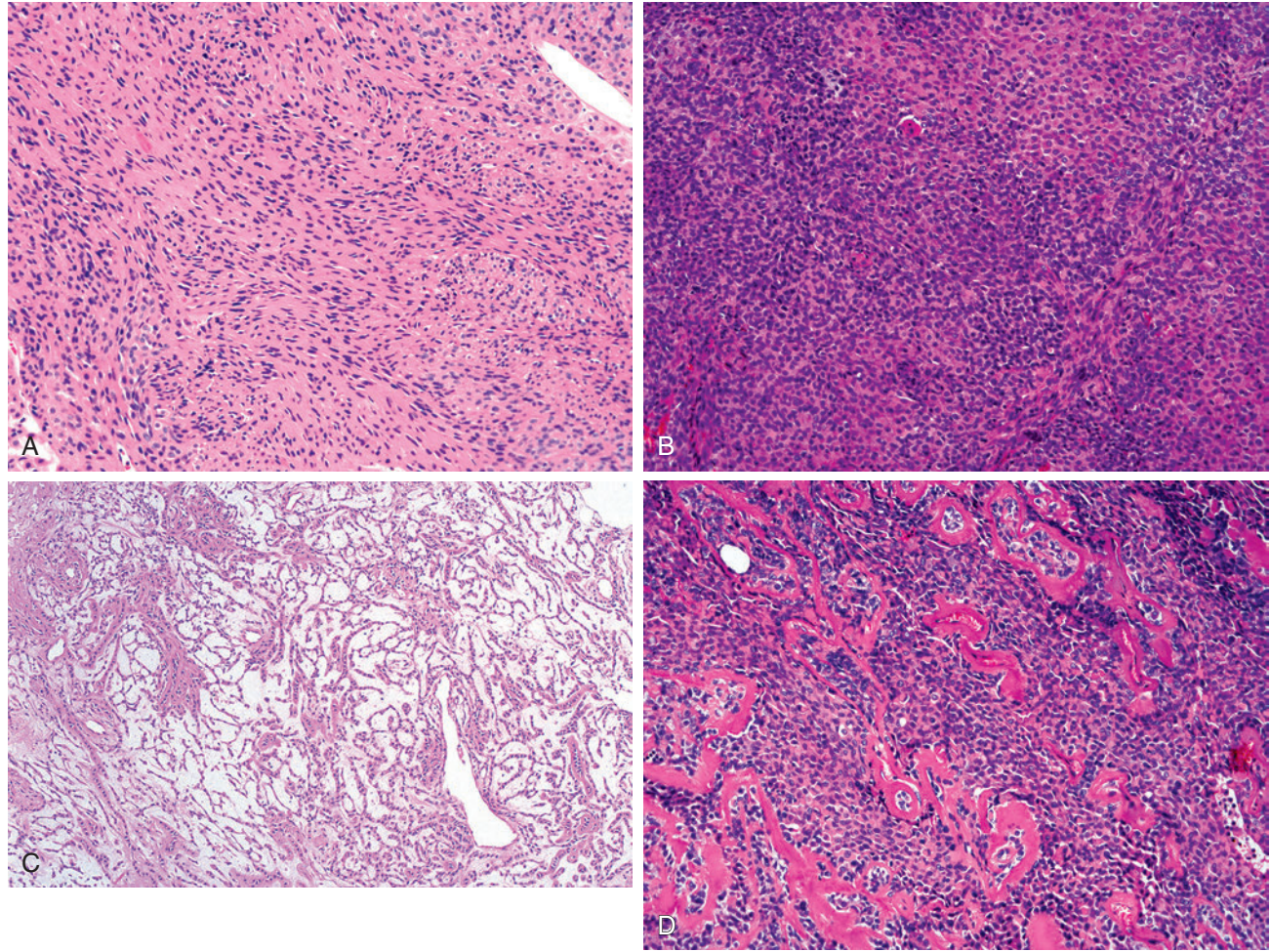


Fig. 20-34. Myoepithelioma.

A variety of growth patterns can be seen in myoepitheliomas including (A) fascicular to storiform; (B) solid; (C) reticular characterized by interconnecting cords with associated loose vascularized stroma; (D) trabecular with stromal and perivascular hyalinization.

- Oncocytic cells:
 - Characterized by presence of abundant granular eosinophilic-appearing cytoplasm
- Mucinous cells referred to as mucinous variant of myoepithelioma:
 - Characterized by cells with abundant eosinophilic to foamy-appearing grayish-blue cytoplasm
 - Contain abundant intracellular mucin material
- For all cell types, mild to moderate cellular pleomorphism may be seen but increased mitotic activity and necrosis are uncommon.
- Stroma may be hyalinized and/or appear myxomatous.
 - Tyrosine-like crystals may be present.
- Immunohistochemistry:
 - Cytokeratins (pancytokeratin, CK14), EMA, p63, calponin, S100 protein, smooth muscle actin, smooth muscle myosin heavy chain, glial fibrillary acidic protein (GFAP), vimentin, EMA, and muscle-specific actin variably positive
 - Desmin, thyroglobulin, TTF-1, CD10, and renal cell carcinoma marker negative
- Electron microscopy:
 - Epithelial features in the form of desmosome, tight junction
 - Myoid features in the form of intracytoplasmic myofilaments with focal densities, pinocytotic vesicles
- Molecular biology:
 - Typically lacks *PLAG1* rearrangement:
 - At least one study reported *PLAG1* immunohistochemical staining in 8 myoepitheliomas
 - Lacks *EWSR1-POU5F1* or *EWSR1-PBX1* gene fusion seen in soft tissue myoepithelial tumors

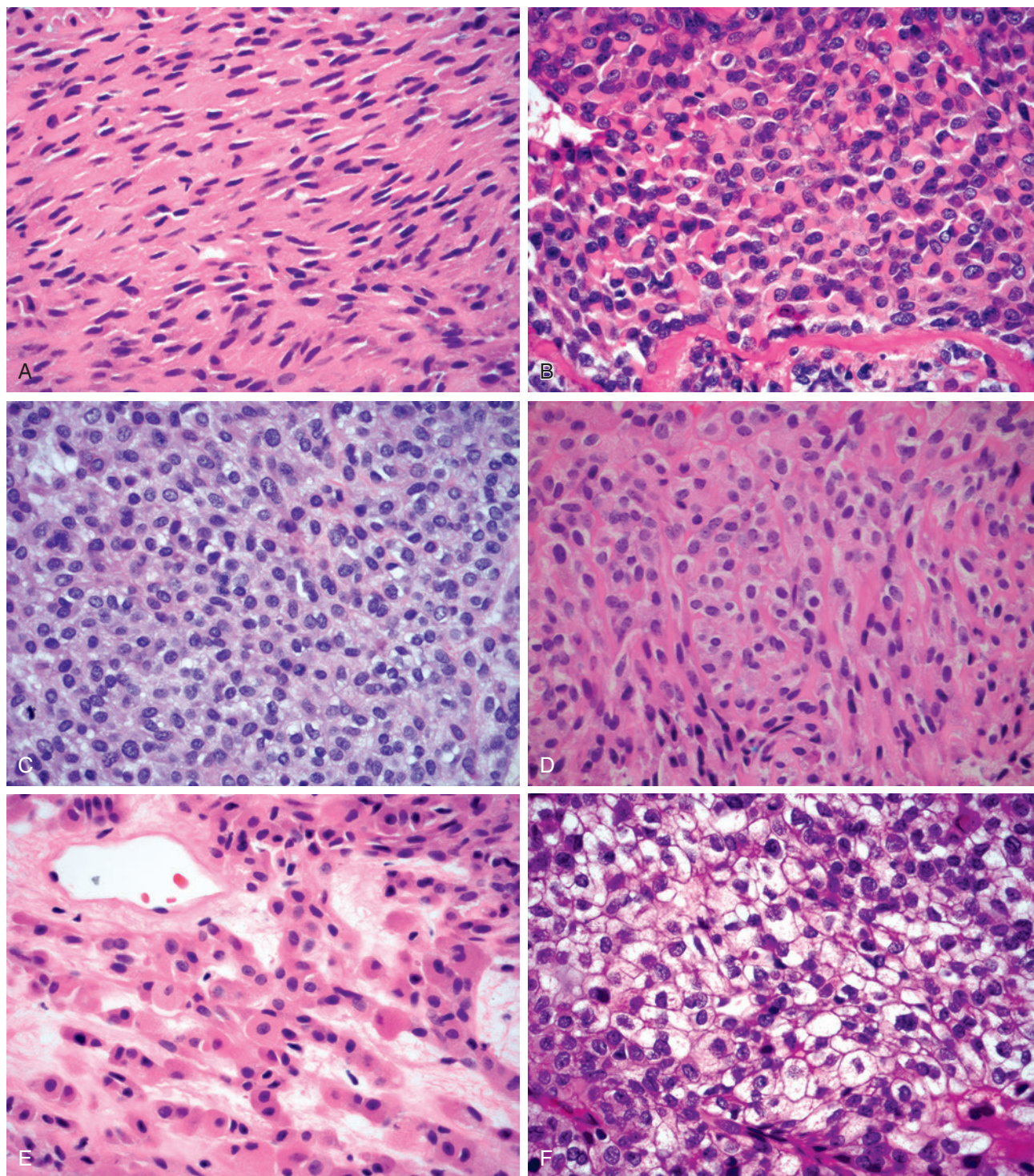


Fig. 20-35. Myoepithelioma.

A variety of cell types can be seen in myoepitheliomas including (A) spindle-shaped (most common); (B) plasmacytoid; (C) epithelioid; (D) spindle-shaped and epithelioid; (E) oncocytic; and (F) clear.

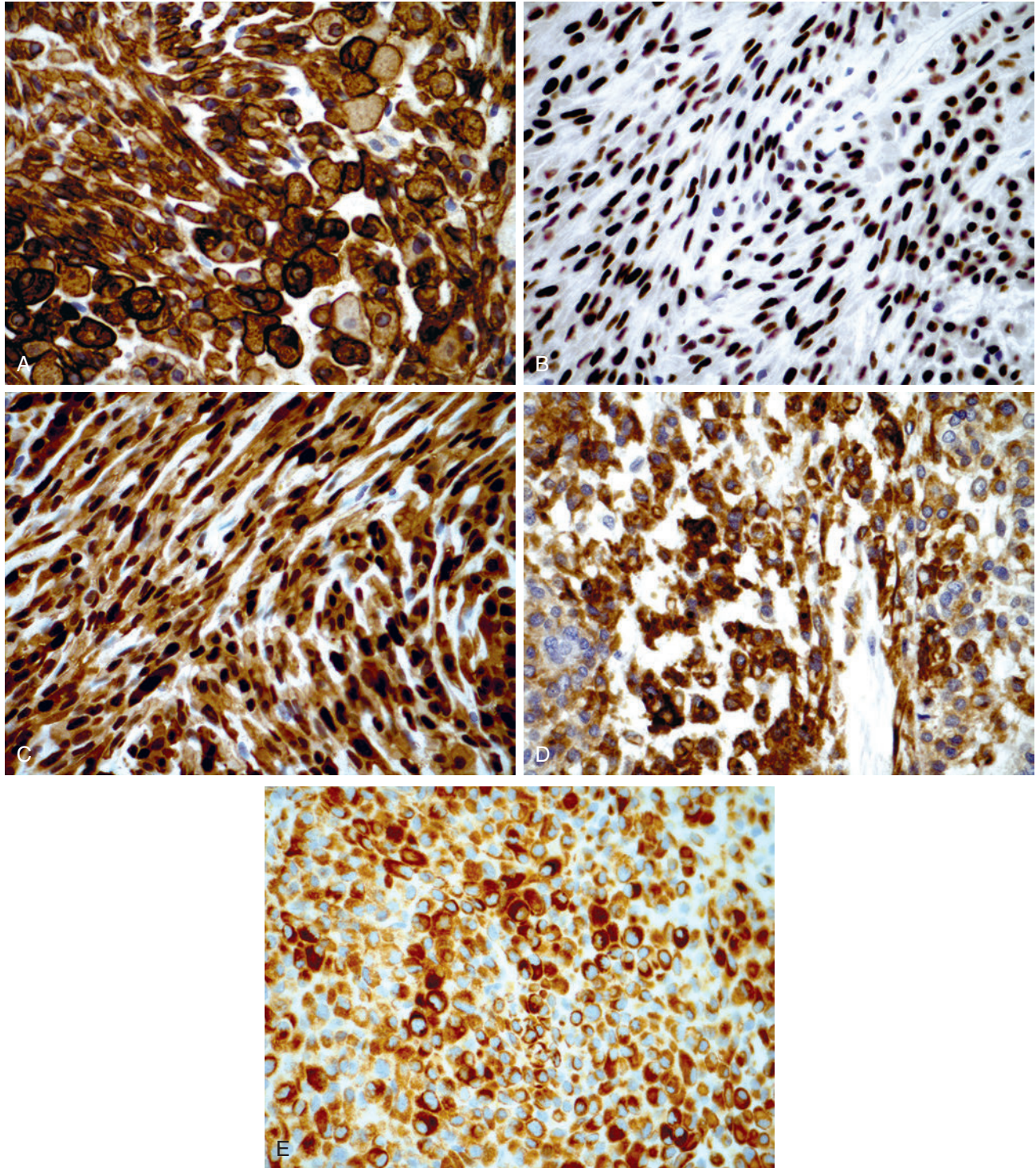


Fig. 20-36. Myoepithelioma.

Immunohistochemical staining in myoepithelioma may include (A) cytokeratin (AE1/AE3); (B) p63 (nuclear); (C) S100 protein (nuclear and cytoplasmic); (D) calponin; and (E) vimentin.

- Structural alterations in chromosomes 1, 9, 12, and 13:
 - t(1;12)(q25;q12)
 - del(9)(q22.1q22.3)
 - del(13)(q12q22)

Differential Diagnosis

- Myoepithelial-predominant pleomorphic adenoma:
 - Although myoepithelial cells predominate, residual foci of pleomorphic adenoma in the form of myxochondroid stroma are present.
- Basal cell adenoma
- Myoepithelial carcinoma
- Epithelial-myoepithelial carcinoma
- Extracranial meningioma
- Peripheral nerve sheath tumors (i.e., neurilemmoma and malignant schwannoma)
- Smooth muscle tumors (i.e., leiomyoma and leiomyosarcoma)
- Extramedullary plasmacytoma
- Spindle cell squamous carcinoma
- For clear cell dominant or exclusive tumors, the differential diagnosis may include metastatic renal cell carcinoma or thyroid carcinoma.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and should include a portion of surrounding uninvolved tissue; if appropriate, a superficial parotidectomy should be performed.
- Local recurrence is related to inadequate excision.
- There is no relationship between cell type (e.g., spindle, plasmacytoid, epithelioid, clear) and prognosis.
- Malignant transformation is rare and occurs in the setting of a long-standing tumor and/or multiply recurrent tumor.

Soft Tissue Myoepithelial Tumors

- Primary myoepithelial tumors of soft tissues are uncommon.
- Classification includes:
 - Benign neoplasm (myoepithelioma)
 - Malignant neoplasms (myoepithelial carcinoma); see [Myoepithelial Carcinoma](#) later in chapter
- As compared with their salivary gland counterpart:
 - A higher proportion of myoepithelial tumors of soft tissues are malignant.
 - Unlike salivary gland myoepithelial carcinoma, in which a majority arise in association with a pleomorphic adenoma (i.e., myoepithelial carcinoma ex pleomorphic adenoma), this occurrence is rare relative to soft tissue myoepithelial carcinoma,

the majority of which occurs as a de novo malignancy.

- Identification of *EWSR1-POU5F1* or *EWSR1-PBX1* gene fusion
- Subset of cutaneous and superficial soft tissue myoepithelial tumors display distinct ductal component, closely resembling pleomorphic adenomas of salivary gland:
 - Recurrent *PLAG1* rearrangement by FISH detected in cutaneous and benign soft tissue myoepithelial tumors, majority with abundant tubuloductal differentiation
 - Leukemia inhibitory factor receptor (*LIFR*)-*PLAG1* fusion confirmed by FISH in one soft tissue myoepithelial tumor with tubular formation
 - Findings indicate that subset of cutaneous and soft tissue myoepithelial tumors appear genetically linked to salivary gland counterparts with frequent *PLAG1* gene rearrangements and occasionally *LIFR-PLAG1* fusion.

SCLEROSING POLYCYSTIC ADENOSIS (SPA)

(Figs. 20-37 and 20-38)

Definition: Rare neoplastic process of salivary glands with histologic similarities to mammary gland fibrocystic disease.

NOTE: Reported presence of associated/superimposed foci of carcinoma in situ, invasive carcinoma, local recurrence, and clonality support classification as true neoplastic lesion rather than nonneoplastic proliferation as initially considered.

Clinical

- Uncommon lesion
- More common in women than in men; occurs over wide age range from the first to the tenth decades of life with a mean of 33 years
- Most common site of occurrence is parotid gland:
 - Much less often submandibular gland and intra-oral salivary minor glands are affected.
 - Rare cases reported in other sites, including sinonasal tract
- Patients present with a slow-growing asymptomatic mass; rarely, pain and/or a “tingling” sensation have been described.
- Majority of cases present as a de novo process but a few cases have been described in association with recurrent pleomorphic adenomas or recurrent chronic parotitis
- Familial occurrence reported in two sisters, suggesting genetic predisposition

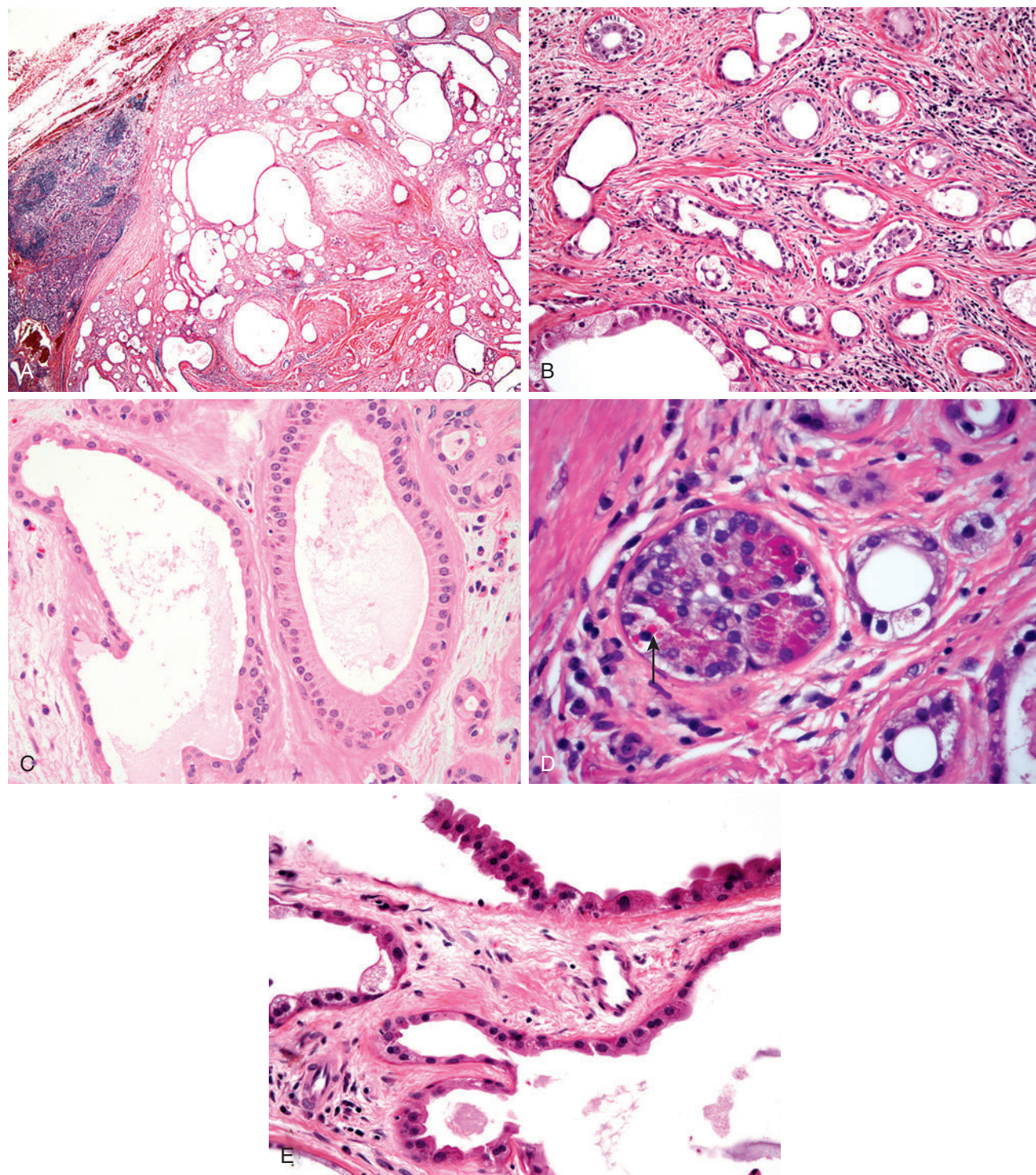


Fig. 20-37. Sclerosing polycystic adenosis.

A, Circumscribed nodular lesion demarcated from the adjacent parotid parenchyma (*left*) and characterized by variably sized cysts and the presence of sclerotic stroma. **B**, Variably sized ductules with associated sclerotic stroma. **C**, Ducts are lined by columnar to cuboidal epithelium. **D**, Cells may show the presence of brightly eosinophilic cytoplasmic granules and/or eosinophilic hyaline globules (*arrow*) that are considered highly characteristic (although not pathognomonic) for the diagnosis. Other cell types that can be seen include (**E**) apocrine-appearing cells;

Continued

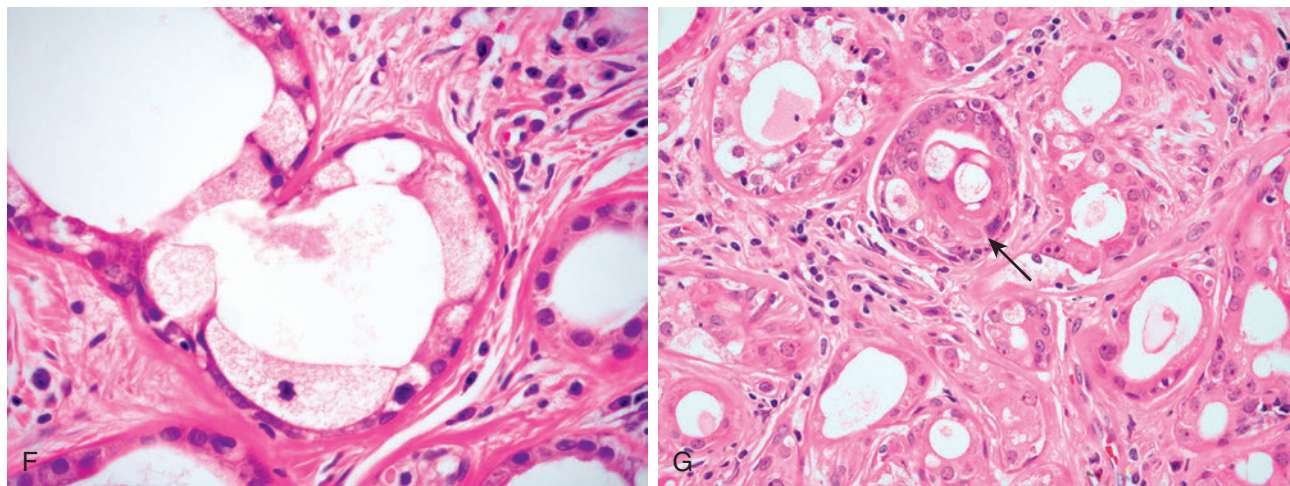


Fig. 20-37, cont'd

(F) sebaceous cells; and (G) squamous metaplasia (*arrow*).

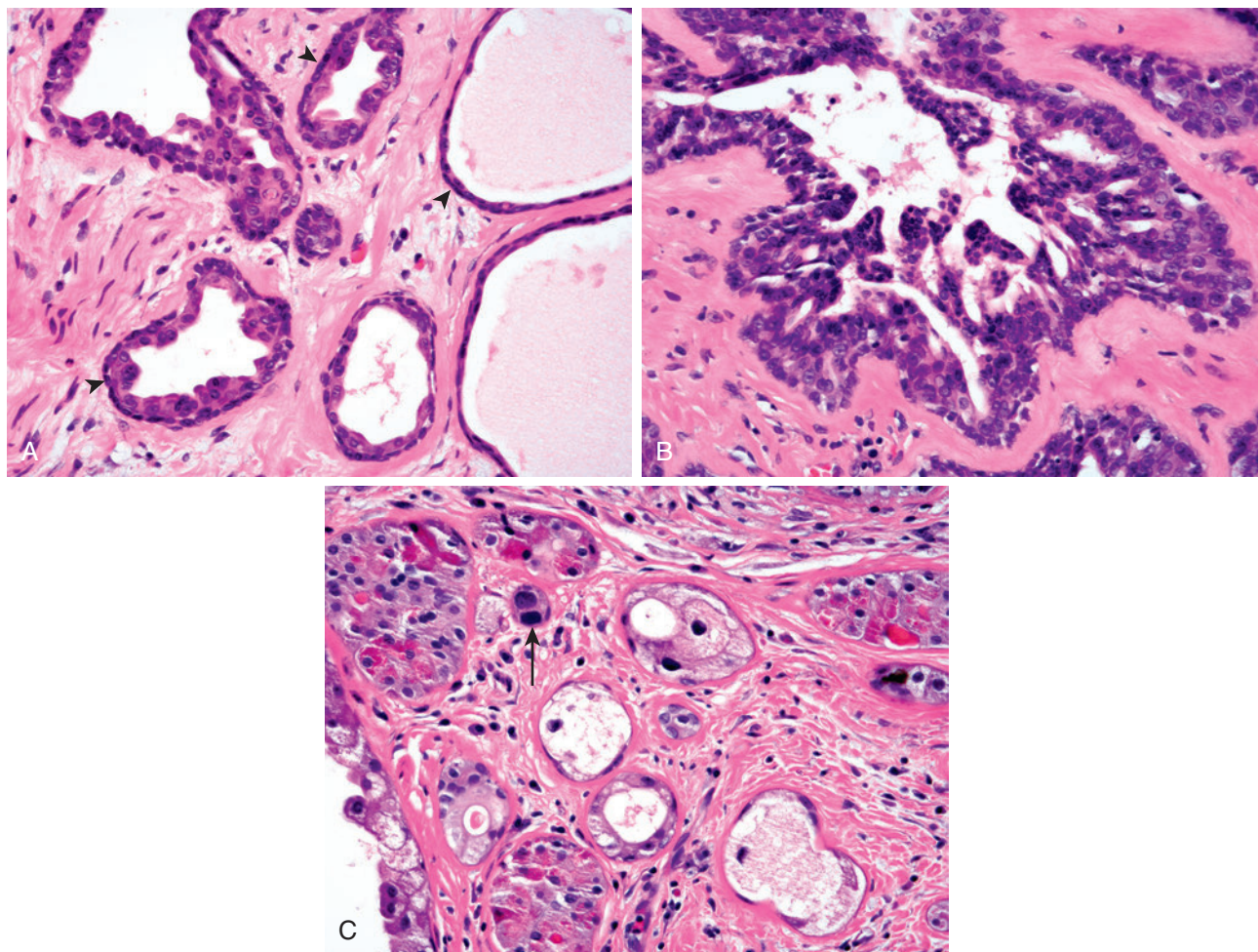


Fig. 20-38. Sclerosing polycystic adenosis.

Additional findings may include (A) intraductal hyperplasia; note presence of outer layer of flattened myoepithelial cells (*arrowheads*), which is reactive for p63 as well as other markers for myoepithelial cells (not shown); (B) micropapillary hyperplasia; (C) areas with atypical (enlarged and hyperchromatic) nuclei (*arrow*).

Pathology

Fine-Needle Aspiration Biopsy

- Aspirate characterized by flat cohesive sheets of epithelial cells with moderate amounts of finely granular oncocytic cytoplasm and enlarged round nuclei with indistinct nucleoli.
- Some epithelial groups form glandular structures with lumens.
- Background may contain small amounts of delicate mucoproteinaceous material.
- Markedly vacuolated cells as well as cells with apocrine change manifested by well-defined apical snouting may be identified.

Gross

- The lesions usually appear as a single, well-circumscribed mass but may be multinodular, ranging in size from 1 to 5 cm in greatest dimension.
- On cut section the lesions are rubbery to firm with a pale, glistening appearance.
- Small cystic foci may be apparent on gross examination.

Microscopic

- Most lesions appear as well-circumscribed and partially encapsulated nodules with a peripheral rim of normal salivary parenchyma.
- Characterized by presence of abundant sclerotic collagenous tissue containing lobular proliferations of epithelial cells with ductal/tubular and acinous differentiation:
 - Ducts vary in size from cystically dilated spaces to small ductules.
 - Epithelial lining includes simple columnar to flattened cuboidal epithelium.
- Hyperplasia of ductal and acinar epithelial cells can be identified with interconnecting bridges or anastomosing cords creating a cribriform pattern, as well as papillary growth.
- Some cells may demonstrate the presence of intensely eosinophilic cytoplasmic granules and/or hyaline globules:
 - Considered highly characteristic although not absolutely pathognomonic
- In addition, apocrine metaplasia, mucous cells, squamous cells, and sebaceous-like cells can be present.
- Degenerative changes that can be found include:
 - Partial or completely denuded epithelium of the cystic ducts with replacement by foamy (xanthomatous) macrophages
 - Cytoplasm of the epithelial cells may be replaced by abundant pale, reticulated cytoplasm, creating

a balloon-like appearance resembling sebaceous cells.

- Intraluminal epithelial proliferation may show a spectrum of alterations ranging from nondescript with mild atypia to higher degrees of epithelial dysplasia, including moderate to severe, that at times border on ductal carcinoma in situ (DCIS):
 - DCIS is histologically identical to mammary ductal carcinoma in situ, and similar to the breast lesions, the salivary gland lesions retain a myoepithelial cell layer (see below).
 - To date, single case of invasive carcinoma arising in SPA reported:
 - Invasive component composed of isolated pleomorphic cells with eosinophilic cytoplasm, large nuclei, and prominent nucleoli diffusely infiltrating normal salivary gland and with focal entrapment of normal salivary ducts
 - Carcinoma in situ identified adjacent to invasive carcinoma
- Histochemistry:
 - Granules in cells with acinar differentiation show diastase-resistant PAS-positive material.
 - These granules are mucicarmine negative, but faint mucicarmine-positive staining can be seen in scattered duct-lining cells.
- Immunohistochemistry:
 - Tubuloacinar cells are immunoreactive for cytokeratin, CEA, BRST2, progesterone receptor (80%), and estrogen receptor (20%).
 - Absence of *HER-2*
 - Myoepithelial cells reactive with variety of myoepithelial cell markers, including p63, calponin, S100 protein, and smooth muscle actin
- Cytogenetics and molecular genetics:
 - PCR analysis of patterns of X-chromosome inactivation using human androgen receptor (HUMARA) locus has shown monoclonal population of cells indicative of monoclonality.

Differential Diagnosis

- Polycystic (dysgenetic) disease (see Chapter 19):
 - Lobular collection of cystic ducts frequently with apocrine metaplasia
 - Unlike SPA, polycystic disease is usually:
 - Bilateral
 - Involves entire gland
 - Shows no acinar proliferation and has minimal fibrosis and inflammation
- Sclerosing sialadenitis:
 - Shows similarities to SPA including presence of fibrosis and inflammation
 - In contrast to SPA, fibrosis is not nodular nor are xanthomatous cells seen in association with the duct ectasia.

Treatment and Prognosis

- Complete surgical resection is preferred treatment:
 - Facial nerve sacrifice not indicated
- Recurrence of the lesion may occur following incomplete excision:
 - 30% recurrence rate reported in some studies.
- Prognosis is very good with the caveat that until longer follow-up becomes available in these patients the biologic behavior may not be completely known.
- To date, no reported metastatic disease or death due to disease reported

CYSTADENOMA (Fig. 20-39)

Definition: Rare benign epithelial tumor characterized by its predominantly cystic (unicystic, multicystic) growth and variable appearing benign epithelial-lining cells.

Synonym: Cystic duct adenoma

Clinical

- Rare tumor type
- More common in women than in men; occurs over a wide age range from the second to ninth decades but most common in the sixth decade of life; rarely occur in the first two decades of life.
- Majority occurs in minor salivary glands, including:
 - Lips > cheek > palate
 - Slightly less than half (approximately 45%) occur in the parotid gland
 - Minority of cases (less than 10%) occur in sub-mandibular gland.
- Majority present as slowly growing, painless masses; minor salivary gland lesions appear as mucosa-covered smooth nodules resembling mucocoeles.

Pathology

Gross

- On cut section these tumors show multiple, variably sized (small) cysts surrounded by salivary gland parenchyma; occasionally a single large cyst may be present.
- Tumor size in major glands varies; typically measure less than 1 cm in minor salivary gland sites

Histology

- Circumscribed lesions that may or may not be encapsulated:
 - Presence of a capsule is variably seen
 - If fibrous capsule is present, it may completely or incompletely encapsulate lesion.
- Characterized by presence of a unicystic or multicystic lesion:

- Cysts vary in size.
- Most are multicystic with cysts separated by a limited amount of intervening dense, fibrous stroma.
- Intervening stroma may be absent.
- Patchy collections of chronic inflammatory cells are often present.
- Epithelial lining cells include single layer of cuboidal to columnar epithelium with bland nuclei lacking atypical features and absent mitotic figures.
 - Tumors with two or more cell layers thick may be present but cytologic atypia is absent.
- Other cell types that may be seen include mucous, oncocytic, sebaceous, and squamous cells:
 - Usually, when these cell types are seen they are scattered and admixed with the cuboidal or columnar cells.
 - Rarely, one of these cell types, in particular mucous cells and oncocytic cells, may predominate.
- Unicystic lesions often have luminal papillary growth:
 - Papillae vary from thin to widened and ramifying projections.
 - Fibrovascular cores are present.
- Mucinous cystadenoma:
 - Includes columnar cells with basally located nuclei and intracytoplasmic mucin-positive material
 - Combination of epidermoid, intermediate, and mucous cells not identified
- Cystadenomas associated with oncocytic features and papillary growth are termed oncocytic papillary cystadenoma:
 - Often seen in association with minor salivary glands, in particular the larynx (see Section 5)
 - Usually composed of a single epithelial layer
- Other findings may include:
 - Cystic spaces containing eosinophilic fluid that may be inspissated
 - Admixed epithelial cells and inflammatory cells may be present.
 - Intraluminal psammomatoid concretions and/or crystalloids may be identified.
- Prominent solid, extraluminal growth is unusual and, if present, should be suspicious for a malignant neoplasm.

Differential Diagnosis

- Cystic lesions associated with duct obstruction:
 - Such lesions include duct ectasia, as well as salivary duct cyst.
 - Typically, duct obstruction primarily affects sub-mandibular gland

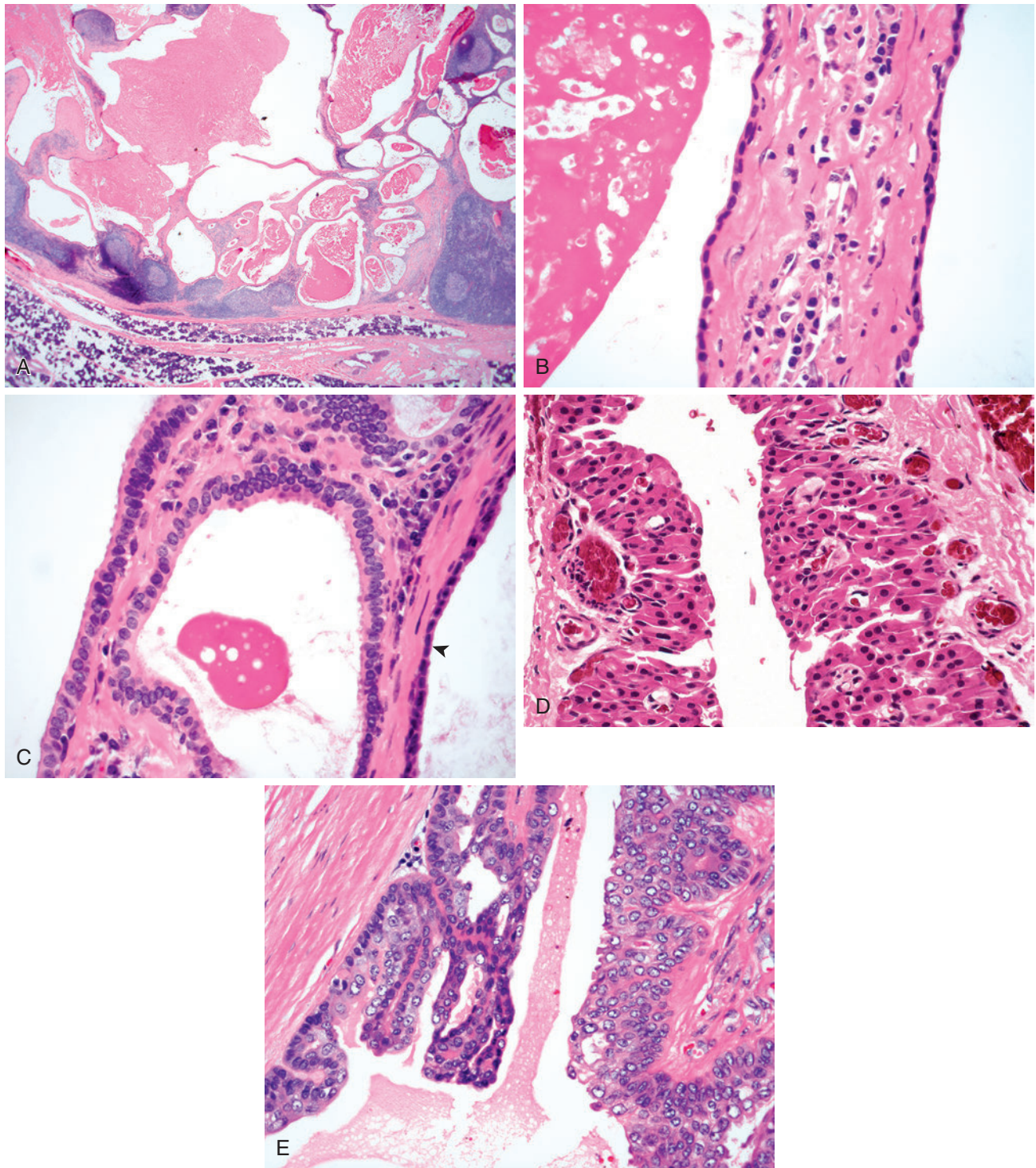


Fig. 20-39. Cystadenoma.

A, Multicystic circumscribed to encapsulated parotid gland lesion; cystic spaces containing eosinophilic fluid; the cyst epithelial lining varies from case to case and may even vary within a given case to include **(B)** single layer of cuboidal cells; **(C)** single layer of columnar cells and cuboidal appearing cells (*arrowhead*); **(D)** multilayered oncocytic cells; **(E)** multilayered epithelium with intracystic papillary growth. In all illustrated examples, there is an absence of cytologic atypia.

- Secondary changes to duct obstruction include fibrosis, acinar atrophy, squamous metaplasia, chronic inflammation, and periductal hyalinization.
- In comparison with cystadenoma, the ectatic or cystic ducts in obstructive lesions are widely separated, may be seen connected to or tracking to the obstructed duct, and usually lack the greater cytologic variability of the intraluminal epithelial proliferation seen in cystadenoma.
- Warthin tumor:
 - Characteristic bilayered epithelial layer and prominent dense lymphoid stroma with germinal centers of Warthin tumor not seen in cystadenoma, including papillary oncocytic cystadenoma
- Intraductal papilloma:
 - Almost invariable a unicystic lesion
 - Occurs in association with a dilated salivary gland duct
 - Intraluminal papillations are more complex and numerous than papillae of cystadenoma.
- Cystadenocarcinoma:
 - Presence of invasive growth differentiates cystadenoma from cystadenocarcinoma.
- Mucoepidermoid carcinoma, low-grade:
 - May share overlapping features with cystadenoma
 - Noncystic epithelial component of mucoepidermoid carcinoma includes an admixture of mucous, epidermoid, intermediate cells, which are absent in cystadenoma
 - Invasive growth, a feature often (but not always) seen in mucoepidermoid carcinoma absent in cystadenoma
- Polycystic (dysgenetic) disease:
 - Presence of diffuse involvement of the affected gland, apocrine lining epithelial cells and spheroliths seen in polycystic (dysgenetic) disease assists in differentiating it from cystadenoma.

Treatment and Prognosis

- Complete (conservative) surgical resection is curative.
- Recurrent tumor and malignant transformation rarely occur.

DUCTAL PAPILLOMAS

Definition: Group of uncommon benign epithelial salivary gland neoplasms with unique histologic features allowing for easy identification.

- Classification includes three types:
 - Sialadenoma papilliferum
 - Intraductal papilloma
 - Inverted ductal papilloma

Sialadenoma Papilliferum (Fig. 20-40)

Definition: Benign salivary gland tumor characterized by exophytic (papillary) and endophytic epithelial proliferation of mucosa or salivary duct origin.

Synonym: So named because of its similarity to the cutaneous syringocystadenoma papilliferum

Clinical

- Uncommon tumor
- More common in men than in women; occurs over a wide age range but is most frequently seen in the sixth to seventh decades of life.
- Most common site of occurrence is the palate (greater than 80%), particularly at junction of the hard and soft palates.
 - Other minor salivary glands sites of involvement include buccal mucosa, retromolar region, tonsillar pillar, lip, and nasopharynx (adenoids).
 - Major gland involvement is rare and in major glands parotid gland is most commonly affected.
- Usually presents as an asymptomatic (painless) lesion generally discovered incidentally; clinical appearance often mistaken for a papilloma; duration of symptoms may be from months to years.
- Origin is disputed; evidence supports salivary gland excretory duct rather than intercalated duct origin.

Pathology

Gross

- Well-circumscribed, papillary or verrucoid, round to oval, tan-pink-appearing lesion measuring from a few millimeters to as large as 7.0 cm
- Base of lesion is broad or pedunculated.

Histology

- Exophytic and endophytic proliferation of surface and ductal epithelium
- Surface has papillary to verrucoid growth composed of a stratified squamous epithelium with a fibrovascular connective tissue core; acanthosis and parakeratosis of the squamous epithelium can be seen.
- Merging with surface epithelium and lying immediately subjacent to squamous epithelium is an endophytic proliferation of ductal epithelium forming dilated and tortuous structures:
 - An abrupt transition from stratified squamous epithelium covering the mucosal papillary proliferation to columnar epithelium lining the ducts identified
 - Glandular component is unencapsulated.
 - Glandular component is composed of rounded or elongated and dilated ductlike structures.
 - In deeper portions ductal structures have papillary luminal projections and microcysts.

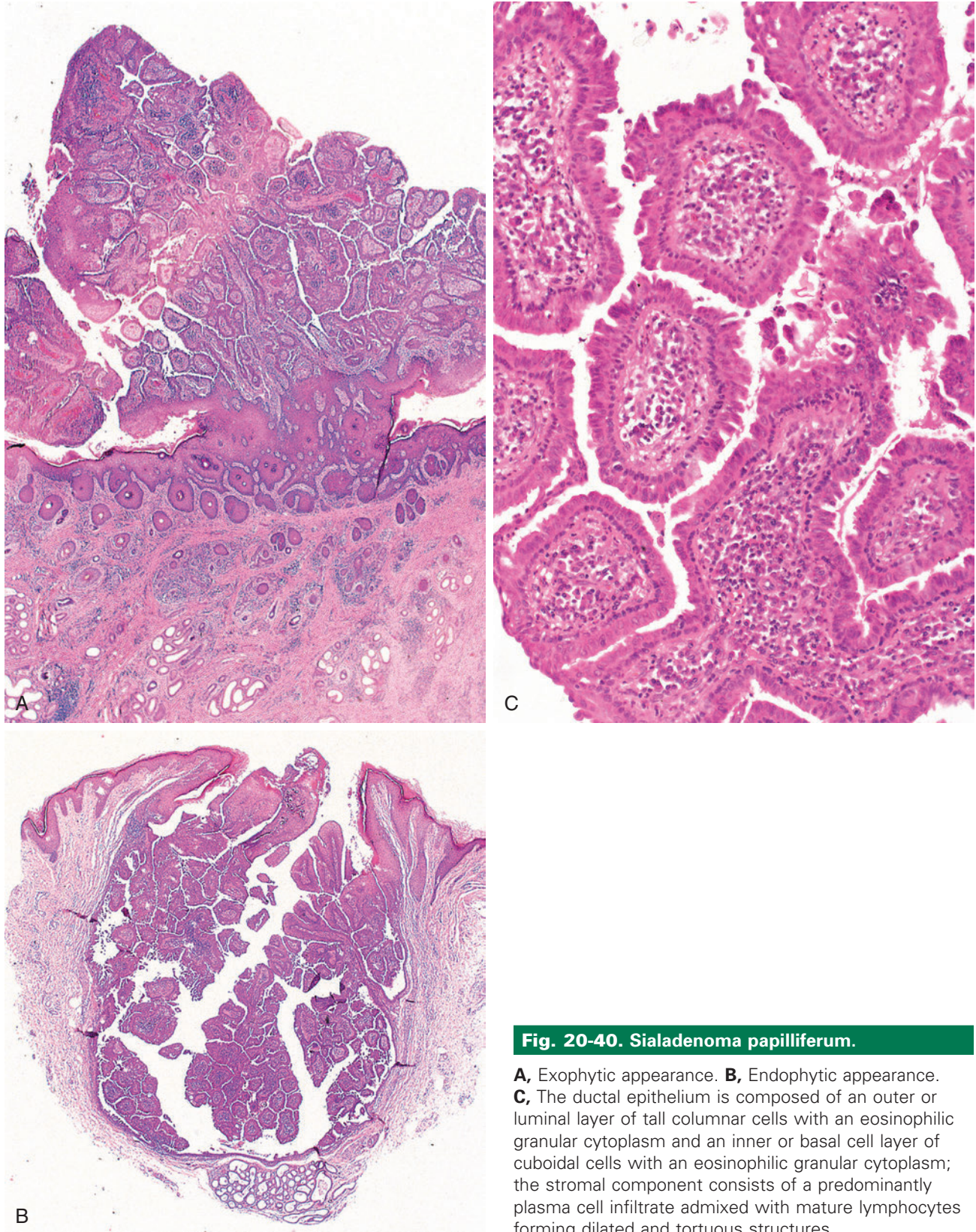


Fig. 20-40. Sialadenoma papilliferum.

A, Exophytic appearance. **B**, Endophytic appearance. **C**, The ductal epithelium is composed of an outer or luminal layer of tall columnar cells with an eosinophilic granular cytoplasm and an inner or basal cell layer of cuboidal cells with an eosinophilic granular cytoplasm; the stromal component consists of a predominantly plasma cell infiltrate admixed with mature lymphocytes forming dilated and tortuous structures.

- Absence of encapsulation and presence of poor circumscription at the base of the lesion may simulate invasive growth and be mistaken for a malignancy.
- Ductal epithelium composed of two cell layers:
 - Outer or luminal layer: tall columnar cells with an eosinophilic granular cytoplasm
 - Inner or basal cell: cuboidal cells with an eosinophilic granular cytoplasm
- Mucous cells can be seen admixed and interspersed throughout the ductal cells and in the squamous component; oncocytic cells may also be seen.
- Chronic inflammatory cell infiltrate predominantly composed of plasma cells admixed with mature lymphocytes is present within the lamina propria of the squamous mucosal component and in the stroma of the glandular component.
- Immunohistochemistry:
 - Ductal luminal cells:
 - Cytokeratins (AE1/AE3, CK7, CK19, CAM5.2), CEA, EMA, S100 protein positive
 - Basal cells:
 - CK7, CK14, S100 protein, and vimentin positive
 - Dendritic (Langerhans) cells identified within the epithelial component stain for S100 protein and CD1a positive.

Differential Diagnosis

- Papilloma of surface epithelial origin
- Inverted ductal papilloma
- Warty dyskeratoma
- Verrucous carcinoma
- Mucoepidermoid carcinoma, low grade

Treatment and Prognosis

- Complete conservative surgical excision is the preferred treatment and is curative.
- Recurrence rarely occurs.
- Rare examples of malignant transformation reported, including:
 - Epithelial-myoepithelial carcinoma
 - Mucoepidermoid carcinoma
 - Carcinoma in situ

Intraductal Papilloma (Fig. 20-41)

Definition: Benign salivary gland neoplasm characterized by unicystic duct dilatation of luminal papillary proliferation arising from a segment of interlobular or excretory duct.

Clinical

- Uncommon tumor
- No gender predilection; affects primarily adults, occurring in the fourth through seventh decades of life

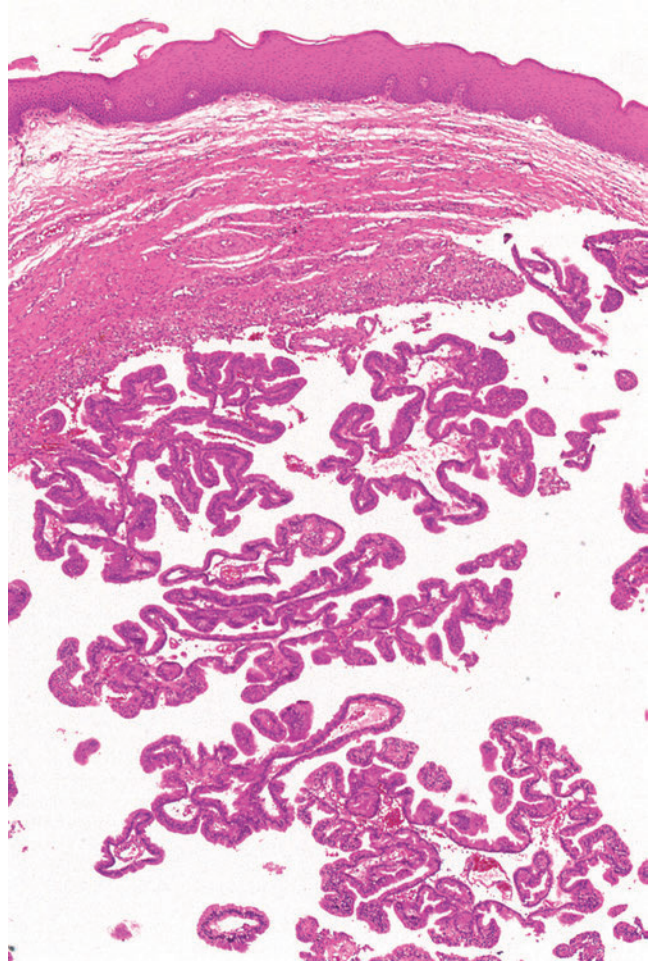


Fig. 20-41. Intraductal papilloma.

Intraductal papilloma consisting of a unicystic cavity lined by one or two layers of cuboidal or columnar epithelium which give rise to numerous papillary fronds having a thin fibrovascular connective tissue core.

- Intraoral minor salivary glands most frequently involved:
 - Buccal mucosa and lips are most commonly affected.
 - Other sites of occurrence include floor of mouth, soft palate, and tongue.
 - Involvement of major glands is rare.
- Symptoms relate to a painless, well-delineated, and solitary (submucosal) mass.

Pathology

Gross

- Well-circumscribed, mucosa-covered nonulcerated nodule measuring from 0.5 to 2 cm in diameter.
- Cut section reveals a unicystic lesion containing friable tissue.

Histology

- Unicystic cavity lined by one or two layers of cuboidal or columnar epithelium with eosinophilic cytoplasm, which give rise to numerous papillary fronds filling the cavity; papillations are covered by a similar epithelium.
- Cytologic atypia is absent; no significant increase in mitotic activity
- Mucocytes in form of goblet cells are seen admixed within the ductal epithelium
- Papillations have a thin fibrovascular connective tissue core.
- Continuity of papillary projections to cyst wall is present but depending on the sections the papillae may not be seen in continuity to the cyst wall and appear to float within the lumen.
- Epithelial component is confined to cyst cavity and there are no extensions into the adjacent stromal tissue.

Differential Diagnosis

- Inverted ductal papilloma
- Papillary cystadenoma
- Low-grade papillary adenocarcinoma of the nasopharynx

Treatment and Prognosis

- Complete conservative surgical excision is the preferred treatment and is curative.

Inverted Ductal Papilloma (Fig. 20-42)

Definition: Benign salivary gland neoplasm characterized by a luminal papillary projection occurring in the terminal portions of excretory ducts arising at the junction of a salivary gland duct and oral mucosal surface epithelium with a characteristic inverted (endophytic) growth.

Synonym: Epidermoid papillary adenoma

NOTE: This minor salivary gland tumor shares histologic features with sinonasal (Schneiderian) inverted papilloma but does not share in the biologic behavior of the sinonasal (Schneiderian) inverted papilloma.

Clinical

- Rare neoplasm
- No gender predilection; occurs primarily in adults over a wide age range but is most frequently seen in the sixth decade of life
- Most common sites of occurrence include:
 - Lower lip and the buccal (vestibular) mucosa
 - Other sites of involvement include the upper lip, floor of mouth, and soft palate.
- Generally asymptomatic and presents as a slow-growing painless, nodular submucosal swelling

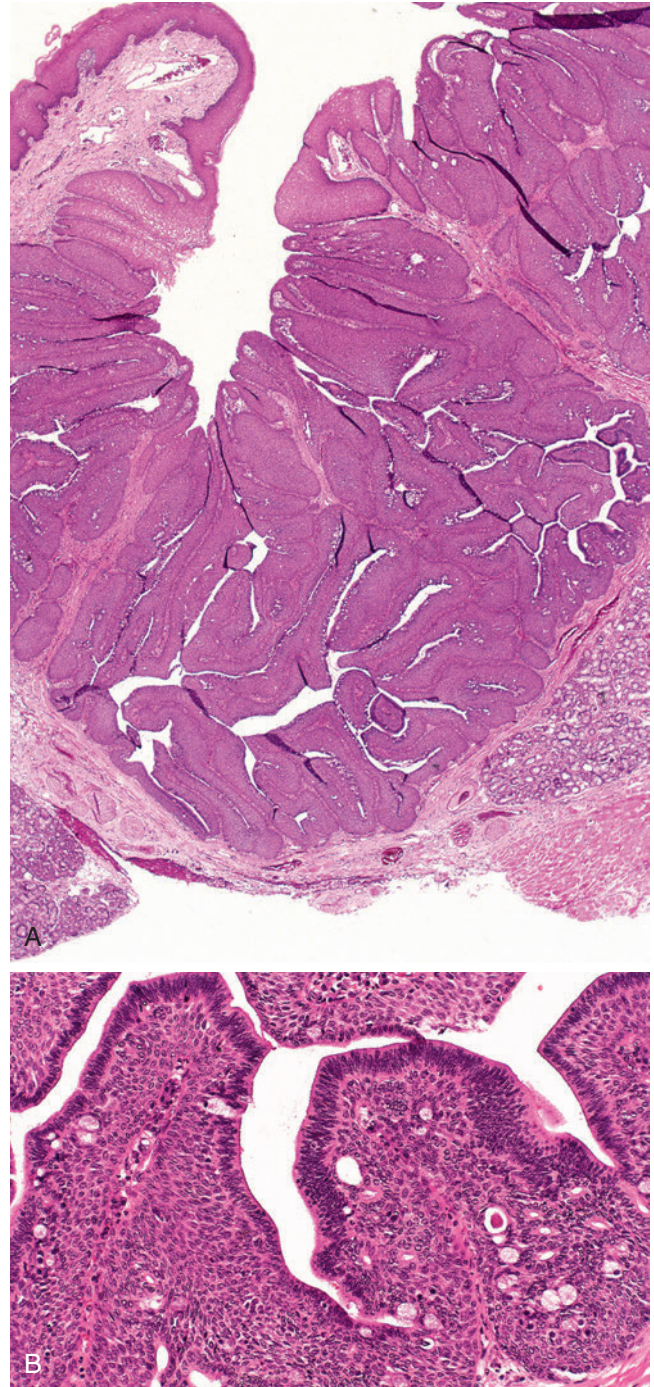


Fig. 20-42. Inverted ductal papilloma.

A, Well-demarcated, endophytic epithelial growth composed of thick, bulbous proliferations contiguous with but not protruding from the surface epithelium; communication with the surface by a narrow opening is seen. **B,** The neoplasm consists of basaloid-appearing epithelial cells composed of cuboidal or columnar cells with a papillary appearance along the luminal surface and squamous/epidermoid cells between which are interspersed mucous cells and microcytes.

Pathology

Gross

- Submucosal firm nodule measuring up to 1.5 cm in diameter; a small surface pore may be seen, which is contiguous with the lumen of the tumor.

Histology

- Unencapsulated but well-demarcated, endophytic epithelial growth composed of thick, bulbous proliferations that are contiguous with but not protruding from the surface epithelium; communication with the surface by a narrow opening may be seen.
- Consists of basaloid and squamous/epidermoid cells between which mucous cells and microcysts may be interspersed; cytologic atypia is absent and there is no significant increase in mitotic activity.
- Luminal surface epithelium composed of cuboidal or columnar cells with a papillary appearance
- Tumor grows downward and appears to fill a luminal cavity:
 - Endophytic growth is “pushing” into the submucosa rather than demonstrating invasion or infiltration.
- Histochemistry:
 - Mucous cells stain positively with mucicarmine and are diastase resistant, PAS positive.

Differential Diagnosis

- Inverted papilloma
- Sialadenoma papilliferum
- Mucoepidermoid carcinoma

Treatment and Prognosis

- Conservative but complete local excision is the preferred treatment and is curative.

OTHER UNCOMMON BENIGN EPITHELIAL NEOPLASMS

- Rare to uncommon benign epithelial neoplasms of salivary glands include:
 - Striated duct adenoma
 - Intercalated duct adenoma
 - Lymphadenoma (nonsebaceous)
 - Keratocystoma
 - Lipoadenoma
 - Adenofibroma
 - Apocrine adenoma
 - Salivary gland anlage tumor

Striated Duct Adenoma

Definition: Unilayered ductal tumor that recapitulates normal striated ducts.

Clinical

- Rare tumor type with very few reported cases
- Most common site of occurrence is parotid gland
 - May occur less often in minor salivary glands (palate)
- Present as a palpable mass

Pathology

- Well-circumscribed to encapsulated lesion ranging in size from 0.5 to 3.0 cm
- Composed of closely apposed small ducts with minimal intervening stroma admixed with cystic ductal spaces that may include:
 - Prominent areas with cystic changes containing colloid-like luminal contents with scalloped edges reminiscent of thyroid parenchyma
 - Focal cysts
 - Absence of cystic spaces
- Ductal epithelial cells:
 - Single layer of cuboidal to columnar eosinophilic cells with bland nuclei, eosinophilic cytoplasm, and prominent cell membranes similar to striations of normal striated ducts:
 - Eosinophilic intranuclear inclusions may be seen.
 - Focal clear cell cytoplasmic change may be present.
 - Absence of epithelial “beading” pattern with abundant stroma seen in canalicular adenoma
 - Absence of chondromyxoid stroma, basal lamina-like material
 - Absence of mitotic activity and necrosis
 - Absence of visible bilayering composed of ductal cells surrounded by basal or myoepithelial cells:
 - In contrast, normal excretory and intercalated ducts contain diffuse bilayering with basal or myoepithelial markers.
- Psammoma bodies and an associated adipocytic component may be identified.
- Immunohistochemistry:
 - Keratins (CK7, pankeratin) consistently present
 - S100 protein in >80%
 - CK5/6 (75%)
 - Generally devoid of myoepithelial cells:
 - Smooth muscle actin (SMA) negative
 - Isolated cells may be p63 positive
 - Pattern identical to striated ducts
 - Focal calponin and smooth muscle myosin heavy chain may be present, forming incomplete rim around ducts
 - Thyroglobulin and TTF1 negative
- Highly vascular lesions with numerous small capillaries, some containing large ecstatic staghorn vessels

Treatment and Prognosis

- Complete resection curative
- No recurrence or metastases

Intercalated Duct Adenoma

(Fig. 20-43)

Definition: Rare benign neoplasm of intercalated duct epithelium. See discussion in Chapter 19 on intercalated duct lesions.

Pathology

- Presence of discrete, rounded, partially to completely encapsulated nodules with well-defined contours
 - Fibrous capsule may vary in thickness and may contain entrapped, irregular-appearing ducts.
- Composed of intercalated ducts lined by single layer of cuboidal to columnar cells with small round nuclei and eosinophilic to amphophilic cytoplasm:
 - There is an absence of nuclear pleomorphism or increased mitotic activity.
 - Minimal intervening stroma present
- Occasionally acinic cells may be interspersed among the ductular structures.
- Immunohistochemistry:
 - Luminal cells reactive for cytokeratin (CK7), DOG1 (apical and membranous), S100 protein, and lysozyme
 - Basal/myoepithelial markers including p63, calponin, CK14, or smooth muscle actin highlight thin layer of myoepithelial cells around ducts:
 - Basal/myoepithelial cells are indistinct by light microscopy.

Lymphadenoma (Nonsebaceous)

(Fig. 20-44)

Definition: Rare benign tumor that is circumscribed to encapsulated and composed of epithelial nests including glands with associated prominent lymphocytic component but without islands of sebaceous cells (unlike sebaceous lymphadenoma).

Clinical

- Uncommon tumor type but more common than sebaceous lymphadenoma
- No gender predilection; primarily disease of adults
- Most commonly arises in parotid gland:
 - Less commonly arises in submandibular gland

Pathology

- Solid or cystic epithelial tumor islands:
 - Solid foci may show trabecular growth or tubules surrounded by a basement membrane-like material.

- Cystic foci may contain proteinaceous material.
- Papillary architecture may occasionally be seen.
- Cells types include squamous cells in the solid nests, cuboidal to columnar cells lining cysts, but an absence of sebaceous cells.
- Cellular components are rather bland, lacking atypical features, significant increase in mitotic activity, and an absence of necrosis.
- Epithelial components are intimately associated with a lymphoid stroma that includes a dense mature lymphocytic cell infiltrate with identifiable lymphoid follicles; this lymphoid component is believed to represent the tumor-associated lymphoid stroma, a finding that can be seen in association with other salivary gland tumors.
- Absence of atypical features, mitotic activity, and necrosis assists in differentiating lymphadenoma from a malignancy (either a primary salivary gland carcinoma or metastatic adenocarcinoma).

Treatment and Prognosis

- Surgical excision is curative.

Keratocystoma

Definition: Benign salivary gland tumor composed of multiple cystic structures and solid nests of purely squamous cells.

Clinical

- Rare tumor type
- No gender predilection; occurs over wide age range, including pediatric and adult ages
- To date, all cases limited to parotid gland
- Present as slowly growing tumors

Pathology

- Cut surface shows multilocular cystic lesions filled with keratin materials.
- Histologically:
 - Multicystic spaces and solid epithelial islands containing lamellated-appearing keratin
 - Lined by stratified squamous epithelium with keratinization, including orthokeratosis and parakeratosis but absence of granular layer
 - Stratification of epithelium always regularly oriented from the outer basal to the inner keratotic cell layer
 - Basal cell layer demarcated by basement membrane from surrounding inflamed fibrous stroma
 - Focally, outer layer shows bud-like protrusions.
 - Solid squamous cell islands surrounded by basement membrane enveloped within collagenous stroma may be present.

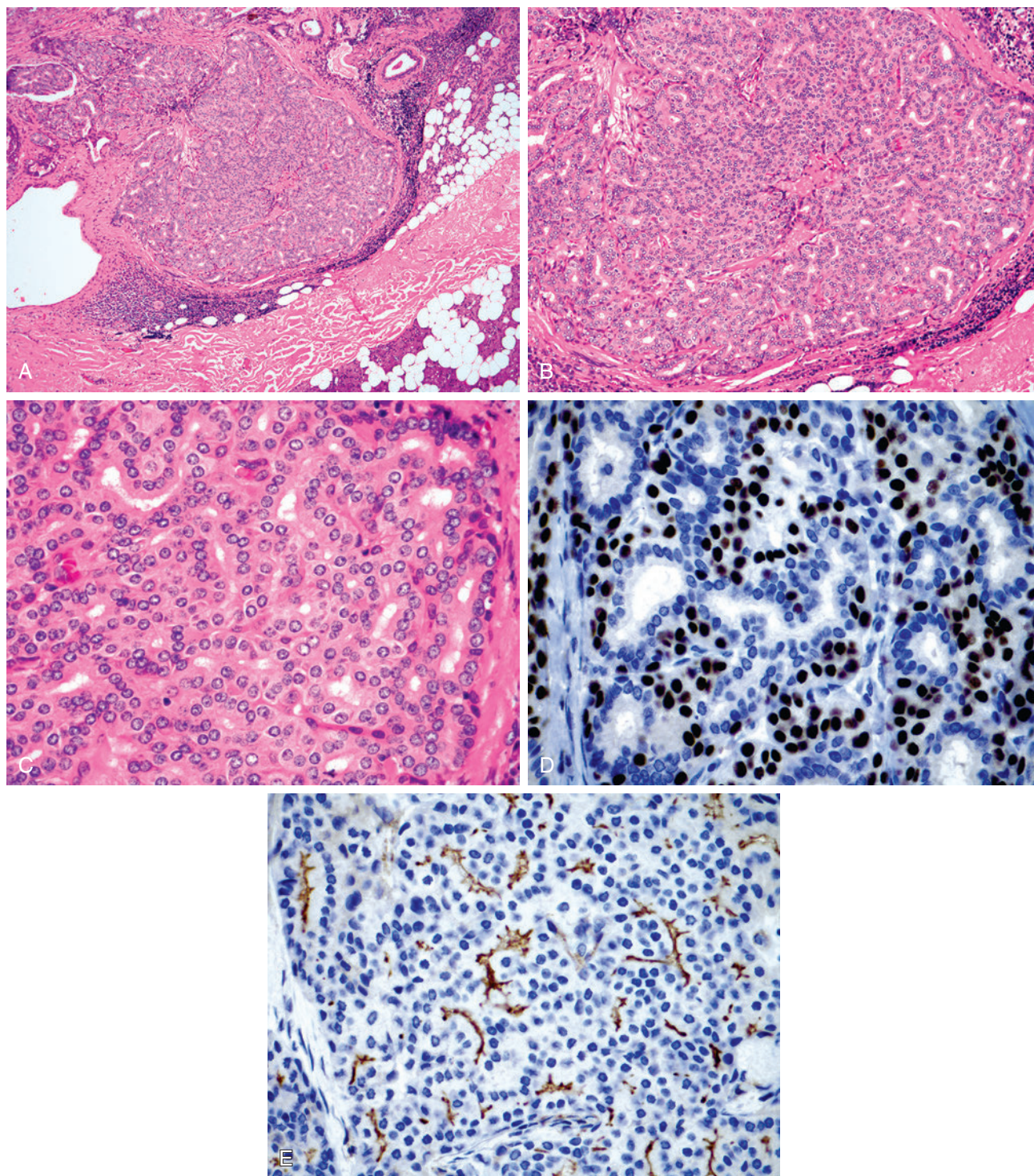


Fig. 20-43. Intercalated duct adenoma.

A, Intraparotid circumscribed to encapsulated cellular proliferation. **B**, Discrete, rounded nodule with well-defined contour. **C**, The tumor is composed of ducts lined by single layer of cells with small round nuclei and eosinophilic cytoplasm; there is an absence of nuclear pleomorphism or increased mitotic activity. **D**, The basal/myoepithelial component is highlighted by p63 staining. **E**, Luminal cells show apical membranous DOG-1 staining.

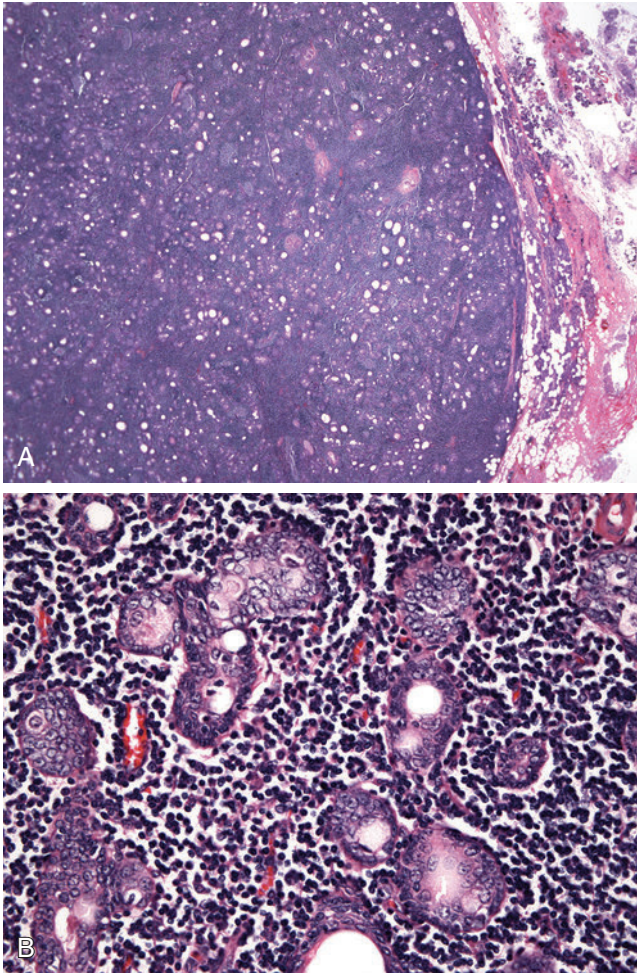


Fig. 20-44. Parotid gland lymphadenoma.

A, Circumscribed to thinly encapsulated tumor that at low magnification is dominated by dense lymphoid proliferation with interspersed "spaces" representing the adenomatous component. **B**, At higher magnification tubules and ductular structures composed of cuboidal to columnar cells lacking sebaceous cells are present associated with a benign lymphoid cell stroma.

- Cystic and solid structures randomly distributed without definite lobular architecture
- Lesional cells composed of uniform, bland nuclei and abundant eosinophilic cytoplasm
- Scattered mitotic figures may be seen usually limited to outer epithelial layer; atypical mitoses not present
- Foreign-body giant cell reaction to keratin debris may be present.
- Immunoreactivity for cytokeratins (AE1/AE3, CK5/6, CK14) but negative for CAM5.2, S100 protein, actin, and calponin

Treatment and Prognosis

- Complete surgical resection is curative.
- No recurrences reported

Lipoadenoma

Definition: Benign neoplasm composed predominantly of mature adipose tissue admixed with adenomatous elements.

Synonym: Sialolipoma

Clinical

- More common in men than in women; occurs over a wide age range from third to eighth decades
- Arises primarily in parotid gland:
 - Less often may occur in submandibular gland and oral minor salivary glands

Pathology

- Solitary and well-circumscribed with light brown to yellow appearance on cut section
- Histologically, composed of an admixture of cells, including:
 - Mature adipose tissue:
 - Usually dominates, representing more than 90% but reported in as little as 5% of a given tumor
 - Benign salivary gland epithelial parenchymal components:
 - Sharply demarcated from fat
 - Composed of ducts and acini:
 - Ductal dilatation may be present.
 - Extensive oncocytic cell population often present
 - Other cell types may include sebaceous cells and squamous cells.
 - Irrespective of cellular components there is an absence of cytologic atypia.
- Other common features include the presence of serous acini, ductal elements, sebaceous glands, and a patchy chronic inflammation.

Treatment and Prognosis

- Complete surgical resection is curative.
- No recurrences reported

Apocrine Adenoma

- Rare tumor type of major and minor salivary glands
- Composed of closely packed small glands lined by cells with apocrine features

Adenofibroma

- Extremely rare tumor type
- Composed of admixture of adenomatous glands and cellular spindle cell stroma:
 - Spindle cells are CD34 positive but negative for p63, S100 protein, and actin

Salivary Gland Anlage Tumor

Definition: Benign tumor with mixed epithelial and mesenchymal elements recapitulating early stages in the embryology of salivary glands between fourth and eighth weeks of development.

Synonym: Congenital pleomorphic adenoma

- See Section 3, Pharynx, for detailed discussion including illustrations.

TUMORS WITH SEBACEOUS DIFFERENTIATION

- Sebaceous tumors of salivary glands are rare and are thought to originate from sebaceous cells or sebaceous glands found in salivary glands.
- Normal sebaceous cells or glands can be found in the oral mucosa, parotid gland, and submandibular gland; sebaceous cells can also be found in intra- and periparotid lymph nodes.
- Salivary gland sebaceous cells or glands are histologically similar to their cutaneous counterparts.
- Benign sebaceous tumors of salivary glands include:
 - Sebaceous adenoma
 - Sebaceous lymphadenoma

Sebaceous Adenoma

Definition: Rare benign epithelial salivary gland tumor that is encapsulated with solid and cystic growth and composed of cells with sebaceous differentiation, as well as squamous differentiation.

Clinical

- Rare tumor accounting for 0.1% of all salivary gland tumors.
- More common in men than in women; occur over a wide age range from the third to tenth decades of life, and a mean in the sixth decade of life
- Most common site of occurrence is parotid gland
 - Other sites of occurrence include the submandibular gland and oral cavity:
 - Sites of involvement in oral cavity include the buccal mucosa and posterior mandibular region.
 - Given the presence of sebaceous cells in oral mucosa (unassociated with minor salivary gland), a definitive minor salivary gland origin cannot be confirmed.
- Generally asymptomatic and presents as a slow-growing, painless, firm mass; duration of symptoms may be from months to years.

Pathology

Gross

- Well-circumscribed, solid and cystic, tan-white– to yellow-appearing lesion ranging up to 3.0 cm in greatest dimension

Histology

- Encapsulated tumors:
 - Capsule may be complete or partial
 - In relationship to cysts capsular irregularities are present so that a well-defined capsule is not identified.
- Composed of solid nests or islands as well as cysts surrounded by fibrous stroma
- Neoplastic cells often predominated by squamous cells with associated sebaceous cells; however, sebaceous cells may predominate:
 - Sebaceous cells are characterized by:
 - Vacuolated or multivacuolated cytoplasm
 - Nuclei that are centrally located and scalloped due to lipid imprints
- Instead of solid nests, some examples have microcystic foci of closely associated ductal or cyst-like structures lined by squamous and sebaceous cells, and separated by a fibrous stroma
- Other cellular elements that can be seen include mucous cells and oncocytic cells.
- Cellular components lack atypical features with no significant increase in mitotic activity and absent necrosis.
- Fibrous stroma contains a variable amount of chronic inflammatory cells:
 - Foreign body giant cell reaction, lipogranuloma formation and collections of foamy histiocytes may be identified.
- Histochemistry:
 - Sebaceous cells contain lipid that can be stained by oil red O on frozen section.
 - Epithelial mucin stains are negative.
- Immunohistochemistry:
 - Sebaceous cells are EMA positive.

Differential Diagnosis

- Sebaceous lymphadenoma
- Sebaceous carcinoma
- Mucoepidermoid carcinoma

Treatment and Prognosis

- Conservative but complete surgical resection is curative.
- Unlike their cutaneous counterparts, salivary gland sebaceous adenomas not associated with increased risk of visceral carcinomas as may occur in Muir-Torre syndrome

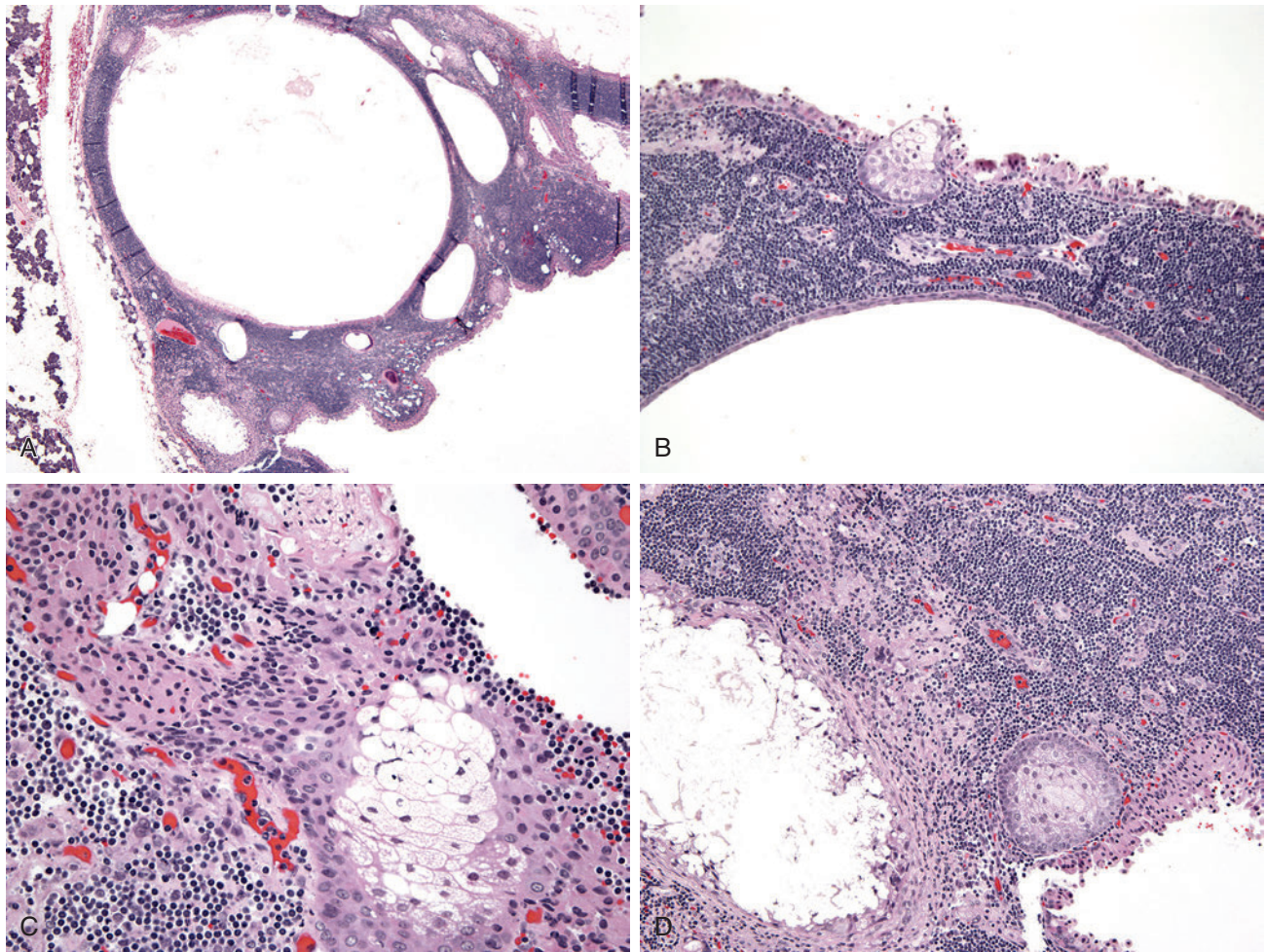


Fig. 20-45. Parotid gland sebaceous lymphadenoma.

A and B, Circumscribed to encapsulated epithelial-lined multicystic tumor with lymphoid cells in the cyst wall; lymphoid follicles are present. **C,** At higher magnifications the cyst lining includes oncocytic-appearing cells, sebaceous cells and attenuated flattened epithelium. **D,** A foreign body giant cell reaction to extravasated sebum is seen within the stroma (lower left).

Sebaceous Lymphadenoma

(Fig. 20-45)

Definition: Rare benign tumor that is circumscribed to encapsulated composed epithelial nests and islands of sebaceous cells surrounded by lymphocytes, including lymphoid follicles.

Clinical

- Rare tumor
- No gender predilection; occurs primarily in the sixth to eighth decades of life
- Majority (more than 90%) occur in parotid gland or in periparotid region
- Other much less sites of occurrence include anterior midline neck and oral cavity.
- Generally asymptomatic presenting as slow-growing, painless mass; duration of symptoms may be from months to years.
- Association with Warthin tumor and basal cell adenoma, membranous type reported
- Similar to Warthin tumor, the suggestion has been made that sebaceous lymphadenoma may arise in salivary gland inclusions within a lymph node; however, there is no definitive proof that this tumor is arising in a lymph node but rather represents the so-called tumor-associated lymphoid stroma (TALP), a phenomenon that can be seen in association with

other salivary gland tumors (e.g., acinic cell carcinoma, mucoepidermoid carcinoma, others).

Pathology

Cytology

- Fine-needle aspiration biopsy:
 - Smears show clusters of epithelial cells in background of abundant lymphoid cells, macrophages, and abundant proteinaceous materials.
 - Predominant epithelial cells are large polygonal cells with abundant cytoplasm filled with multiple, uniform, small, and clear vacuoles, ill-defined cytoplasmic borders, and small centrally located round nuclei with finely granular chromatin, conspicuous nucleoli, and indented nuclear membranes.
 - Other cells include polygonal or flat cells with less or more dense cytoplasm, indistinct cell borders, and round or oval small nuclei with smooth nuclear membranes corresponding to basaloid cells.
 - Large three-dimensional clusters of nonkeratinized squamous cells with oval nuclei containing evenly distributed chromatin, and scant to moderate dense cytoplasm arranged in “stream of fish” pattern
 - Rare granulomas and cystic contents (degenerated cells, inflammatory cells, macrophages, and abundant granular debris/proteinaceous material) may also be seen.

Gross

- Well-circumscribed to encapsulated, solid to multicystic, yellow- to yellow-white-appearing lesion ranging up to 6.0 cm in greatest dimension

Histology

- May have a complete capsule but may also be partially encapsulated or unencapsulated:
 - Unencapsulated tumors have delineated or circumscribed periphery that may abut but does not infiltrate adjacent salivary gland parenchyma or connective tissues.
- Consists of islands and ductlike structures composed of squamous cells and sebaceous cells; cuboidal, columnar, and oncocytic cells may also be present
- Cysts may also be identified lined by admixture of squamous, sebaceous, and columnar cells; small intraluminal nodular excrescences may be present.
- Epithelial component intimately associated with dense lymphoid component:
 - Well-developed lymphoid follicles can be seen in many cases.
- Generally devoid of myoepithelial cells
- Foreign body giant cell reaction and collections of histiocytes may be identified in stroma, representing secondary reaction to extravasated sebum.

- Cellular epithelial components lack atypical features with no significant increase in mitotic activity and absent necrosis.
- Histochemistry:
 - Sebaceous cells contain lipid that can be stained by oil red O on frozen section.
 - Epithelial mucin stains are negative.
 - Duct epithelial cells may show mucicarminophilia.
- Immunohistochemistry:
 - Sebaceous cells are EMA positive.
 - Epithelial cells express basal cell markers including p63, 34BE12, and/or CK5/6.
 - Luminal glandular cells express CK7.
 - Lymphoid stroma is reactive for both B- and T-cell markers.
 - No evidence of HPV, EBV, and HHV-8

Differential Diagnosis

- Sebaceous adenoma
- Lymphadenoma, nonsebaceous, of salivary gland origin:
 - Similar to sebaceous lymphadenoma but lacks sebaceous cell component
 - See previously in chapter for more complete discussion.
- Warthin tumor
- Lymphoepithelial sialadenitis
- Mucoepidermoid carcinoma
- Lymphoepithelial carcinoma
- Metastatic adenocarcinoma to periparotid or intraparotid lymph node

Treatment and Prognosis

- Conservative but complete surgical resection is curative.
- Rarely, single cases of malignant transformation to sebaceous carcinoma and basal cell adenocarcinoma reported

BENIGN SOFT TISSUE TUMORS

- Benign mesenchymal tumors of salivary glands are uncommon, accounting for approximately 2% to 5% of all major salivary gland neoplasms.
- Mesenchymal neoplasms of salivary glands are rare:
 - In first 2 decades of life mesenchymal tumors represent a significant proportion of all parotid gland tumors and may in fact be more common than epithelial tumors.
 - Hemangioma and lymphangioma most common
- Benign mesenchymal tumors of salivary glands much more common than salivary gland sarcomas
- Benign mesenchymal tumors account for less than 5% of all salivary gland tumors

- Parotid gland is most common site of occurrence:
 - >95% arise in parotid gland
- Although virtually any mesenchymal tumor can occur, among all salivary gland mesenchymal tumors the most common are of vascular origin, including hemangiomas.
 - Much less common benign mesenchymal tumors that may be seen in salivary glands include:
 - Lymphangioma
 - Lipoma
 - Benign peripheral nerve sheath tumors (i.e., schwannoma, neurofibroma)
 - Solitary fibrous tumor
 - Nodular fasciitis
 - Giant cell tumor
- Consumptive coagulopathy disorder (i.e., Kasabach-Merritt syndrome)
- Intraparotid hemangiomas in adults are uncommon.

Pathology

Gross

- Lobulated, dark red tumor measuring from 2 to 8 cm in diameter
- Overlying skin may have a bluish discoloration accentuated by crying episodes

Histology

- Majority of cases are in proliferative phase characterized by:
 - Unencapsulated cellular neoplasm with intralobular growth and replacement of salivary gland acini:
 - Despite replacement by a cellular proliferation, residual ducts and acini remain identifiable.
 - Near-solid masses of small capillaries consisting of epithelioid to plump endothelial cells and peripherally placed pericytes that invest endothelial cells
 - Distinct lobular architecture with lobules lacking encapsulation or fibrosis; lobules are separated by normal tissue elements and/or stroma of the involved site, and an intralobular central feeding artery may be identified.
 - Evidence of vascular differentiation (i.e., endothelial-lined lumina) may be limited:
 - Vascular lumina may be compressed and indistinct due to increased cellularity.
 - Evidence of vascular differentiation may best be identified at the periphery of the tumor.
 - Capillaries lined by two or more layers of endothelial cells, which have oval to spindle-shaped nuclei and eosinophilic granular cytoplasm
 - Mitoses frequently seen and may be numerous, but atypical mitoses are not present
 - Mast cells are present.
 - Neural pseudoinvasion, in which intralesional nerves show peri- and intraneural “invasion” by lesional capillaries:
 - Neural pseudoinvasion is a commonly identified and diagnostic feature as it is rarely seen in other benign vascular lesions.
 - Presence of neural pseudoinvasion and increased mitotic activity invasion do not render a diagnosis of malignancy and have no impact on behavior.
 - Histochemistry:
 - Reticulin stain delineates the outlines of the vascular sheath, within which is the endothelial cell proliferation.

Hemangioma, Capillary Type or Infantile (Juvenile) Hemangioma (Fig. 20-46)

Definition: Benign vascular tumor of infancy.

Synonyms: Benign (infantile) hemangioendothelioma; congenital or juvenile hemangioma; cellular hemangioma; immature capillary hemangioma

Clinical

- Common benign vascular tumor of infancy (affecting approximately 4% of children)
- Approximately 60% occur in head and neck.
 - Most common in the skin and subcutis
 - May occur in other locations, including salivary (parotid) glands
- Represents most common salivary gland tumor in pediatric population, accounting for greater than 90% of parotid gland tumors in children less than 1 year old
- More common in females than in males; may occur over a wide age range but most frequently seen in the first decade of life
- Almost exclusively involves parotid gland:
 - Occasionally the submandibular gland may be affected.
- Usually discovered at birth as a unilateral, compressible mass and bluish discoloration of overlying skin that may be accentuated during crying
 - Rapid enlargement and facial asymmetry may be seen, raising clinical suspicion for a malignancy
 - Extension to adjacent sites such as the hypopharynx may occur.
 - Ulceration of the overlying skin may occur.
- Generally appearing within weeks after birth, proliferate rapidly during the first year of life, and then spontaneously involute over a period of several years
- No association with:
 - Familial disorders such as von Hippel-Lindau syndrome or hereditary telangiectasia

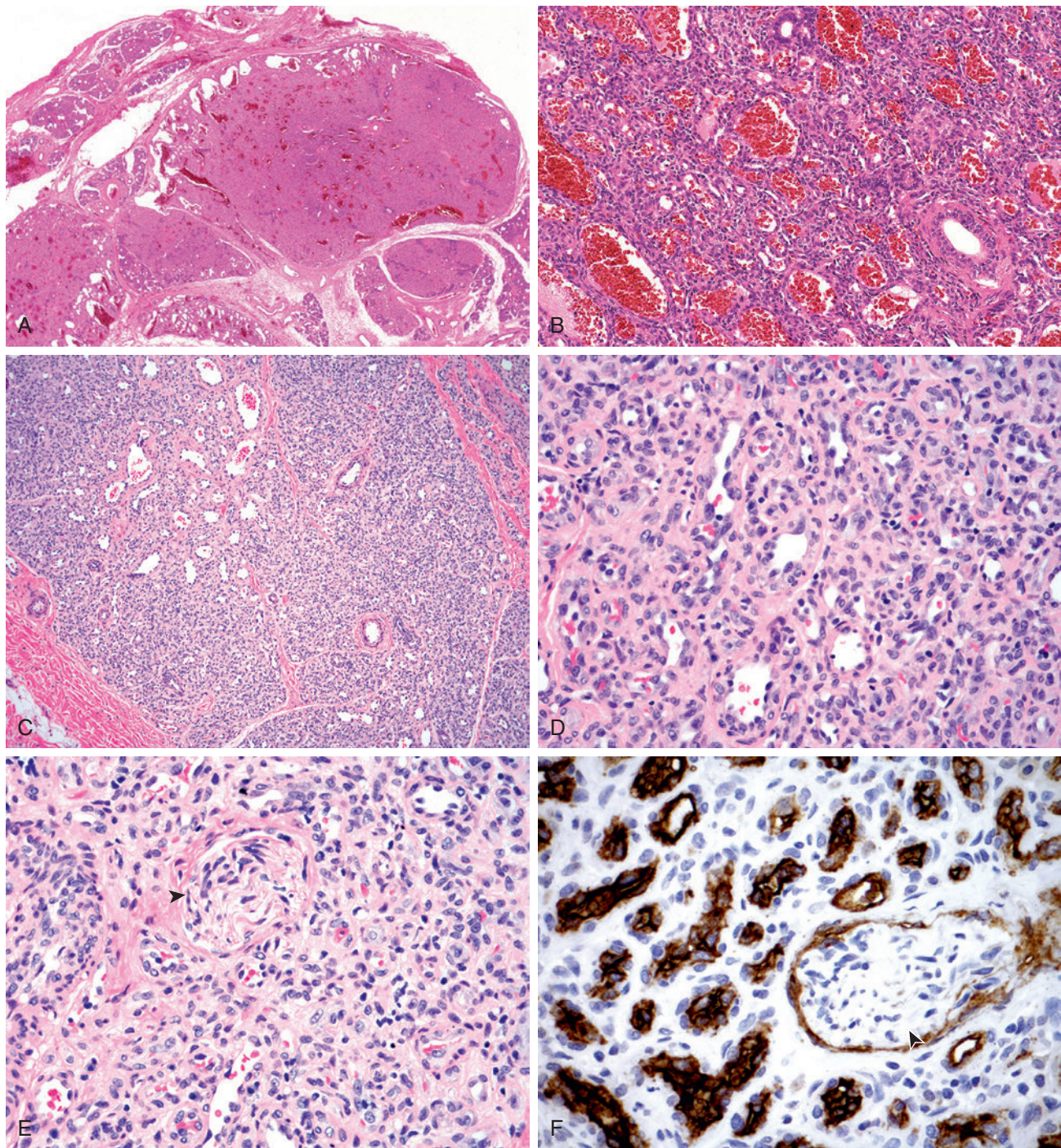


Fig. 20-46. Infantile hemangioma involving the parotid gland.

A, The tumor is unencapsulated, multilobular, and cellular with intralobular growth. **B**, Variably sized blood-filled vascular channels replacing the salivary gland parenchyma; despite replacement by a cellular proliferation, residual ducts and acini remain identifiable. **C** and **D**, The tumor is composed of capillary-sized vessels, although many of the vascular lumina are compressed and indistinct due to increased cellularity. **E**, Neural pseudoinvasion (*arrowhead*) characterized by the presence of lesional capillaries located around nerves; this is a common finding and essentially diagnostic feature and is not indicative of malignancy. **F**, In addition to typical immunoreactivity for endothelial cell markers including CD31, CD34, and Factor 8–related antigen (not shown), lesional cells are characteristically reactive for glucose transporter 1 (GLUT1). Note the absence of expression in a nerve (*arrowhead*) surrounded by tumor, but GLUT1 expression is seen in peripherally situated normal perineurial cells, which is a consistent finding.

- Immunohistochemistry:
 - Lesional cells are immunoreactive for:
 - Glucose transporter protein isoform 1 (GLUT1)
 - Presence of GLUT1 reactivity (as well as other markers including Lewis Y antigen, Fc gamma receptor II, merosin, and others) is similar to that of the vasculature of the placenta demonstrating that infantile hemangiomas have a placenta-associated phenotype (**NOTE:** there is an absence of trophoblastic elements and villous architecture) in infantile hemangiomas
 - CD31, CD34, factor VIII–related antigen
- A minority (approximately 15%) of cases, vascular lesions may be relatively prominent at birth following a static or rapidly involuting course referred to as congenital nonprogressive hemangiomas, which are further subdivided into:
 - Rapidly involuting congenital hemangioma (RICH)
 - Noninvoluting congenital hemangioma (NICH)
- Congenital nonprogressive hemangiomas are histologically and immunophenotypically distinct from infantile hemangiomas:
 - Overall histology of lesional cellular proliferation similar to that of infantile hemangioma
 - In contrast to infantile hemangioma:
 - Tumor lobules are separated by dense fibrous tissue rather than normal tissue elements and/or stroma.
 - Sclerosis often extends into tumor lobules.
 - In cutaneous sites (most common location) there is skin atrophy with loss of dermal adnexal appendages.
 - Small foci of extramedullary hematopoiesis can be found.
 - Small arterial feeders can be found but typically lack intralobular central feeding artery.
 - Absence of neural pseudoinvasion
 - Absence of GLUT1 immunoreactivity as well as other markers that may suggest a placenta-associated phenotype
- With regression there is increased interstitial fibrosis; infarction secondary to thrombosis may be present.
- Immunohistochemistry:
 - Factor VIII–related antigen, *Ulex europaeus*, CD31, and CD34 positive
 - Glucose transporter protein isoform 1 (GLUT1) negative
- Tendency to occur in older children and adults
- Female predilection
- Primarily involve parotid gland
- Involve the extralobular connective tissue
- Characterized by presence of dilated, thin-walled vessels lined by flattened endothelial cells
- GLUT1 negative
- Do not regress and therefore requires complete surgical excision
- Lymphatic malformation (lymphangioma/cystic hygroma):
 - See Section 4, Neck, for more complete discussion.
 - Involvement of the parotid gland is less common than hemangiomas.
 - Most occur during childhood.
 - Histology is similar to lymphangiomas of more common locations, including the presence of variably sized, endothelial-lined spaces with or without intraluminal eosinophilic material, and surrounding collagenous stromal tissue
 - Complete surgical resection is the preferred treatment.
- Epithelioid hemangioma:
 - Formerly referred to as angiolymphoid hyperplasia with eosinophilia
 - Rarely involves salivary glands
 - See Section 7, Ear and Temporal Bone, for complete discussion.
- Angiosarcoma
- Kaposi sarcoma
- Hemangioendothelioma

Treatment and Prognosis

- Majority (75% to 90%) involute by 7 years of age; current recommendation in absence of an enlarging neoplasm with compromise of external ear canal and/or facial distortion, is delay surgery until an older age in the hope that the tumor will involute (spontaneously regress) over time.
 - Regression (involution) may occur in phases, initially slowly over the first 5 years of life and then with continuous regression through the first decade of life.
- Variable success has been reported with the use of corticosteroids, interferon, and compression therapy.
- (Oral) propranolol has replaced corticosteroids as preferred first-line therapy for management of infantile hemangiomas:
 - >94% of patients demonstrate response to treatment with size reduction, color changes, softened texture, and/or healing of ulceration.
 - Topical β -blocker timolol now an alternative to oral propranolol with watchful waiting for smaller infantile hemangiomas

Differential Diagnosis

- “Adult” hemangiomas:
 - May uncommonly be identified in salivary glands and are noted for:

- In presence of a rapidly enlarging lesion and/or disfiguring lesion complete surgical excision is preferred treatment with preservation of the facial nerve
 - Facial nerve in infants is in a more superficial location than in an older age; therefore surgical intervention in infancy may be associated with a greater incidence of damage to the facial nerve.
- Rarely, life-threatening growth may occur:
 - In this situation, preoperative combined radiation and chemotherapy may be indicated.
- Malignant transformation does not occur.

MALIGNANT NEOPLASMS

MUCOEPIDERMOID CARCINOMA (MEC)

(Figs. 20-47 through 20-56)

Definition: Malignant epithelial salivary gland neoplasm composed of a variable admixture of epidermoid, mucous, and intermediate cells.

- No benign counterpart, so the presence of a neoplasm with a marked cellular proliferation including requisite cell types is diagnostic for MEC, whether invasive or noninvasive

Clinical

- Most common malignant salivary gland tumor and second to pleomorphic adenoma as most frequent occurring neoplasm among all salivary gland tumors:
 - Represents approximately 30% of all malignant salivary gland tumors of major and minor salivary glands
 - Represents approximately 10% to 15% of all salivary gland neoplasms
- Slightly more common in women than in men; occurs over a wide age range but most frequently seen in the third to seventh decades of life with a mean age in the fifth decade of life:
 - In pediatric age group, MEC represents most common malignant salivary gland neoplasm, in particular in the second decade of life
- Occurs in major and minor salivary glands:
 - Slightly more than 50% occur in major salivary glands:
 - Among major glands, MEC by far is most common in parotid gland (45%) followed (much less frequently) by the submandibular gland (7%) and then sublingual gland (1%).
 - Most common minor salivary gland site of involvement is palate; additional minor salivary gland sites of occurrence in decreasing order include the buccal mucosa, lips (lower > upper), retromolar region, and tongue (base of tongue)
 - May occur in sinonasal tract and nasopharynx but are considered uncommon in these sites
- Clinical presentation in major glands may vary according to histologic grade:

- For low-grade and intermediate-grade MEC:
 - Slow-growing, solitary, painless mass
- For high-grade MEC:
 - Generally presents as rapidly enlarging, painful mass
- Additional symptomatology may include drainage from the ipsilateral ear, dysphagia, trismus, and facial paralysis.
- Two thirds of patients are asymptomatic.
- In the majority of patients, the duration of symptoms is within a 6-month period of time and average period is 1½ years.
 - Duration of symptoms may be greater, including years to decades
- In minor salivary glands symptoms may include pain, paresthesia, numbness, dysphagia.
- Etiology:
 - May be related to prior therapeutic radiotherapy with latent periods from the time of radiation to the head and neck to the development of a MEC of 7 to 32 years
 - Human papillomavirus (HPV):
 - Recent studies implicated HPV as a cause of MEC.
 - However, other studies using RNA in situ hybridization targeting high-risk HPV mRNA E6/E7 transcripts did not detect HPV in any MECs with or without MAML2 rearrangement (see below).
 - High-risk HPV does not appear to play any significant role in the development of MEC.

Pathology

Gross

- Unencapsulated or incompletely encapsulated, delineated to invasive, round to oval, predominantly solid, tan-white to pink mass measuring from less than 1 cm up to 12 cm in greatest dimension
- Cysts of variable size and prominence can be seen on sectioning of the tumor.
- Mucosal lesions (e.g., palate) may appear as bluish swelling underneath an intact mucosa and simulate the appearance of a mucocele; less often, mucosal



Fig. 20-47. Mucoepidermoid carcinoma.

A, Mucoepidermoid carcinoma of the parotid gland appearing as large ovoid mass at the angle of the mandible. The tumor was slowly enlarging and painless.

B, The resected and transected specimen revealing a poorly delineated solid and cystic neoplasm; cystic spaces were filled with clear to blood-tinged fluid. Histologically, the tumor proved to be low grade.

tumors may have a papillary or granular-appearing surface mucosa.

Fine-Needle Aspiration Biopsy (FNAB)

- Low-grade MEC:
 - Due to cystic nature aspirates may be acellular or hypocellular.

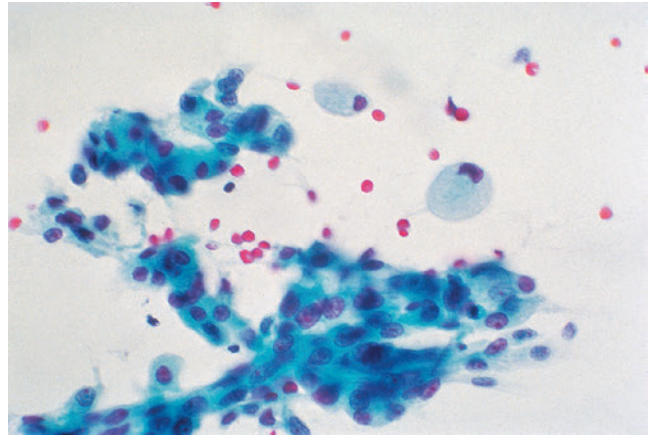


Fig. 20-48. Low-grade mucoepidermoid carcinoma, fine-needle aspiration biopsy.

The aspirate includes aggregates of cells, including epidermoid cells and scattered mucocytes; in addition, intermediate cells composed of bland cells with round to oval nuclei are present. These findings are diagnostic for low-grade mucoepidermoid carcinoma.

- Extracellular mucin may be the dominant finding:
 - May simulate the appearance of the mesenchymal component of pleomorphic adenoma but in contrast to mesenchymal component of pleomorphic adenomas, mucin:
 - Does not appear fibrillar
 - Does not stain as intensely
- Aggregates of cells, including epidermoid cells and mucocytes (mucus-secreting cells):
 - Epidermoid cells:
 - May appear relatively bland and result in the false impression of a nonneoplastic lesion or a benign neoplasm
 - Mucocytes:
 - Cells with distended cytoplasm and or perinuclear vacuoles due to presence of mucin
 - Mucin appears as intracytoplasmic, red granular material by Romanowsky staining.
 - Due to intracytoplasmic mucin the nucleus is eccentrically located.
 - In histologic sections mucocytes often represent a small percentage of the neoplastic cells, so they also tend to be limited by FNAB.
 - Predominantly cystic MECs often have a larger percentage of mucocytes, which translates into more readily identifiable mucocytes by FNAB.
- Intermediate cells appear as bland cells with round to oval nuclei with moderate amount of cytoplasm.

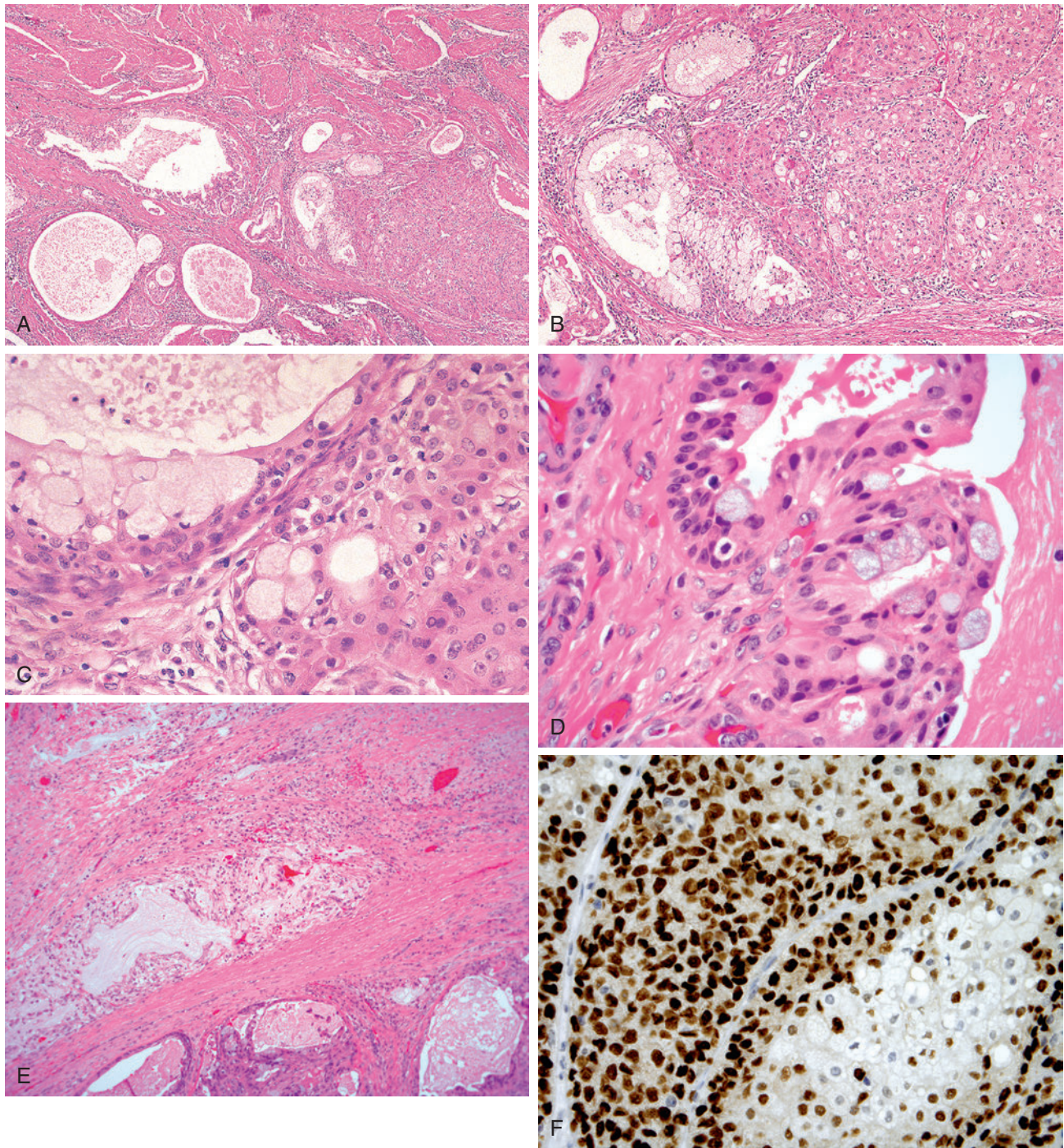


Fig. 20-49. Low-grade mucoepidermoid carcinoma, parotid gland.

A and B, Infiltrative cystic and solid neoplasm with readily identifiable and numerous mucocytes. **C and D,** At high magnification the neoplasm is comprised of an admixture of mucous cells, epidermoid cells characterized by polygonal shaped cells with eosinophilic cytoplasm and smaller more hyperchromatic-appearing intermediate cells with less cytoplasm. **E,** Extravasated mucin into fibroconnective tissue with associated inflammatory cell infiltrate and fibrosis. **F,** Epidermoid cells are diffusely and strongly p63 positive (nuclear staining) but mucocytes are negative for p63.

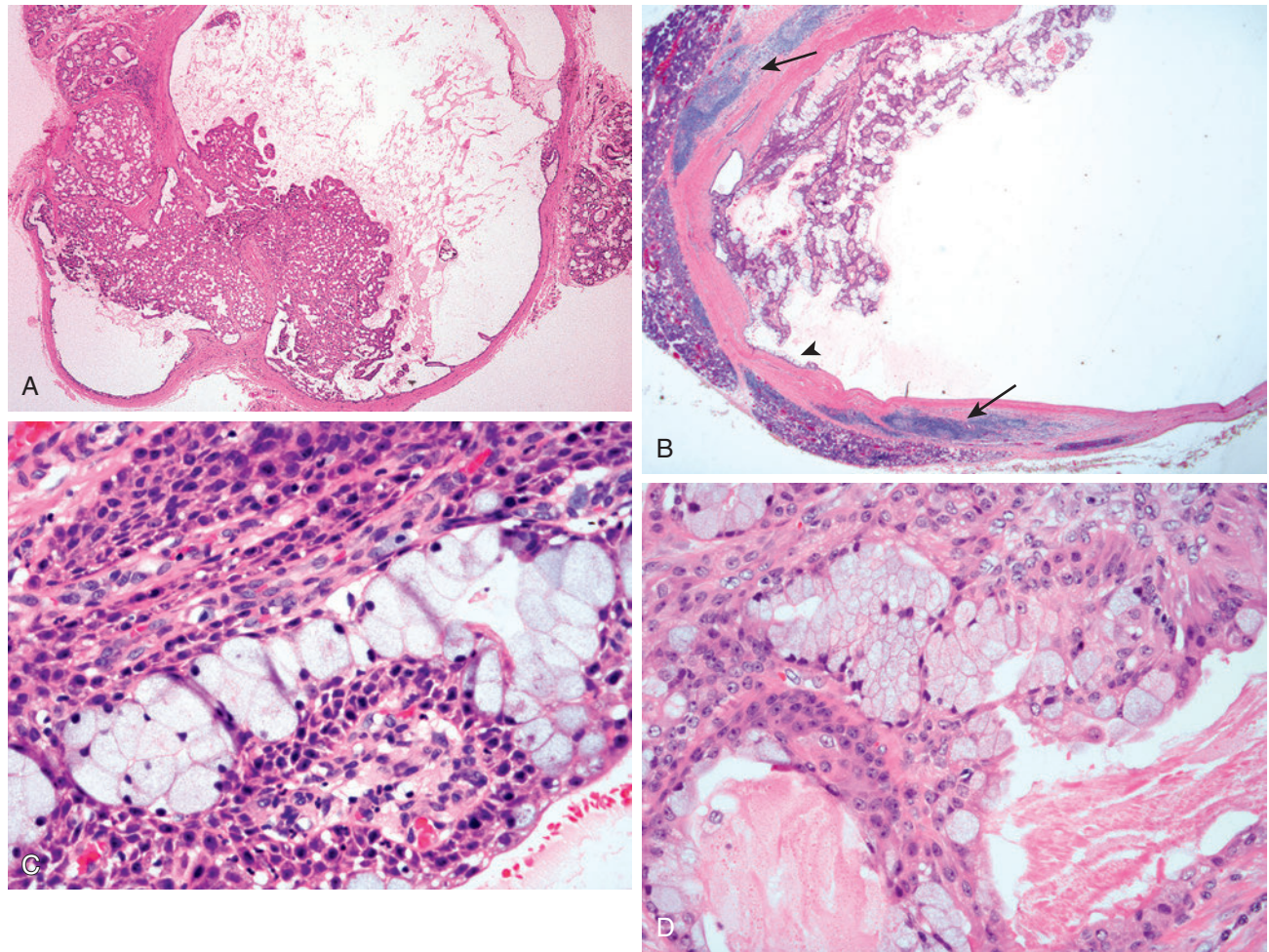


Fig. 20-50. Cystic low-grade mucoepidermoid carcinoma.

A, Encapsulated predominantly cystic lesion with area of more densely cellular intracystic proliferation with solid, papillary, and cribriform growth; focally, the tumor is separate from the parotid parenchyma (extreme right) but is infiltrative into the cyst wall (*arrow*), extending toward uninvolved parotid parenchyma. Although too difficult to appreciate at this magnification the remainder of the cyst is lined by a cuboidal epithelium lacking the overall diagnostic features for mucoepidermoid carcinoma. **B**, Another predominantly cystic encapsulated neoplasm with area of more densely cellular intracystic proliferation; tumor-associated lymphoid proliferation (TALP) is present (*arrows*) lying in between the cystic tumor and the surrounding parotid gland. The remainder of the cyst is lined by nondescript cuboidal epithelium focally exclusively comprised of mucous cells (*arrowhead*) lacking the overall diagnostic features for mucoepidermoid carcinoma. **C** and **D**, Proliferative areas comprised of an admixture of mucous cells, epidermoid cells, and intermediate cells diagnostic for mucoepidermoid carcinoma. In the presence of invasive growth the diagnosis is readily established but even in the absence of invasion, the presence of mucous cells, epidermoid cells, and intermediate cells would be diagnostic for mucoepidermoid carcinoma.

- High-grade MEC:
 - Readily identifiable as malignant but due to the scarcity of mucocytes even in tissue sections, a specific diagnosis of high-grade MEC may not be achievable.
 - In face of an aspirate with obviously high-grade malignant cytology, a definitive diagnosis of MEC is less important as the treatment for high-grade malignant epithelial tumors of the salivary glands should be similar.

Histology

- Characteristic features for all histologic grades (see below) include the presence mucous cells (mucocytes), epidermoid cells, and intermediate cells:
 - Mucous cells identified lining cystic spaces or admixed within nests or solid areas with epidermoid cells are large, ovoid, goblet, balloon-shaped, or columnar cells with distinct cell borders composed of pale-staining or

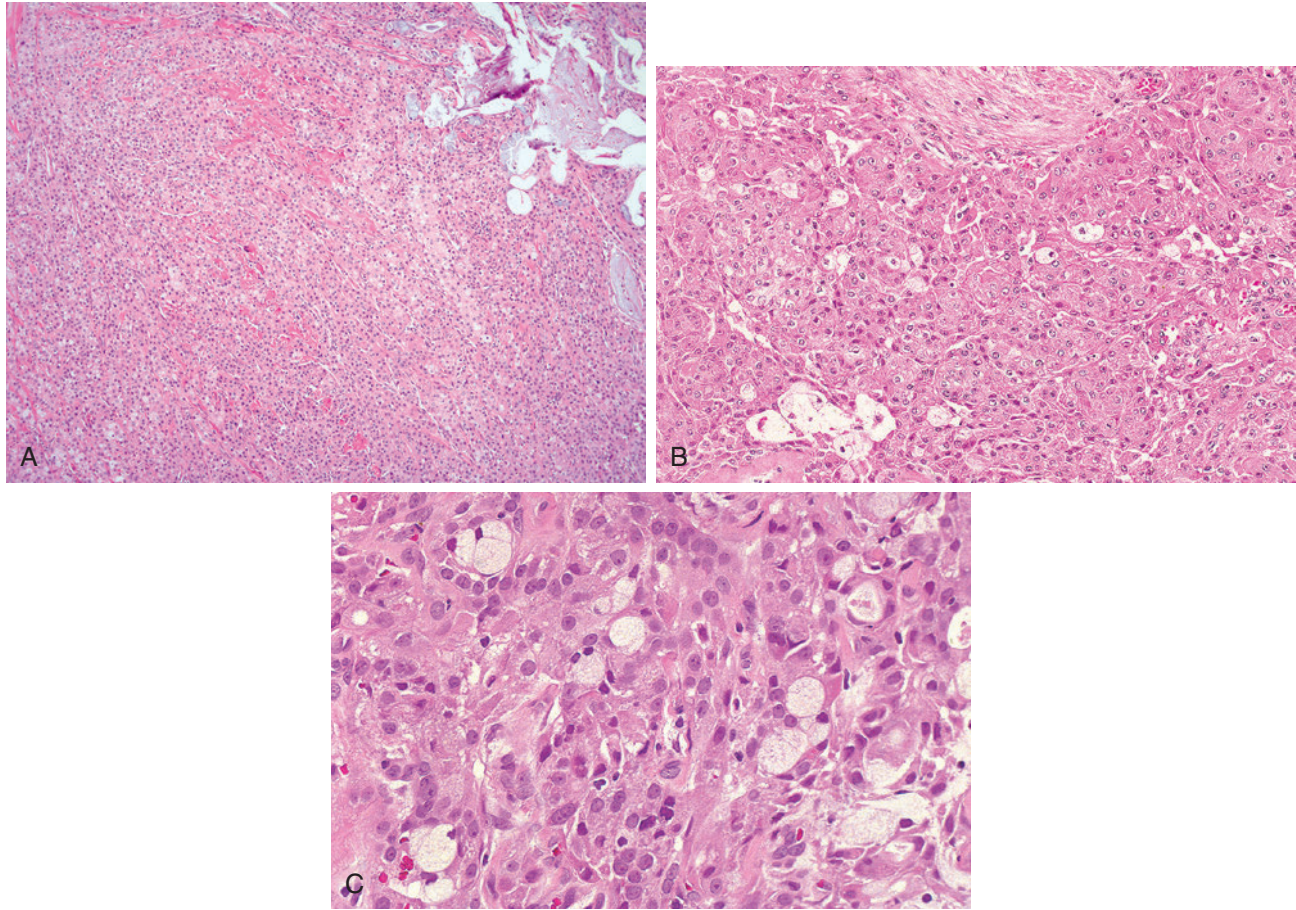


Fig. 20-51. Intermediate-grade mucoepidermoid carcinoma.

A, In comparison with low-grade tumors, intermediate-grade mucoepidermoid carcinomas are more solid and predominantly composed of epidermoid cells with residual cystic foci that include mucous cells (*upper right*). **B,** There is a shift in the ratio of mucous cells to epidermoid and intermediate cells with a larger percentage of the latter cells identified. **C,** In comparison to the low-grade cancers the cells in intermediate grade show a greater degree of nuclear pleomorphism as compared with low-grade mucoepidermoid carcinoma but significantly less nuclear pleomorphism, mitotic activity, and necrosis as compared with high-grade mucoepidermoid carcinoma.

- foamy-appearing cytoplasm with peripherally placed, small, dark staining nuclei:
 - Most numerous and readily identifiable in low-grade MEC
 - Less numerous but still readily identifiable in intermediate-grade MEC
 - Least numerous and not readily identified without histochemical staining (e.g., mucicarmine, PAS with diastase) in high-grade MEC
- Epidermoid cells form nests and/or solid areas have a pavement-like arrangement and are polygonal with vesicular nuclei and abundant eosinophilic cytoplasm.
 - In some examples epidermoid cell differentiation may be focal and limited in extent.
 - Individual cell keratinization and keratin pearl formation may be seen but are considered uncommon.
- Keratin (squamous) pearls, extensive keratinization, and intercellular bridges do not predominate.
- Foci of keratinization (individual cell and/or keratin pearl formation) may occur in inflamed tumors.
- Absence of keratin (squamous) pearls, extensive keratinization, and intercellular bridges assist in separating mucoepidermoid carcinoma from such tumors as adenosquamous carcinoma.
- Intermediate cells include both small basal cells and larger polygonal cells appearing in clusters of solid sheets or scattered and admixed with the other cell types:
 - Basal cells: characterized by the presence of round to oval, small, dark-staining nuclei and scanty, eosinophilic cytoplasm



Fig. 20-52. Mucoepidermoid carcinoma.

High-grade mucoepidermoid carcinoma appearing as a large, ulcerating and necrotic hard palate mass.

- Larger polygonal cells: round to ovoid cells with vesicular chromatin and more abundant cytoplasm
- Transitional areas from smaller basal cells to larger polygonal cells can be seen.
- Other cell types that may be seen include:
 - Clear cells composed of round to oval cells with distinct cell borders, peripherally placed, small, dark nuclei and their hallmark clear cytoplasm:
 - May range from very focally identified to predominating (i.e., clear cell variant, see below)
 - Oncocytic cells characterized by presence of a brightly eosinophilic and granular-appearing cytoplasm
 - Often can be seen focally and occasionally predominate (i.e., oncocytic variant, see below)
 - Columnar cells can be seen lining cysts and duct-like structures and tend to be less numerous than mucous cells.

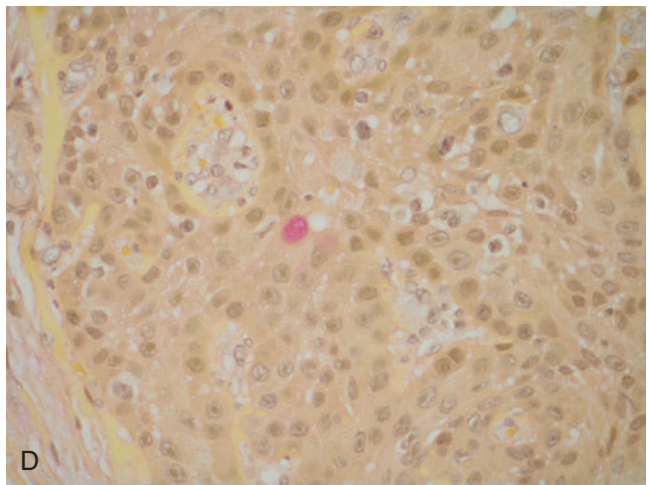
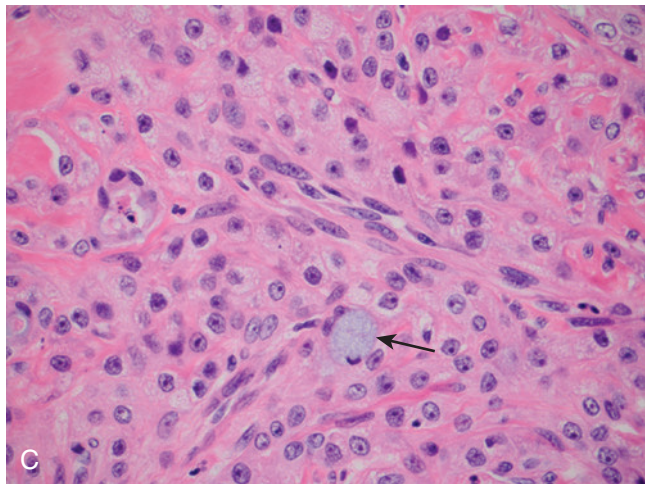
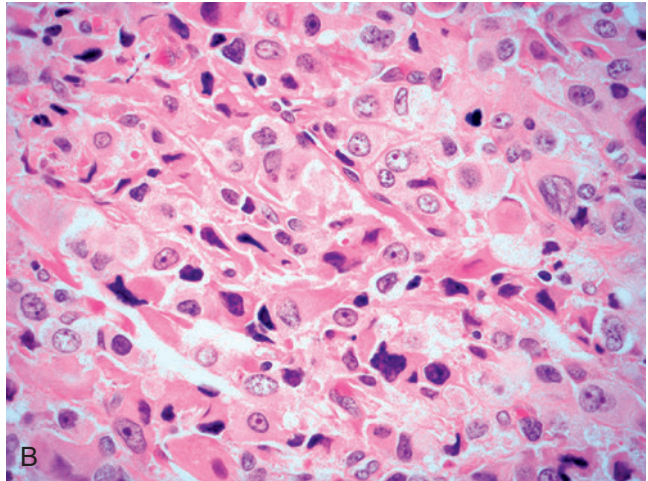
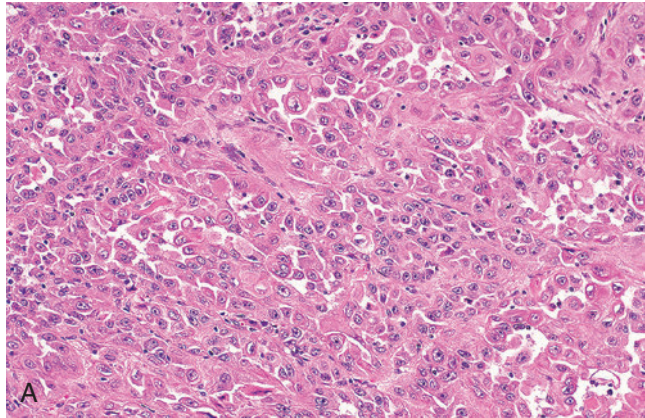


Fig. 20-53. High-grade mucoepidermoid carcinoma.

A, Neoplastic proliferation with solid growth composed of epithelial cells. **B**, Marked nuclear pleomorphism with increased mitotic activity. **C**, Rare mucocytes (*arrow*) may be seen by light microscopy. **D**, Intracytoplasmic mucicarmine positive material.

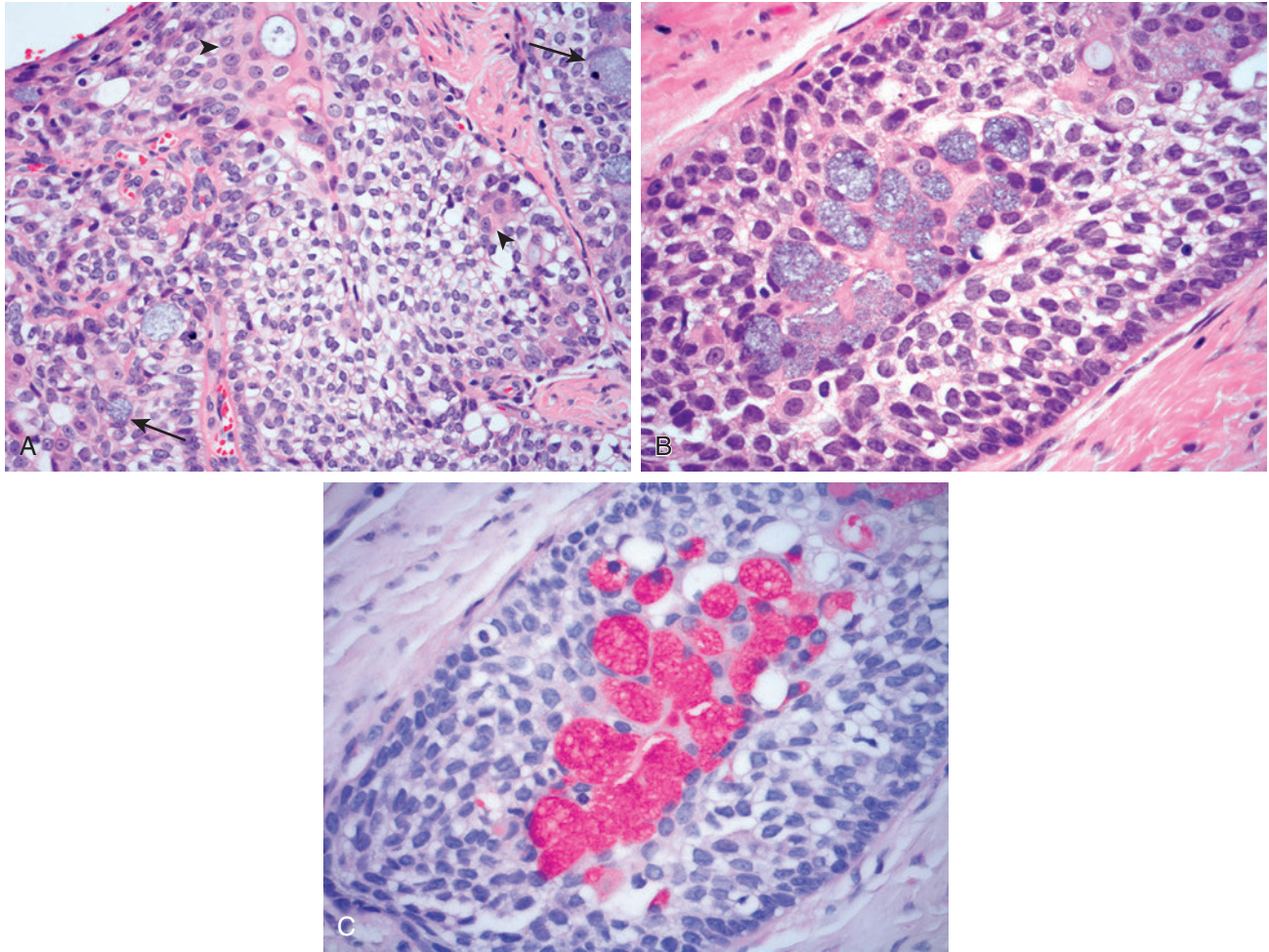


Fig. 20-54. Clear cell variant of mucoepidermoid carcinoma.

A, Cellular components predominated by cells with clear cytoplasm with admixed foci of epidermoid cells (*arrows*) and mucous cells (*arrowheads*). **B,** Higher magnification shows predominant clear cell component with identifiable mucocytes. **C,** Mucocytes show the presence of intracytoplasmic mucin-positive material but the clear cells are mucicarmine negative. The clear cells contain glycogen as evidence of the presence of diastase-sensitive, PAS-positive material (not shown).

- Spindle-shaped cells may focally be present.
- Rarely pigmentation (melanin-containing) cells may be present.
- Tumors may be encapsulated or unencapsulated with or without invasion:
 - Diagnosis of MEC can be established even in the absence of invasive growth based on identifying the constituent cell types (see above):
 - Benign neoplastic counterpart to MEC composed of mucous cells, intermediate cells, and epidermoid cells not known to exist
 - Encapsulated (noninvasive) MECs tend to be histologically lower grade.
 - Benign nonneoplastic lesions as well as benign neoplasms may be cystic and composed of
 - varying cell types, including mucocytes and epidermoid cells:
 - Degree of cellular proliferation is much greater in MEC than in these other lesions.
 - Intermediate cells are typically absent in these nonmalignant lesions but may also be difficult to appreciate in MECs
- Growth patterns include predominantly cystic, predominantly solid, or admixture of cystic and solid:
 - Additional growth patterns may include papillary, glandular, or duct-like:
 - Cysts are lined by mucous, columnar, and epidermoid cells.
 - Origin from duct epithelium may occasionally be identified.

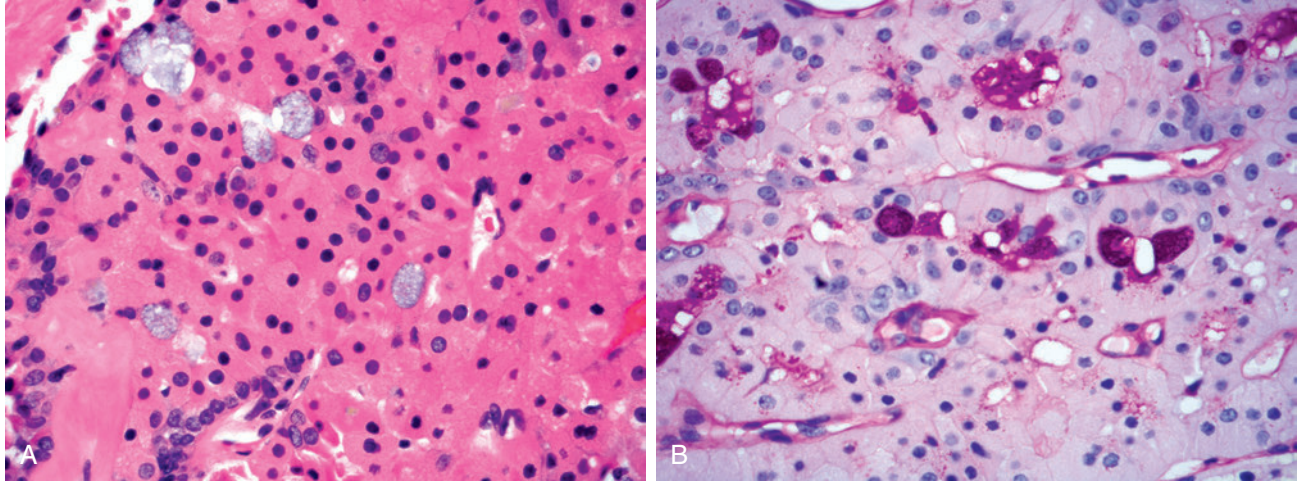


Fig. 20-55. Oncocytic cell variant of mucoepidermoid carcinoma.

A, The tumor is predominated by cells with oncocytic cytoplasmic change but scattered identifiable mucous cells are present. **B**, The mucocytes show the presence of intracytoplasmic diastase-resistant, PAS-positive material. The presence of mucocytes usually would differentiate oncocytic mucoepidermoid carcinoma from other oncocytic lesions/neoplasms (e.g., oncocytoma, oncocytic carcinoma). Residual foci of usual mucoepidermoid carcinoma, including epidermoid cells, mucous cells, and intermediate cells (which may or may not be present) and/or diffuse p63 reactivity would confirm a diagnosis of oncocytic MEC.

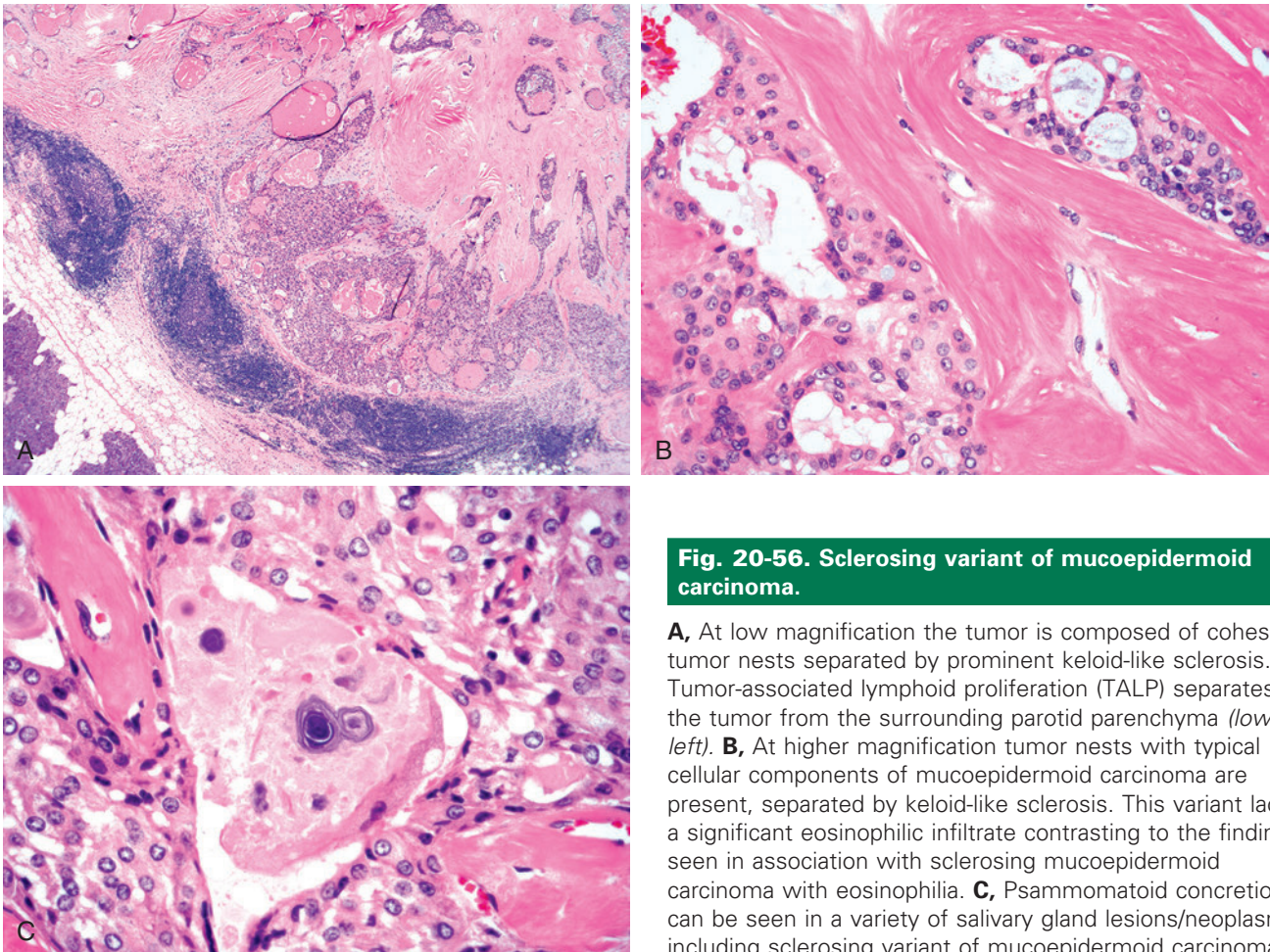


Fig. 20-56. Sclerosing variant of mucoepidermoid carcinoma.

A, At low magnification the tumor is composed of cohesive tumor nests separated by prominent keloid-like sclerosis. Tumor-associated lymphoid proliferation (TALP) separates the tumor from the surrounding parotid parenchyma (*lower left*). **B**, At higher magnification tumor nests with typical cellular components of mucoepidermoid carcinoma are present, separated by keloid-like sclerosis. This variant lacks a significant eosinophilic infiltrate contrasting to the findings seen in association with sclerosing mucoepidermoid carcinoma with eosinophilia. **C**, Psammomatoid concretions can be seen in a variety of salivary gland lesions/neoplasm, including sclerosing variant of mucoepidermoid carcinoma.

- Stroma is often fibrous and may be sclerotic/hyalinized:
 - Tumors with extensive stromal sclerosis have been referred to as sclerosing MEC (see below).
- Prominent lymphoid tissue with or without lymphoid follicles may be evident:
 - Referred to as tumor-associated lymphoid proliferation (TALP)
 - TALP may lead to mistaken interpretations of primary tumors as nodal metastasis or benign lymphoepithelial lesion.
 - Primary salivary gland tumors including MEC may originate from salivary gland parenchyma incorporated within peri- and intranodal lymph nodes; as such, TALP must be differentiated from tumor within a lymph node.
 - Presence or absence of a subcapsular sinus will differentiate bona fide lymph node parenchyma (with subcapsular sinuses) from non-lymph node parenchyma (without subcapsular sinuses).
- Intraluminal mucus can be seen in cysts and/or gland-like structures:
 - Extravasation of mucin appearing as extracellular mucous pools or “cysts” may be seen.
- Cellular pleomorphism, mitoses, necrosis, and hemorrhage are generally absent:
 - Such findings when identified are more common in histologically higher-grade tumors.
- A variable degree of local invasion may be seen:
 - Invasion into surrounding cyst wall, fibroconnective tissue, residual nonneoplastic salivary gland parenchyma often is present
 - Such invasive growth essentially similar irrespective of histologic grade

- Perineural and/or lymph-vascular invasion may be identified:
 - More commonly seen in histologically higher-grade MEC

Histologic (Microscopic) Grading

- Three histologic grades recognized:
 - Low grade
 - Intermediate grade
 - High grade
- Basis for histologic grading into low, intermediate, and high categories dependent on:
 - Architectural growth pattern
 - Cellular components
 - Cytomorphology
- Microscopic grading remains subject of debate
- Criteria for histologic grading include (single or in combination):
 - Proportion of the tumor composed of cystic spaces relative to solid growth
 - Proportion of cell types
 - Degree of maturation of cell types
 - Mitotic rate
 - Extent of invasiveness, including pattern of invasion, neurotropism, and vascular space invasion
 - Presence of necrosis
- A quantitative grading system based on specific histologic features suggested (Table 20-5):
 - According to Armed Forces Institute of Pathology (AFIP) grading scheme:
 - 0 to 4 are considered low grade (Grade I)
 - 5 to 6 are considered intermediate grade (Grade II)
 - 7 or more are considered high grade (Grade III)

TABLE 20-5 Mucoepidermoid Carcinoma: Microscopic Grading

Feature	Grade	Tumor Grade	Point Score
<i>Auclair et al[*]; Goode et al[†]</i>			
Intracystic component less than 20%	2	Low-grade	0-4
Neural invasion	2	Intermediate-grade	5-6
Necrosis	3	High-grade	7 or more
Four or more mitoses	3		
Anaplasia	4		
<i>Brandwein et al[‡]</i>			
Intracystic component less than 25%	2	Low-grade	0
Tumor front invades in small nests and islands	2	Intermediate-grade	2-3
Pronounced nuclear atypia	2	High-grade	4 or more
Lymph-vascular invasion	3		
Bony invasion	3		
Four or more mitoses	3		
Perineural invasion	3		
Necrosis	3		

*Cancer 69:2021-2030, 1992.

†Cancer 82:1217-1224, 1998.

‡Am J Surg Pathol 25:835-845, 2001.

- According to Brandwein et al grading scheme:
 - 0 are considered low grade (Grade I)
 - 2 to 3 are considered intermediate grade (Grade II)
 - 4 or more are considered high grade (Grade III)
- Most useful features for histologic grading, particularly in predicting high-grade tumors, include:
 - Intracystic component of less than 20% (predominantly solid growth)
 - Four or more mitotic figures per 10 high-power fields
 - Cellular anaplasia, necrosis, neural invasion, angioinvasion, and osseous invasion
- With exceptions, typical histologic features associated with different histologic grades include:
 - Low grade:
 - Numerous cystic spaces
 - All three cell types identified including numerous/readily identifiable mucocytes
 - Overall absence of nuclear pleomorphism, increased mitotic activity, and necrosis
 - Absence of perineural invasion
 - Intermediate grade:
 - Predominantly solid but still cystic
 - Composed of all three cell types perhaps with greater percentage of epidermoid cells and less percentage of mucocytes
 - Greater degree of nuclear pleomorphism as compared to low-grade MEC but significantly less nuclear pleomorphism, mitotic activity, and necrosis as compared with high-grade MEC
 - High grade:
 - Diffuse sheet-like or solid growth
 - Cystic spaces make up less than 20% of the tumor or
 - Cellular anaplasia with marked nuclear pleomorphism, increased mitotic activity, including atypical mitoses and necrosis
 - Limited identifiable mucocytes
 - Tend to be extensively infiltrative, including perineural invasion and lymph-vascular invasion
- Percentage of cell types do not necessarily correlate with behavior.
- Histochemistry:
 - Mucocytes:
 - Intracytoplasmic diastase-resistant, PAS-positive, and mucicarmine-positive staining
 - Gland-like spaces:
 - Intraluminal diastase-resistant, PAS-positive, and mucicarmine-positive staining
 - Epidermoid cells may be faintly PAS positive but are mucicarmine negative.
 - Intermediate cells and clear cells show no staining with either PAS or mucicarmine.
- Immunohistochemistry:
 - Cytokeratin (pancytokeratin, CK5/6, others) and epithelial membrane antigen (EMA) positive
 - p63 positive (strong nuclear staining)
 - S100 protein, calponin, glial fibrillary acidic protein, muscle-specific actin, and carcinoembryonic antigen are at best variably positive and more often negative.
 - May be mammaglobin positive but typically focal lacking moderate to strong staining in significant proportion of cells (i.e., more than 25%)
 - GATA3 (nuclear) staining may be present but when present is focal rather than diffuse:
 - Diffuse GATA3 staining in salivary gland neoplasm typically limited to salivary duct carcinoma and mammary analogue secretory carcinoma
 - Androgen receptor negative
 - *HER-2* overexpression typically absent
 - Sox10 negative
 - Express membrane-bound mucins, including:
 - MUC1, MUC4, MUC5AC, and MUC5B
- Electron microscopy:
 - Presence of two cell types, including luminal cells with microvilli, goblet cell formation, and mucus secretion, and the nonluminal intermediate cells felt to represent the counterpart of the modified myoepithelial cells seen in mixed tumors
- Cytogenetics and molecular biology:
 - Mucoepidermoid carcinoma translocated 1 (*MECT1*) and mastermind-like gene family (*MAML2*) translocation located at chromosome 19p13 and 11q21 represent most frequent genetic alteration
 - Detected by RT-PCR or fluorescence in situ hybridization
 - Identified in large proportion of MEC
 - Present in 66% MEC
 - 100% non-MEC negative for translocation
 - Low- to intermediate-grade MEC higher frequency of translocation (75%) than high-grade MEC (46%)
 - *CRTC1* (CREB-regulated transcription coactivator-1) used in place of *MECT1*
 - Presence of *CRTC1-MAML2* translocation identified as useful adjunct to histologic scoring as prognostic indicator:
 - Low-grade, fusion-positive MEC with no or few genomic imbalances and favorable prognosis
 - High-grade, fusion-positive MEC with multiple genomic imbalances and unfavorable prognosis
 - Heterogeneous group of high-grade, fusion-negative adenocarcinomas with multiple

genomic imbalances and unfavorable outcome

- A less common gene fusion includes *CRTC3* (CREB-regulated transcription coactivator-3) on chromosome 15q26 and *MAML2*:
 - Associated with favorable prognosis
- *PLAG1* translocation negative
- *ETV6* translocation negative

Histologic Variants of MEC

Clear Cell Variant

- Characterized by predominance of large cells with clear-appearing cytoplasm and discrete cell membranes
- Residual foci of usual or classic MEC typically present including mucocytes containing epithelial mucin
- Typically histologically low-grade lacking significant nuclear pleomorphism, increased mitotic activity, and necrosis
- Histochemical stains show the presence of intracytoplasmic diastase-sensitive, PAS-positive material indicative of glycogen
- Mucicarmine negative
- Cytokeratins and p63 positive
- *EWSR1-ATF1* gene fusion identified in clear cell carcinoma of salivary glands is negative in clear cell variant of MEC.
- More common variant relative to palate MEC

Oncocytic Variant

- Characterized by cells with abundant granular eosinophilic cytoplasm (i.e., oncocytes) but percentage of oncocytic cells necessary for diagnosis not well defined
- Predominantly solid growth pattern
- Scattered mucocytes containing epithelial mucin (mucicarmine and/or diastase-resistant, PAS-positive) identified:
 - Presence of mucocytes usually but not always differentiates oncocytic MEC from other oncocytic lesions/neoplasms that may rarely contain such cells, including:
 - Oncocytosis, oncocytoma, oncocytic carcinoma
 - Presence of foci of classic MEC and/or diffuse p63 reactivity assist in confirming diagnosis of oncocytic MEC
- Typically lack significant nuclear pleomorphism, increased mitotic activity, and necrosis
- Residual foci of usual or classic MEC may or may not be present.
- *CRTC1-MAML2* translocation present
- In spite of solid growth, this variant is histologically (and biologically) low grade:
 - Single reported case purportedly of a high-grade oncocytic MEC

- Predominantly but not exclusively a parotid gland neoplasm:
 - May occur in submandibular gland and minor salivary glands

Sclerosing Variant

- Histologically typical MEC albeit with prominent central (keloid-like) sclerosis
 - May be paucicellular in areas of sclerosis with more typically neoplastic foci along periphery
- Associated lymphoplasmacytic infiltrate located along periphery of the neoplasm
- Absence of significant eosinophilic infiltrate
- Absolute number of IgG4 plasma cells as well as proportion of IgG4/IgG plasma cells increased in sclerosing MEC as compared with the regular type
- Possible relationship to IgG4-related diseases remains to be determined.

Sclerosing MEC with Eosinophilia

- Rare variant and may be related to sclerosing variant without eosinophilia
- Histologically composed of epithelial nests that may include mucin-containing cells embedded in a sclerotic stroma
- Fibrosclerotic stroma densely infiltrated by chronic inflammatory (lymphoplasmacytic) cells and eosinophils
- Lesional cells may appear squamoid including presence of keratinization.
- Inflammatory infiltrate and stromal fibrosclerosis may also be seen in non-neoplastic salivary gland tissue adjacent to tumor.
- Immunohistochemically, many plasma cells may be IgG4-positive.
- Postoperative serum IgG4 level may be elevated.
- Possible relationship to IgG4-related diseases remains to be determined.

Differential Diagnosis (Table 20-6)

- Low and intermediate MEC:
 - Necrotizing sialometaplasia
 - Non-neoplastic true epithelial cystic lesions, including:
 - Lymphoepithelial cyst and salivary duct cyst
 - Pleomorphic adenoma with squamous and mucous cell metaplasia
 - Metaplastic Warthin tumor
 - Sclerosing polycystic adenosis
 - Cystadenoma and cystadenocarcinoma
 - Acinic cell adenocarcinoma
 - Mammary analogue secretory carcinoma
- High-grade MEC:
 - Conventional squamous cell carcinoma (primary or secondary)
 - Adenosquamous carcinoma

TABLE 20-6 Mucoepidermoid Carcinoma: Differential Diagnosis

	MEC, Low Grade	SCC	NS
Architecture/growth	Haphazard, infiltrative growth; may be encapsulated	Haphazard, infiltrative growth	Retention of lobular architecture
Cellular components	Admixture of mucous, intermediate ("basaloid"), and epidermoid cells; bland cytology; irregular cell nests	Nests and cords of squamous cells characterized by keratinization and intercellular bridges with irregular outlines and variable amount of cytologic atypia; may entrap residual glands but the tumor itself contains no mucin	Smooth round to oval nests of metaplastic squamous epithelium with bland cytology; may show residual ductal lumina with mucous cells
Cyst formation	Present (prominent component)	Absent	Absent
Surface epithelium	Uninvolved; not connected with tumor	Often dysplastic and/or in direct continuity with the carcinoma; may be ulcerated	May show PEH; usually not connected with NS
Extravasated mucin	May be present	Absent	May be present
Necrosis	Absent	May show tumor necrosis	Lobular necrosis of salivary gland acini
Inflammation	May be prominent with mucin extravasation	May be present; associated desmoplasia	May be prominent
Cytogenetics	<i>CRTC1-MAML2</i> translocation	None known	None known

MEC, Mucoepidermoid carcinoma; NS, necrotizing sialometaplasia; PEH, pseudoepitheliomatous hyperplasia; SCC, squamous cell carcinoma.

- Salivary duct carcinoma
- Cystadenoma and cystadenocarcinoma
- Clear cell variant MEC:
 - Clear cell carcinoma
 - Metastatic renal cell carcinoma
- Oncocytic variant MEC:
 - Oncocytosis
 - Oncocytoma
 - Oncocytic carcinoma

Treatment and Prognosis

- Therapy is primarily surgical:
 - Stages I and II treated by:
 - Wide local surgical excision with preservation of the facial nerve (for parotid neoplasms)
 - Patients with partial parotidectomies with clear surgical margins fare as well as patients who undergo total parotidectomies.
 - May recur locally if incompletely excised but metastatic disease infrequently occurs
 - Submandibular gland tumors should be treated by complete surgical glandectomy.
 - Palatal-based lesions that are small (less than 2 cm) and do not involve bone can be managed by wide local excision down to the periosteum with at least 1-cm clear lateral surgical margins:
 - Block excision of underlying bone is done if there is evidence of bone destruction.
 - Regional nodal metastasis for low- and intermediate-grade MECs of major (except submandibular gland) and minor salivary glands considered uncommon not necessarily warranting elective neck dissection unless clinically suspicious neck disease
 - Likelihood of occult cervical lymph node metastasis for patients with clinical N0 salivary gland carcinoma of major and minor salivary glands low and driven predominantly by histologic subtype; reported incidence of 21% (25 of 110):
 - Highest among patients with high-grade MEC and adenocarcinoma, high-grade, not otherwise specified
 - Most common site of cervical lymph node metastasis level II > level III > level IB
 - Adjuvant radiotherapy does not offer any advantage over complete surgical extirpation with free surgical margins for low-grade and intermediate-grade tumors:
 - Radiation may be useful in the local control of disease if residual tumor is found at the surgical margins in a patient no longer amenable to surgery.
 - Due to worse prognosis associated with submandibular gland tumors, combined surgery and radiotherapy have been advocated as the initial planned treatment.
 - High-grade MEC:
 - Treatment depends on clinical stage but in general wide block surgical excision is

preferred treatment, which may necessitate sacrifice of the facial nerve (parotid gland tumors) or the hypoglossal and lingual nerves (submandibular tumors).

- Radical palatotomy is required for palatal-based large lesions with involvement of bone.
- Associated with high rates of recurrence and metastasis and owing to frequency of metastasis to regional lymph nodes, neck dissections are usually included in the surgical management.
- Adjuvant postoperative radiotherapy is advocated for patients with high-stage disease (Stages III and IV), especially for high-grade tumors with tumor margins involved.
- Role of chemotherapy in the treatment of salivary gland carcinomas remains speculative.
- Prognosis:
 - In general, low-stage and/or low-grade and intermediate-grade tumors have excellent prognosis with approximately 90% 5-year survival rates.
 - In children (who have predominantly histologic low-grade and/or low-stage tumors), 5-year overall survival of 98% and 10-year overall survival of 94% reported
 - No difference in outcome reported between low and intermediate grade in all grading schemes
 - Overall 40% 5-year survival rates for high-stage and/or high-grade MEC
- Factors influencing prognosis:
 - Histologic grade influential in prognosis (Table 20-7), with the exception of submandibular gland involvement, which is not felt to be as reliable a predictor of behavior as compared with other salivary gland sites

- Mortality rates based on histologic grade include:
 - For AFIP, mortality rates based on their grading scheme include:
 - Grade I: 0
 - Grade II: 5%
 - Grade III: 46%
 - For Brandwein et al, mortality rates based on their grading scheme include:
 - Grade I: 0
 - Grade II: 5%
 - Grade III: 65%
- *CRTC1-MAML2* fusion-positive MEC, regardless of grade, manifest a more stable genome and better clinical behavior.
- Negative prognostic factors include:
 - High histologic grade
 - Advanced clinical stage
 - Perineural invasion
 - Positive surgical margins
 - Extraparenchymal extension
 - Submandibular location
 - Nodal metastases
 - Distant metastases
 - *CRTC1-MAML2* fusion-negative cases represent distinctly different pathway characterized by marked genomic instability and relatively aggressive tumors
 - Aneuploidy, high proliferation indices (>10%)
 - Increase expression of MUC1 (>75%)

ACINIC CELL CARCINOMA

(Figs. 20-57 through 20-61)

Definition: Malignant epithelial salivary gland neoplasm characterized by a variety of histologic growth patterns and tendency for neoplastic cells to recapitulate appearance of normal serous acinous cells characterized by the presence of cytoplasmic (zymogen type) secretory granules.

Clinical

- Represents approximately 18% of all malignant salivary gland neoplasms and 6.5% of all salivary gland neoplasms
- Slightly more common in women than in men; wide age range from children to older adults with a peak incidence in the seventh decade of life:
 - Approximately 4% occur in children.
 - In children, the majority of cases occurs in the second decade of life.
 - Represents second most common malignant epithelial neoplasm to occur in children; mucoepidermoid carcinoma is most common pediatric malignant salivary gland neoplasm
- Majority of cases (more than 80%) arise in the parotid gland:

TABLE 20-7 Mucoepidermoid Carcinoma: Microscopic Grading and Prognosis

Microscopic Grade	Percent Dead of Disease [§] or Prognosis
<i>Auclair et al</i> [*] ; <i>Goode et al</i> [†]	
Low grade	0
Intermediate grade	5
High grade	46
<i>Brandwein et al</i> [‡]	
Low grade	No recurrences, metastases, or deaths
Intermediate grade	Local recurrence 30%; nodal metastasis 18%; 5% dead of disease
High grade	Local recurrence 70%; nodal metastasis 63%; 65% dead of disease

^{*}Cancer 69:2021-2030, 1992.

[†]Cancer 82:1217-1224, 1998.

[‡]Am J Surg Pathol 25:835-845, 2001.

[§]Reflects cumulative statistics from Auclair et al and Goode et al studies, including major and minor salivary glands.

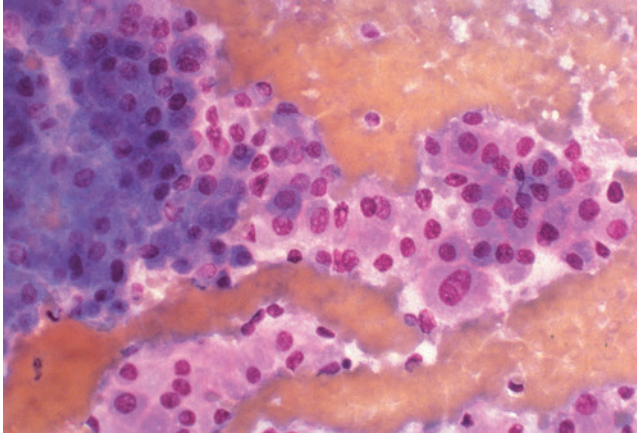


Fig. 20-57. Cytology of acinic cell adenocarcinoma.

Acinic cell adenocarcinoma of the parotid, fine-needle aspiration biopsy. Cellular aspirate composed of serous acinar cells characterized by large cells with round, relatively uniform, centrally situated nuclei, inconspicuous to conspicuous nucleoli, and abundant, granular-appearing cytoplasm.

- Uncommon but may also be identified in the submandibular and sublingual glands
- May also occur in all minor salivary glands, especially those of intraoral sites:
 - Most common intraoral sites are the buccal mucosa and upper lip.

NOTE: Prior to diagnosing acinic cell carcinoma of a nonparotid gland site, exclusion of other diagnostic considerations, especially mammary analogue secretory carcinoma (MASC), is mandatory as many acinic cell carcinomas of nonparotid gland sites have been reclassified as another tumor type (e.g., MASC).

- Bilateral parotid gland, and less often submandibular gland, involvement may uncommonly occur (approximately 3% of cases):
 - Represents most common malignant salivary gland neoplasm to present with bilateral disease
- Most common presentation is that of a slow-growing, solitary mass without fixation to surrounding structures:
 - Associated pain may or may not be present.
 - Facial paralysis may occur in up to 10% of patients.
 - Fixation to surrounding structures may uncommonly occur.
 - Duration of symptoms typically is less than a year but may occur from several years to decades.
- Thought to arise from distal (terminal) portions of the salivary duct system, specifically the intercalated duct reserve/stem cells
- Etiology:
 - No known causes

Pathology

Gross

- Well-demarcated and/or encapsulated, round or multilobulated, soft to rubbery, tan-gray to yellow or pink mass usually measuring from 1 to 3 cm in greatest diameter but occasionally may reach sizes up to 13 cm
- Most neoplasms have homogeneous appearance but may be cystic and hemorrhagic.
- Recurrent neoplasms are less well demarcated and tend to be multinodular in appearance.

Fine-Needle Aspiration Biopsy

- Aspirates tend to be cellular except for the papillary-cystic and follicular variants, which may have low numbers of serous acinar cells.
- Cytologic diagnosis rests on presence of identifying serous acinar cells characterized by:
 - Large cells with round, relatively uniform dark-staining nuclei, inconspicuous to conspicuous nucleoli, and abundant, granular-appearing cytoplasm
 - Appearance in clusters resembling normal acini or as individual cells
 - Presence of stripped or naked nuclei may be present in the background and may be mistaken for lymphocytes.
 - Centrally situated nuclei lacking polarity, which contrasts to normal (non-neoplastic) serous acinar cells, in which the cells have basally oriented nuclei
- An associated benign lymphocytic cell infiltrate may be apparent in aspirates.
- Psammomatoid concretions may be identified in aspirates.
- Serous acinar cells may be mistaken for oncocytic cells and in conjunction with a lymphocytic cell infiltrate may be misdiagnosed as Warthin tumor.

Histology

- May be circumscribed, encapsulated, or infiltrative
- Characterized by a variety of growth patterns including solid, microcystic, papillary-cystic, and follicular:
 - Solid and microcystic:
 - Most common patterns and often seen in association with each other
 - Solid growth consists of sheets or aggregates of tumor cells in lobules or organoid arrangement
 - Microcystic consists of numerous small cystic spaces.
 - Microcysts may appear as empty spaces or may contain eosinophilic to basophilic material.

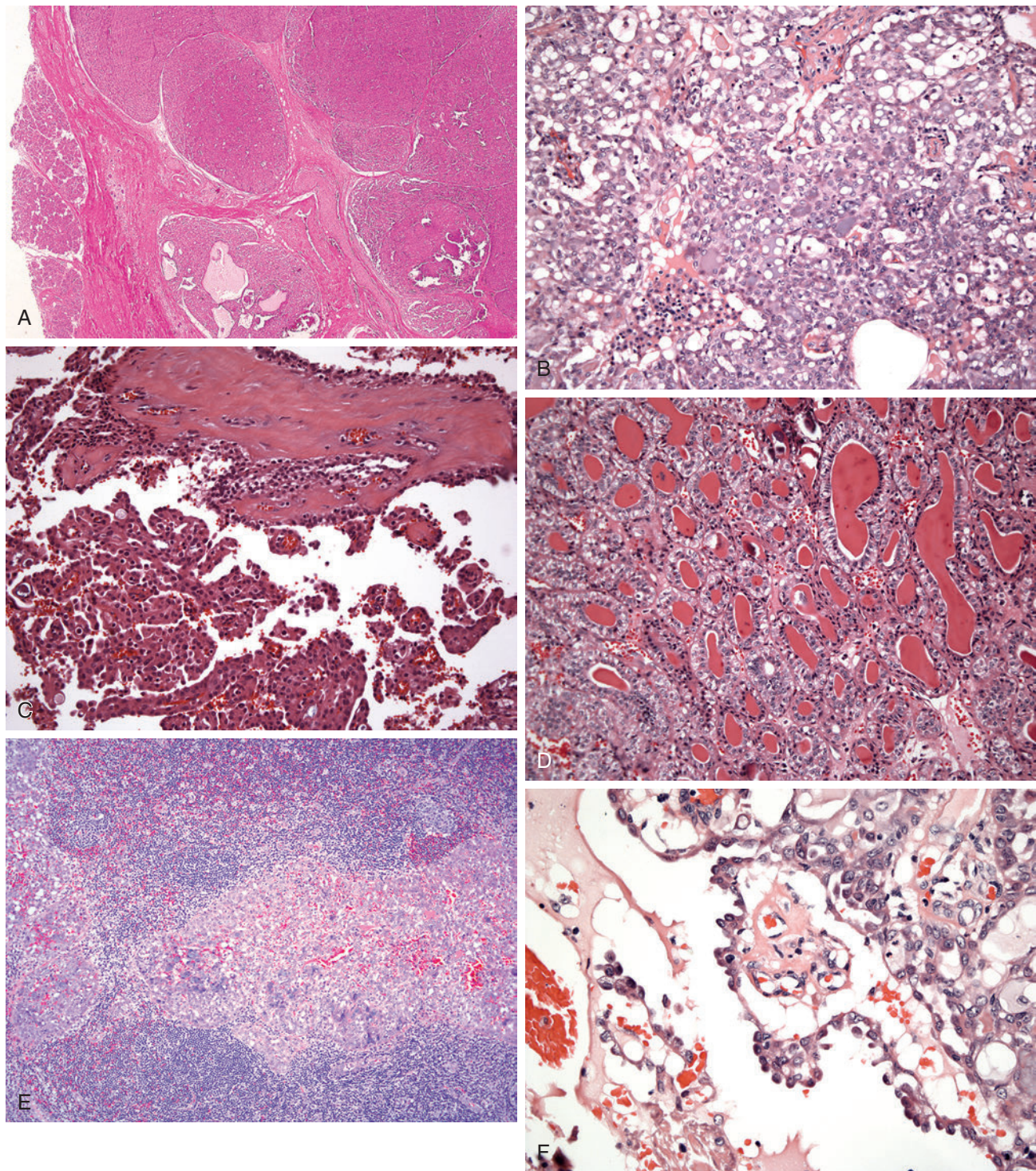


Fig. 20-58. Acinic cell carcinoma.

Multiple growth patterns can be seen from case to case and even within a single case including (A) solid and focally cystic; (B) microcystic; (C) papillary-cystic; and (D) follicular. E, A coexisting lymphoid cell infiltrate referred to as tumor-associated lymphoid proliferation (TALP) is often but not uniquely seen in association with acinic cell carcinoma. The presence of TALP may suggest tumor within a lymph node but the absence of subcapsular sinuses would allow discrimination from tumor within a (periparotid) lymph node. F, The epithelial proliferation may appear to be "floating" in cystic spaces with bulging of the epithelial cells into the lumen in an uneven manner resulting in a hobnail or "tombstone row" appearance.

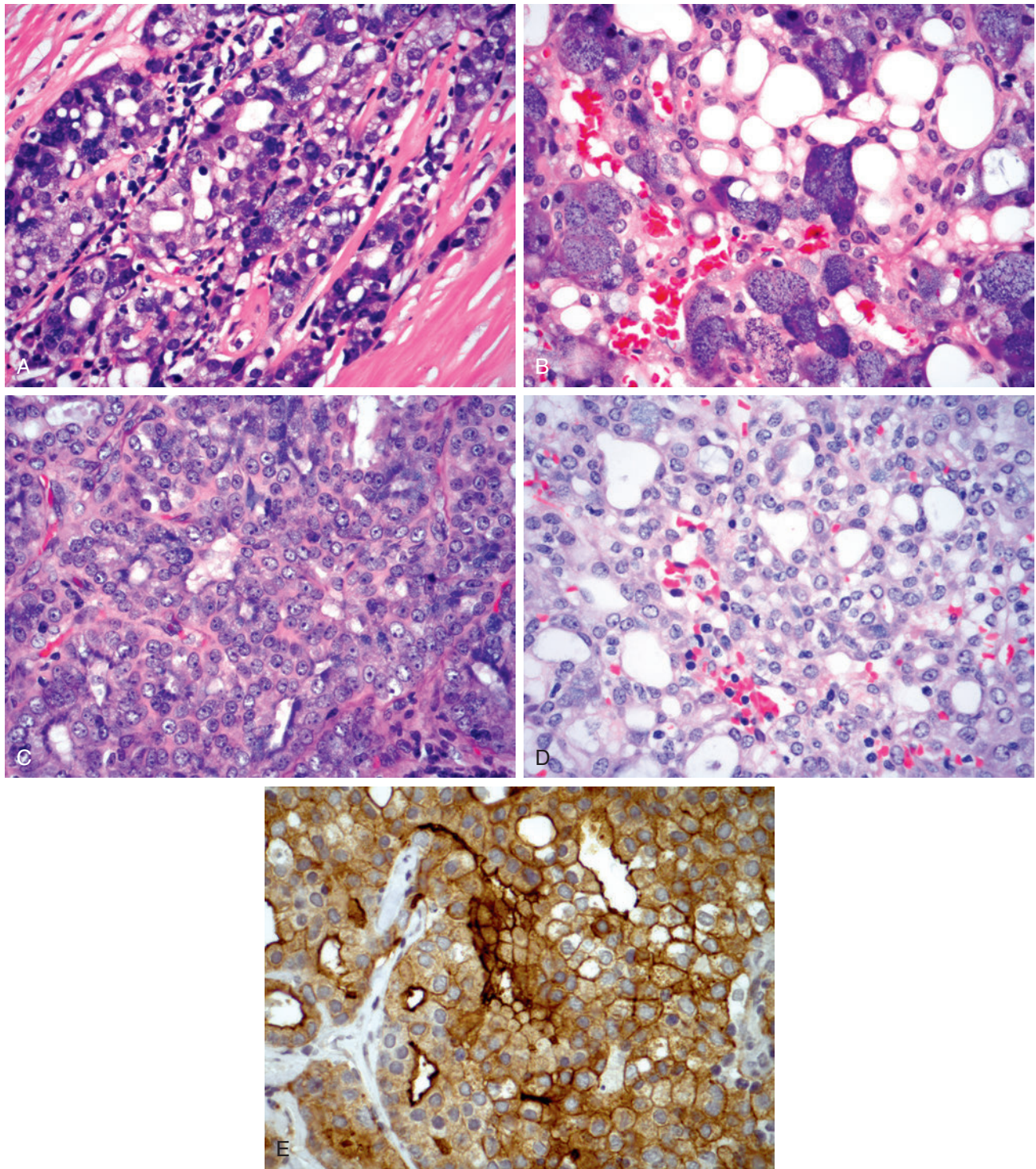


Fig. 20-59. Acinic cell carcinoma.

The cytomorphic features in acinic cell carcinoma include (**A** and **B**) polyhedral cells with eccentrically placed nuclei and characteristic abundant basophilic granular cytoplasm with admixed vacuolated cells characterized by clear cytoplasmic vacuoles; (**C**) intercalated duct-like cells characterized by amphophilic cytoplasm and sparse to absent basophilic granules; (**D**) nonspecific glandular cells are round to polygonal shaped with round nuclei, amphophilic to eosinophilic cytoplasm and indistinct or ill-defined cell borders; (**E**) DOG1 immunoreactivity is positive in acinic cell carcinoma showing complex mixture of intense apical membranous, complete membranous and cytoplasmic staining.

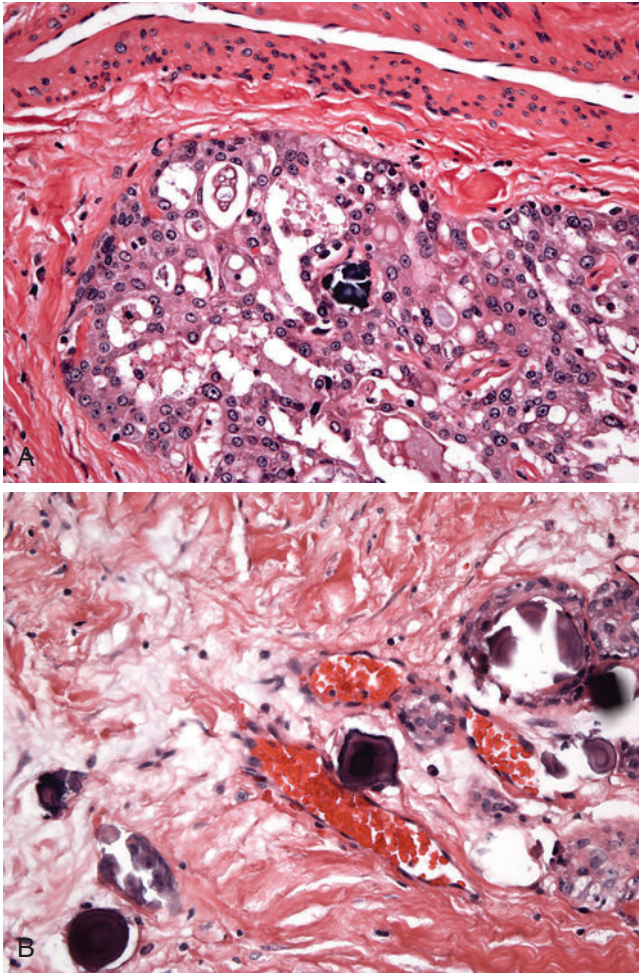


Fig. 20-60. Acinic cell carcinoma.

Psammoma bodies can be identified but are not unique to acinic cell carcinoma, being present in other salivary gland neoplasms.

- Papillary-cystic and follicular:
 - Less common patterns (papillary/cystic more common than follicular)
 - Papillary-cystic consists of variable-sized cystic spaces associated with papillary projections supported by a thin fibrovascular core:
 - Epithelial proliferation may appear to be “floating” in cystic spaces
 - Epithelial cells may bulge into the lumen in an uneven manner, resulting in a “tombstone row” appearance.
 - Follicular pattern resembles thyroid parenchyma with epithelial-lined lumens containing eosinophilic proteinaceous material lined by cuboidal to columnar cells.
- Cytologic variation present from case to case and even within a given case, including presence of:
 - Acinic or acinar cells:
 - These cells are diagnostic (pathognomonic).
 - Polyhedral with small, dark, eccentrically placed nuclei and characteristic abundant basophilic cytoplasm with cytoplasmic (zymogen-like secretory) granules; zymogen-like secretory granules define these as acinar cells.
 - These cells may predominate in well-differentiated tumors, but in any given tumor they may represent a minority of neoplastic cells.
 - May be vacuolated that in contrast to vacuolated (nonacinar) cells retain their cytoplasmic diastase-resistant, PAS-positivity
 - Intercalated duct-like cells:
 - Cuboidal or columnar with centrally placed small dark nuclei and eosinophilic to amphophilic cytoplasm
 - Found in majority of tumors but usually represent a smaller percentage of cellular components
 - May predominate in about one third of cases
 - Vacuolated cells:
 - Contain clear cytoplasmic vacuole, which may be numerous, vary in size, and distend the cell membranes.
 - These cells are more commonly seen in acinic cell adenocarcinoma than in other salivary gland neoplasms but are identified in other salivary gland neoplasms and are not in and of themselves diagnostic for acinic cell carcinoma.
 - Clear cells:
 - Round to oval cells with distinct cell borders, peripherally placed, small, dark nuclei and hallmark clear cytoplasm
 - Result from fixation and/or tissue processing
 - Considered an uncommon cell type in acinar cell carcinoma
 - Likely “pure” clear cell variant of acinic cell carcinoma does not exist.
 - Nonspecific glandular cells:
 - Lack specific features seen in other cell types
 - Are round to polygonal with round nuclei, amphophilic to eosinophilic cytoplasm, and indistinct or ill-defined cell borders
 - Tend to be more cellular and pleomorphic with a syncytial growth
- Although a single growth pattern and cell type may predominate in any given tumor, it is not uncommon to see multiple growth patterns and cell types in a single tumor.
- No established histologic grading system associated with acinic cell carcinomas

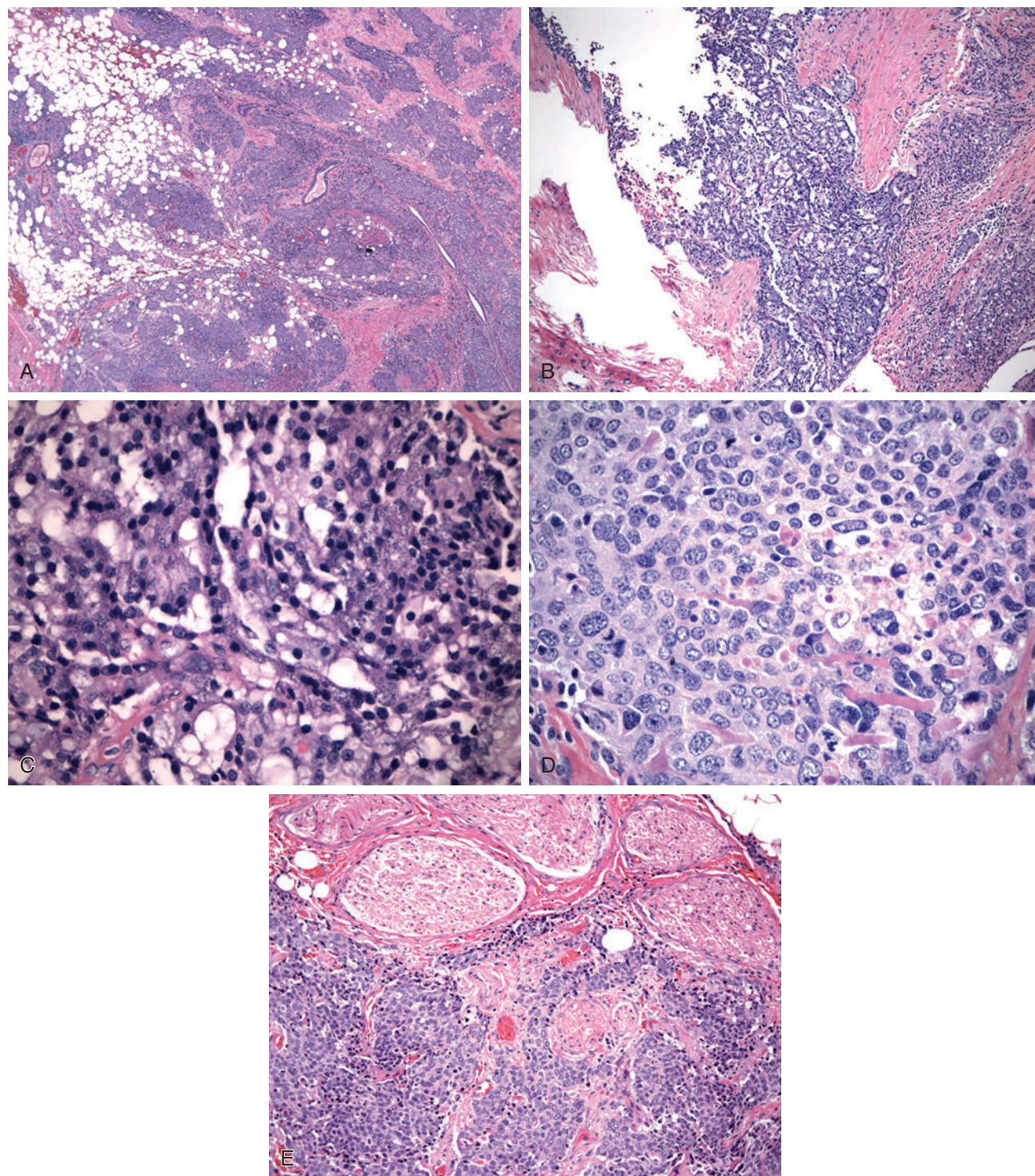


Fig. 20-61. High-grade transformation (dedifferentiation) of acinic cell carcinoma.

A, Infiltrative parotid gland tumor with trabecular and solid growth; in areas residual foci of (differentiated) acinic cell carcinoma characterized by **(B)** microcystic growth pattern and **(C)** cells with basophilic granular cytoplasm were seen; **(D)** transformation to high-grade undifferentiated carcinoma; **(E)** invasive growth with perineural invasion.

- Cellular pleomorphism and mitotic activity are typically absent.
 - Typically, stroma is scant but occasionally may be dense and hyalinized.
 - A prominent lymphoid component with germinal centers representing tumor-associated lymphoid proliferation (TALP) present in many tumors.
 - Occasionally, psammomatoid concretions similar to those seen in thyroid papillary carcinoma may be present.
 - Hemorrhage may be present including in connective tissue and within epithelial cells:
 - Intracytoplasmic hemosiderin pigment appears finely granular.
 - Most often seen in association with the papillary-cystic growth pattern
 - Not uniquely seen in acinic cell carcinoma
 - Diagnosis can be rendered even in the absence of invasive growth based on architecture, cytomorphology, and immunohistochemical staining (see below) as there is no known benign counterpart to acinic cell carcinoma.
 - Marked reactive and degenerative may be seen occurring spontaneously or secondary to prior traumatic event such as a fine-needle aspiration biopsy that may include:
 - Infarction
 - Cystic degeneration
 - Hemorrhage including recent and remote with hemosiderin deposition in lesional cells, fibroconnective tissue, and histiocytes
 - Mixed chronic inflammatory cell infiltrate
 - Cholesterol granuloma formation
 - Lipogranulomatous reaction
 - Rarely, amyloid deposition may be present
 - Histochemistry:
 - Acinar cells and intercalated duct cells:
 - Diastase-resistant, PAS-positive cytoplasmic granules
 - Mucicarmine and alcian blue typically negative but may be weakly positive:
 - Presence of some intracytoplasmic mucicarmophilic material can be seen and does not exclude the diagnosis.
 - Vacuolated cells:
 - PAS negative
 - Mucicarmine and alcian blue negative
 - Clear cells:
 - PAS negative
 - Mucicarmine and alcian blue negative
 - Nonspecific glandular cells:
 - PAS negative
 - Mucicarmine and alcian blue negative
 - Microcystic pattern:
 - Eosinophilic to basophilic material may stain for PAS and mucicarmine.
 - Papillary-cystic pattern:
 - Intraluminal and extracellular PAS-positive and mucicarmine-positive material may be present.
 - Follicular pattern:
 - Luminal material may be PAS positive and weakly mucicarmine positive.
- Immunohistochemistry:
 - Discovered on GIST-1 (DOG-1) positive:
 - Relative to salivary gland lesions/neoplasms considered marker of acinar cells and to a lesser extent intercalated duct differentiation
 - All acinic cell carcinomas reported to be DOG-1 positive
 - Demonstrates complex mixture of intense (3+) apical membranous, cytoplasmic, and complete membranous staining:
 - Strong staining used to support diagnosis of acinic cell carcinoma
 - Other tumor types that may express DOG-1 include adenoid cystic carcinoma and epithelial-myoepithelial carcinoma, showing distinctive combined apical ductal and membranous/cytoplasmic myoepithelial staining profile but lack intensity associated with acinic cell carcinoma
 - Pancytokeratins, low-molecular-weight cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK19), EMA and CEA positive
 - Amylase positive:
 - Of limited diagnostic utility as only a minority of cases (15%) express amylase
 - Sox10 positive
 - Variable immunoreactivity seen with S100 protein and vimentin:
 - S100 protein may be positive but typically focal or limited in extent.
 - Mammaglobin typically absent but may be focally positive
 - p63, calponin, actins negative
 - GATA-3 (nuclear) staining may be present but when present is focal rather than diffuse:
 - Diffuse GATA-3 staining in salivary gland neoplasm typically limited to salivary duct carcinoma and mammary analogue secretory carcinoma
 - Low labeling indices as seen by Ki67 staining
 - Absence of thyroglobulin and TTF1
- Electron microscopy:
 - Ultrastructural findings are characterized by the presence of numerous round, electron-dense cytoplasmic secretory granules.
 - Rough endoplasmic reticulum and mitochondria are present; junctional complexes and microvilli may be identified.
 - Basal lamina separates tumor cells from stroma.

- Cytogenetics and molecular biology:
 - Absence of *ETV6* translocation
 - No specific findings:
 - Alterations of chromosome 4p, 5q, 6p, and 17p
 - Loss of heterozygosity (LOH) in at least one of the 20 loci on chromosomes 1, 4, 5, 6, and 17

High-Grade Transformation (“Dedifferentiated”) of Acinic Cell Carcinoma

- Composed of histomorphologically “conventional” acinic cell carcinoma with associated high-grade carcinoma
- May occur rarely at initial presentation or in a long-standing or recurrent tumor
- Clinical presentation may include rapidly enlarging lesion, pain, cranial neuropathy (e.g., facial nerve palsy)
- High-grade carcinoma may include undifferentiated/poorly differentiated carcinoma or poorly differentiated adenocarcinoma characterized by presence of sheets of epithelial cells sometimes with cribriform growth lacking evidence of cellular differentiation with marked nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio, increased mitotic figures including atypical mitoses, necrosis, and high proliferation indices.
- Immunohistochemical staining of high-grade component may be characterized by strong membrane staining for CK18 and beta-catenin, and nuclear staining for cyclin-D1.
- Associated with poor prognosis

Differential Diagnosis

- Normal salivary gland parenchyma:
 - Retention of normal lobular architecture of the salivary gland parenchyma as well as the presence of other salivary gland cellular components (e.g., striated ducts, interlobular ducts) assist in differentiating normal gland from acinic cell adenocarcinoma.
- Mammary analogue secretory carcinoma (MASC):
 - Share overlapping histomorphologic features with acinic cell carcinoma but in contrast to acinic cell carcinomas, MASCs:
 - Lack cells with basophilic cytoplasm and zymogen-like secretory granules
 - Show diffuse and strong mammaglobin and S100 protein
 - Have *ETV6* translocation
- Mucoepidermoid carcinoma
- Cystadenocarcinoma
- Salivary and nonsalivary gland neoplasms containing clear cells, including:
 - Oncocytoma
 - Myoepithelioma

- Mucoepidermoid carcinoma
- Epithelial-myoepithelial carcinoma
- Clear cell adenocarcinoma
- Metastatic renal cell carcinoma

- Acinic cell adenocarcinomas with follicular pattern may simulate thyroid follicular epithelial neoplasms.

Treatment and Prognosis

- Complete surgical excision is preferred treatment and may consist of either conservative parotidectomy when the tumor is limited to the superficial lobe or total parotidectomy when the deep lobe of the parotid is involved.
- Radiation therapy is generally not used as a primary mode of treatment but may be used for:
 - Tumors that cannot be completely resected
 - Metastatic disease
- Generally are indolent neoplasms cured by complete surgical removal, however:
 - Approximately 35% recurrence rate
 - Approximately 16% metastatic rate:
 - Depending on primary site of occurrence regional lymph node metastasis may include the pre-auricular lymph nodes (parotid tumor), submandibular and upper jugular chain lymph nodes (submandibular tumor), submental lymph nodes (lip tumor), base of skull (palate tumor), submandibular, post-auricular and level II accessory lymph nodes (intraoral tumors)
 - Distant visceral spread includes lungs, liver, bone, and brain
 - Approximately 16% disease-associated death rate
- Most recurrences and metastases occur within 5 years of initial therapy; however, recurrent tumor and metastatic disease may occur years/decades after initial treatment.
- Survival statistics include:
 - 5-year 91%
 - 10-year 83%
 - 20-year 67%
- Adverse prognostic factors may include:
 - Multiple recurrences and metastasis (regional lymph nodes, distant visceral)
 - Short duration of symptoms
 - Submandibular tumors more aggressive than parotid tumors
 - Patients more than 30 years of age
 - Neoplasms larger than 3 cm
- Clinical staging is better predictor of prognosis than histology with poorer outcome associated with:
 - Large size and infiltrative growth
 - Involvement of the deep lobe of parotid
 - Incomplete resection

- Favorable prognostic factors may include:
 - Occurrence in minor salivary glands
 - Longer duration of symptoms
 - Patients under 30 years of age
 - Presence of dense lymphoid stroma with well-developed germinal centers
- Histologic high-grade transformation associated with poor prognosis:
 - Increase in locoregional (lymph node) and distant visceral metastases:
 - High propensity for nodal metastases indicates need for neck dissection at the time of diagnosis.
 - Increase in mortality rates due to tumor dissemination
 - Median overall survival of 4.3 years reported with range of 1 to 9 years
- Histologic features that may be associated with adverse prognosis include:
 - High proliferation indices (more than 5%)
 - Neurotropism
 - Anaplasia
 - Necrosis
 - Depletion of lymphocytes in stroma

MAMMARY ANALOGUE SECRETORY CARCINOMA (MASC) (Figs. 20-62 through 20-66)

Definition: Distinctive recently described low-grade salivary gland neoplasm with features resembling acinic cell carcinoma and (low-grade) cystadenocarcinoma displaying strong similarities to secretory carcinoma of breast including t(12;15)(p13;q25) translocation resulting in *ETV6-NTRK3* gene fusion.

Synonym: “Zymogen-poor” acinic cell carcinoma: in all likelihood all/most previous designations as zymogen-poor acinic cell carcinomas are in reality MASCs.

Clinical

- Slightly more common in males than females; occurs over a wide age range of 21 to 75 years, with a mean age of 46 years
- Most common in parotid gland but may occur in other major glands as well as in minor salivary glands
- Most common presentation is as a painless mass
- Etiology:
 - No known causes

Pathology

Fine-needle aspiration biopsy:

- Variably cellular smears
- Architectural patterns may include:

- Intact clusters with sheet-like or papillary structures
- Dispersed and dissociated cells
- Cytomorphology consists of bland tumor cells with small to medium-sized round to oval nuclei, with a smooth contour and indistinct or small nucleoli, and vacuolated cytoplasm lacking intracytoplasmic zymogen granules
- Many histiocytes, some of which contained hemosiderin pigments, and variously shaped mucinous material may be evident in background or within the epithelial clusters.
- Absence of matrix tissue or stromal spindled cells

Histology

- Circumscribed but unencapsulated lesion often with lobulated appearance divided by fibrous septa
- Growth patterns may include microcystic, (macro) cystic, tubular, papillary, solid, and follicular (thyroid-like):
 - Multiple growth patterns may be seen in a single case.
- Invasion often present, including infiltration of non-neoplastic salivary gland parenchyma and fibroconnective tissue:
 - Perineural and lymph-vascular invasion may be present.
 - Extraparenchymal extension may be identified.
- Lesional cells are cuboidal to polygonal with round to oval nuclei with vesicular to finely granular chromatin, small distinct centrally located nucleoli surrounded by pale pink granular or vacuolated-appearing cytoplasm:
 - Serous acinar differentiation in form of intracytoplasmic basophilic granules not a feature
- Intraluminal secretions including bluish to eosinophilic material variably present within microcystic and tubular spaces
- Absence of significant nuclear pleomorphism, increased mitotic activity, or necrosis
- Reactive and degenerative changes similar to those seen in acinic cell carcinoma may be present, including:
 - Infarction and necrosis
 - Hemorrhage, recent and remote (i.e., hemosiderin deposition):
 - Intracytoplasmic hemosiderin deposition can be seen within tumor cells
 - Cholesterol granuloma formation
 - Calcifications
- Histochemistry:
 - Intraluminal secretory material positive for mucicarmine, PAS with and without diastase, and alcian blue

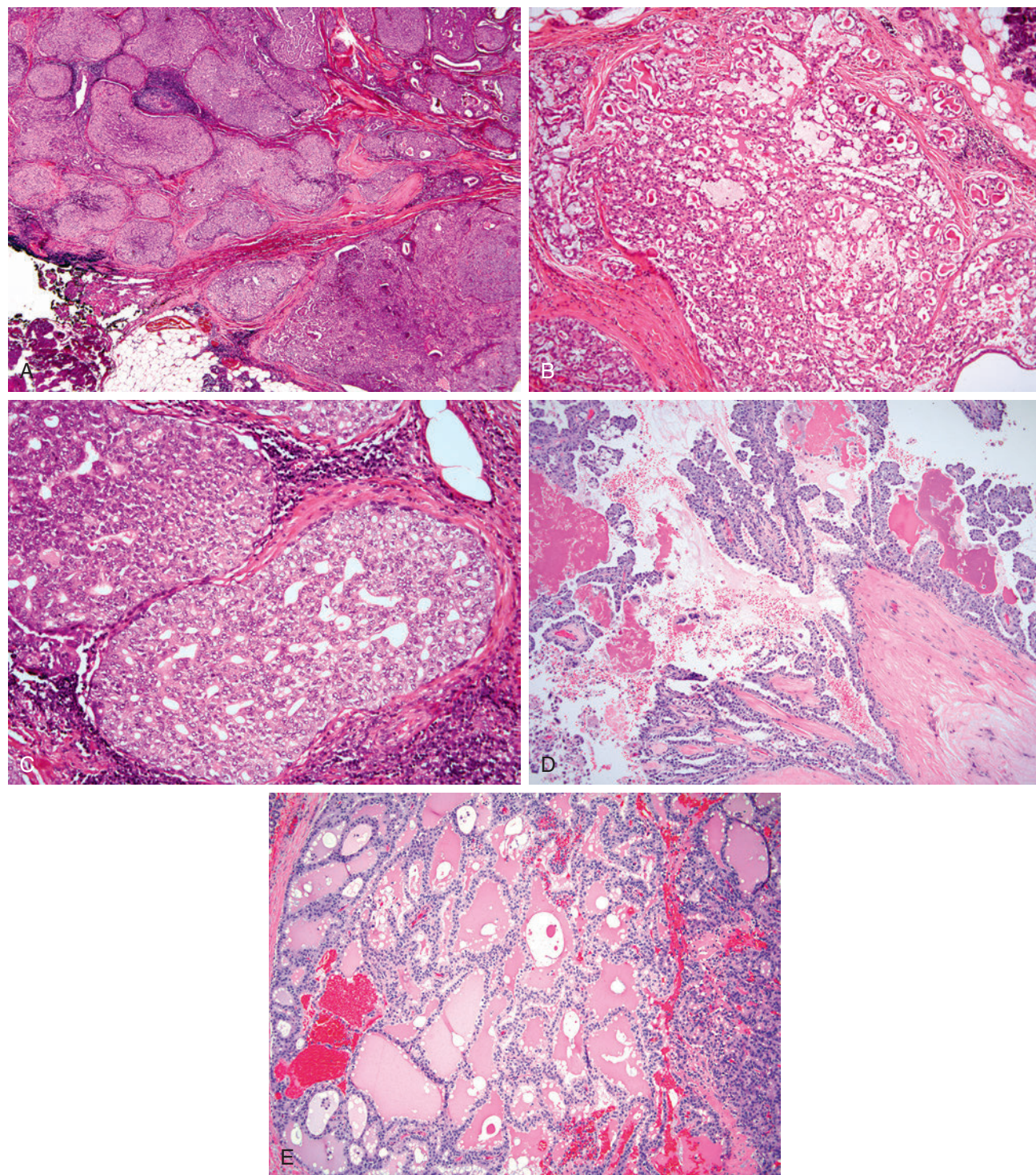


Fig. 20-62. Mammary analogue secretory carcinoma.

A, Circumscribed but unencapsulated lesion with lobulated appearance divided by fibrous septa composed of solid tumor nests. Additional growth patterns that may be seen from case to case and even within the same case include **(B)** tubular (secretory); **(C)** microcystic and solid; **(D)** papillary and cystic; **(E)** follicular (thyroid-like). Intraluminal eosinophilic appearing secretions are variably present within microcystic and tubular spaces.

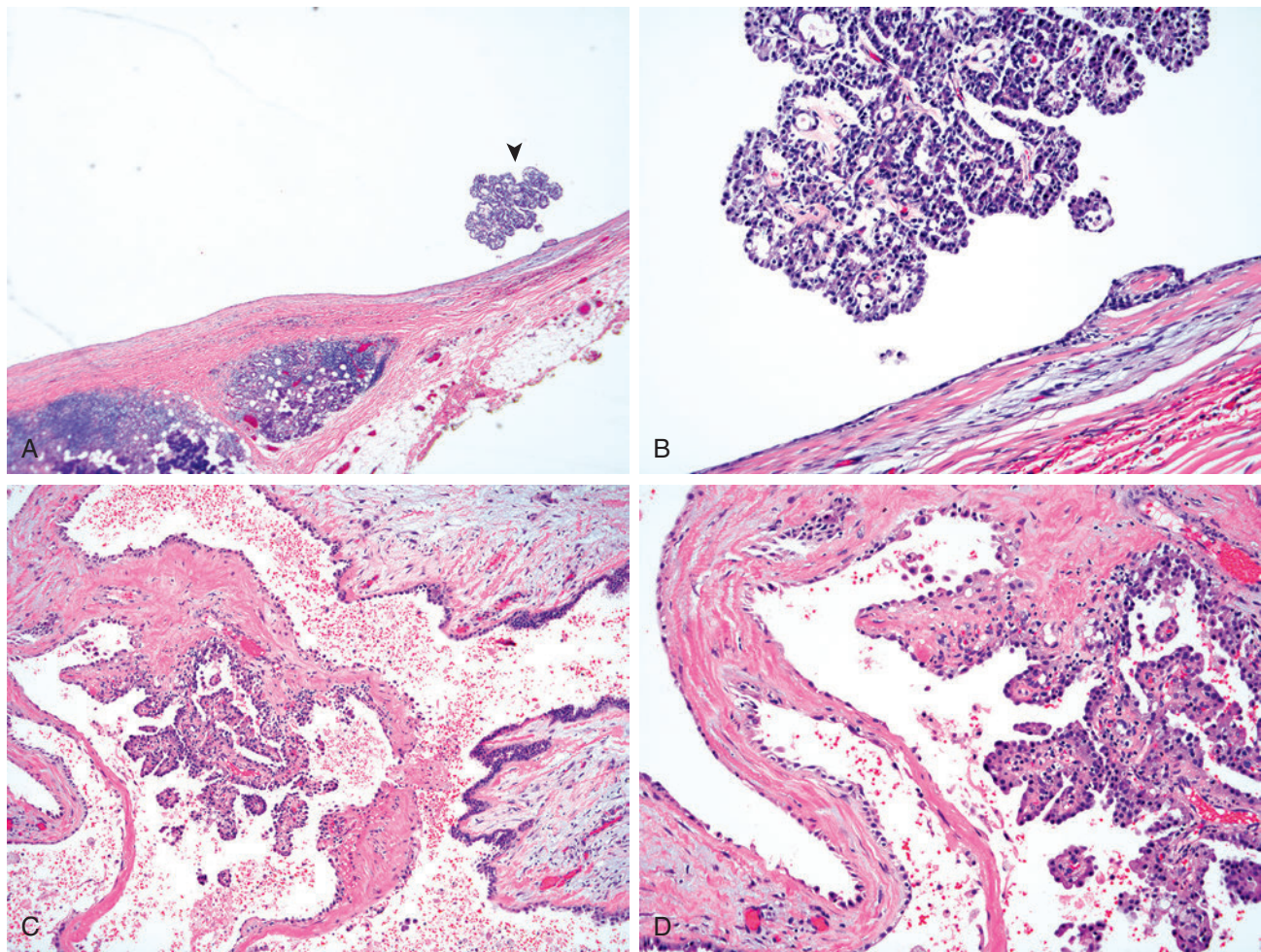


Fig. 20-63. Macrocystic mammary analogue secretory carcinoma.

A-D, Uncommonly, the tumor may have predominant or exclusive macrocystic growth. Limited but identifiable characteristic cellular foci are seen (*arrowhead* in **A** and seen at higher magnification in **B**). Note the single layer of lesional cells lining the cyst are histologically similar to those in the cellular foci.

- Immunohistochemistry:
 - Mammaglobin
 - Diffuse and strong reactivity ranging from 50% to 100% of cells (mean 91%)
 - Present in cytoplasm and intraluminal secretory material
 - Mammaglobin highly sensitive for MASC but may be present in variety of tumors that do not harbor the ETV6 translocation
 - Absent or limited (focal) reactivity in acinic cell carcinoma
 - Should not be indiscriminately used as a confirmatory test for MASC
 - S100 protein
 - Diffuse and strong reactivity
 - Seen in a wide variety of salivary gland lesions/neoplasms
 - In conjunction with diffuse and strong mammaglobin staining as well as appropriate histologic findings, can be used to diagnose MASC even without cytogenetic testing (see below)
 - GATA binding protein 3 (GATA-3):
 - A member of GATA family of zinc finger transcription factors that regulate normal development of various tissue and cell types including breast, T-lymphocytes, kidney, nerve, and skin
 - Initially, immunohistochemical nuclear staining for GATA-3 believed to be restricted mostly to neoplasms of breast and urothelial origin
 - Evidence now shows GATA-3 staining in salivary gland neoplasms but consistent strong and diffuse (nuclear) staining (i.e., >50% of cells) limited to MASC and salivary duct carcinoma

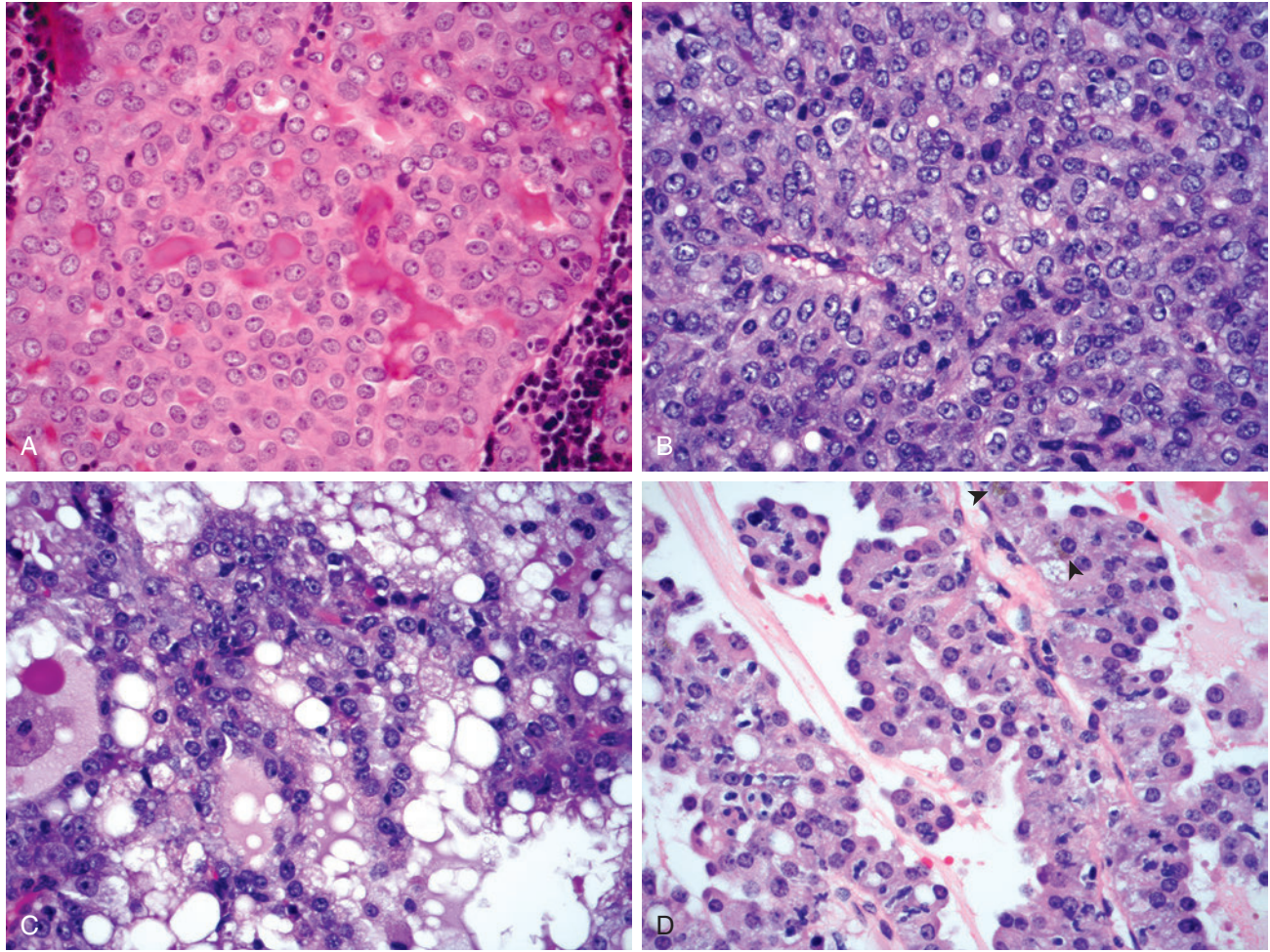


Fig. 20-64. Mammary analogue secretory carcinoma.

A through **D**, Lesional cells are cuboidal to polygonal with round to oval nuclei, vesicular to finely granular chromatin, small distinct to larger nucleoli surrounded by pale pink granular or vacuolated-appearing cytoplasm. Focally intracytoplasmic hemosiderin deposition may be seen within lesional cells (**D**, arrowheads). The overall features are reminiscent of those seen in acinic cell carcinoma, except there is an absence of serous acinar differentiation in the form of intracytoplasmic basophilic granules. Nevertheless, immunohistochemical staining and/or molecular analysis may be required to differentiate mammary analogue secretory carcinoma from acinic cell carcinoma.

among GATA-3 positive salivary gland neoplasms:

- Other GATA-3+ salivary gland tumors include:
 - Acinic cell carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, mucoepidermoid carcinoma, oncocytic carcinoma, oncocytoma, pleomorphic adenoma, Warthin tumor
 - Staining in these other neoplasms tends to be less than diffuse and/or strong.
 - Some of these other neoplasms may include diffuse and/or strong reactivity but

histologically would not be confused with MASC, including oncocytoma and Warthin tumor

- Cytokeratins:
 - Diffuse and strong staining for AE1/AE3, CAM5.2, CK7, CK8, CK18, CK19
- Other markers:
 - Diffuse and strong vimentin, EMA and STAT5a (signal transducer and activator of transcription 5a) staining
 - Significant reactivity for gross cystic disease fluid protein 15 (GCDFP-15) especially intraluminal secretory material

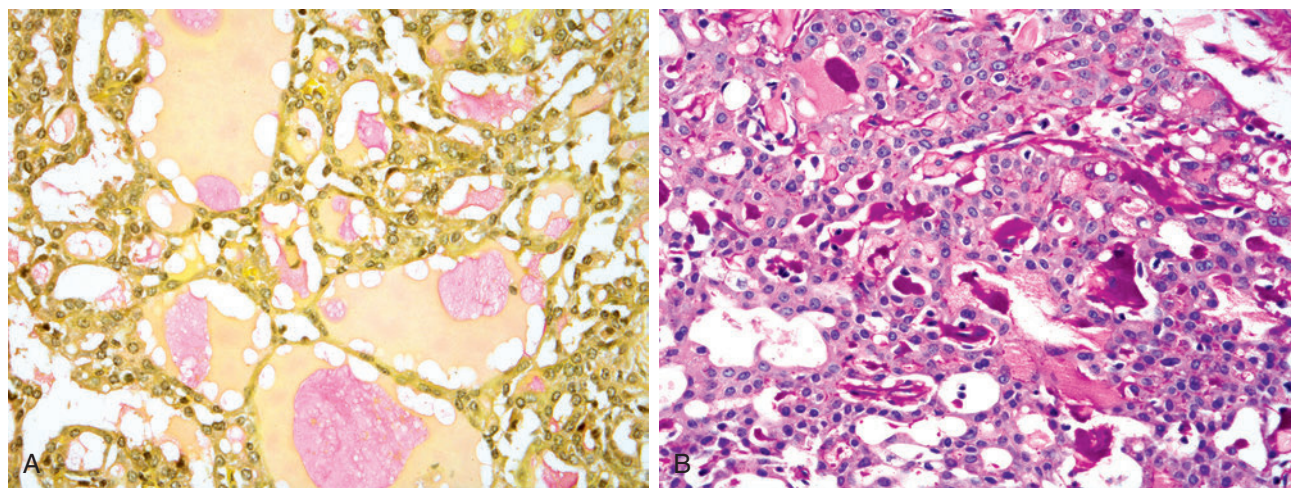


Fig. 20-65. Mammary analogue secretory carcinoma.

Intraluminal secretory material is positive for (A) mucicarmine and (B) periodic acid Schiff with diastase.

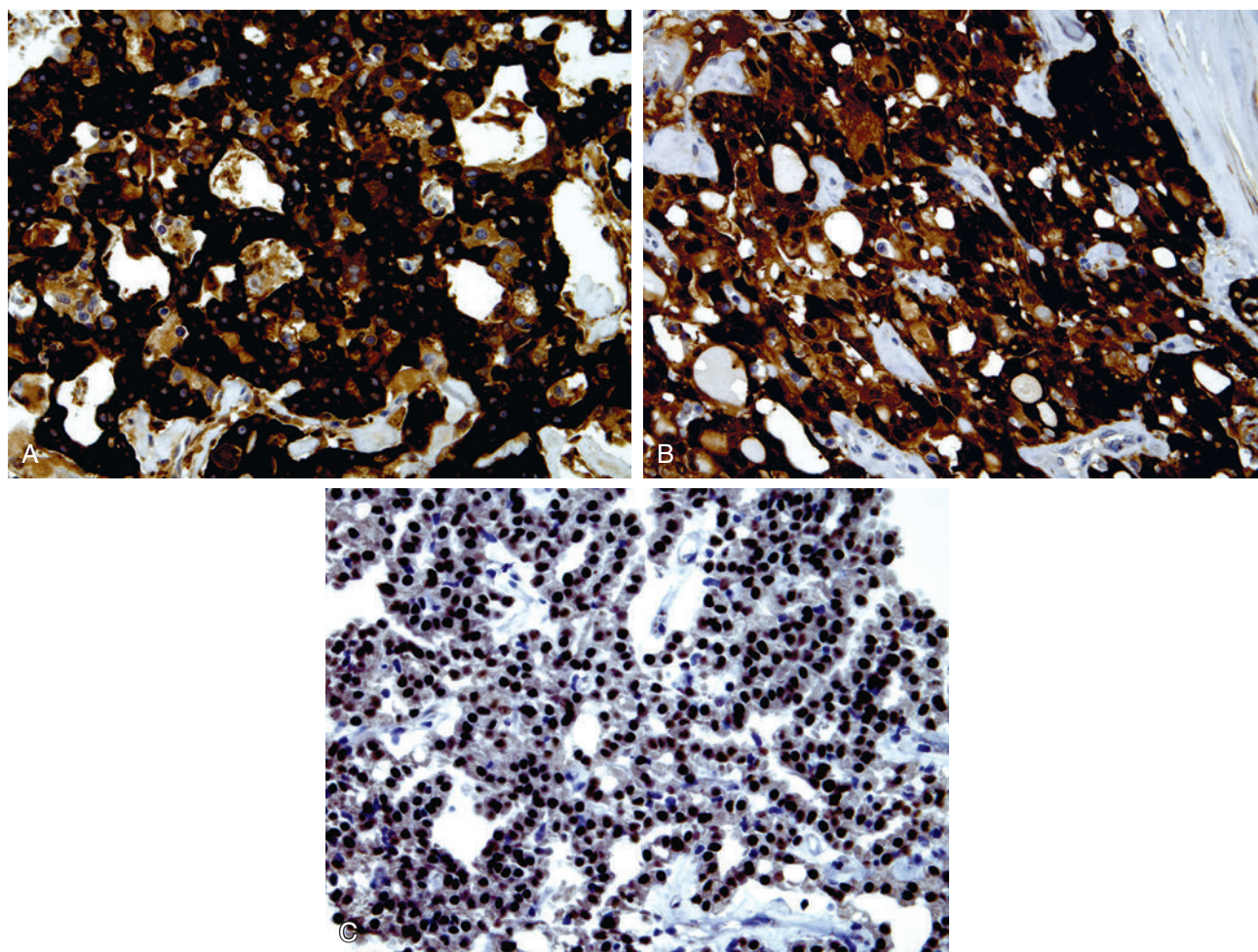


Fig. 20-66. Mammary analogue secretory carcinoma.

Immunohistochemical staining includes diffuse reactivity for (A) mammaglobin, (B) S100 protein, and (C) GATA3 (nuclear).

- Basal cell/myoepithelial cell markers:
 - p63, calponin, CK14, smooth muscle actin, and CK5/6 are essentially negative
 - Isolated nuclear p63 positive may be identified.
- Discovered on GIST1 (DOG-1):
 - Typically negative
- Cytogenetics and molecular genetics:
 - t(12;15)(p13;q25) chromosomal translocation resulting in *ETV6-NTRK3* gene fusion
 - To date, restricted to MASCs
 - May be identified by FISH or RT-PCR

High-Grade Transformation (“Dedifferentiated”) of MASC

- Rare and recently reported occurrence in three cases located in parotid gland
- Characterized by accelerated clinical course in a long-standing lesion (23 years), relatively recent identified lesion (2 years), or recurrent neoplasm
- Histologically, composed of two distinct sharply delineated carcinomatous components including:
 - Conventional MASC (see previous)
 - High-grade transformation characterized by anaplastic cells arranged in trabecular pattern with marked nuclear pleomorphism and absence of intraluminal secretory material
 - Perineural invasion, necrosis (comedotype), and desmoplastic stroma consistently identified
 - Extraglandular invasion including into skin consistently identified
- Immunohistochemical staining included:
 - Ki67 (MIB1)
 - For low-grade component median proliferation index was 23% (range 15 to 35)
 - For high-grade component, significant increase in proliferative activity with Ki67 index between 45% and 70% (median 53%)
 - Strong membranous staining for *EGFR* particularly in high-grade component
 - Median cyclin-D1 index higher in high-grade component (50%; range 40% to 60%) as compared with low-grade component (8.3%; range 5% to 15%)
 - p53 protein absent in low-grade component in two of three cases, but increased p53 immunoreactivity in high-grade component in all three cases
 - High-grade component revealed strong membrane staining for *EGFR* and β -catenin, cytoplasmic/nuclear staining for S100 protein
 - Cytokeratins (AE1/AE3, CK7, CK8, CK18, CK19), vimentin, S100 protein and mammaglobin stained both components with equally strong and diffuse intensity

- Cells of both components showed focal staining with EMA, GCDFP-15, and STAT5a
- Staining with calponin, CK14, CK5/6, CK20, p63 protein, androgen receptor, and *HER-2/neu* negative in both components
- Analysis for presence of the *ETV6-NTRK3* fusion transcript revealed positivity in both high-grade and “conventional” or low-grade component of MASC in two of three cases reported:
 - One case was negative in both its elements for the t(12;15) translocation, but *ETV6* gene rearrangement was detected in both components in all three cases.
- Analysis of *TP53* and *CTNNB1* gene mutations in the HG component of MASCs as well as detection of copy number aberration of *EGFR* and *CCND1* gene did not harbor any abnormalities.
- All three patients died of disseminated disease within 2 to 6 years after diagnosis:
 - Locoregional (nodal) metastasis, with or without extranodal extension
 - Distant metastasis

Differential Diagnosis

- Acinic cell carcinoma:
 - Presence of cells with basophilic granular cytoplasm
 - Presence of DOG1 immunoreactivity
 - Absence of diffuse and strong mammaglobin, S100 protein, and GATA-3 staining
 - Absence of *ETV6-NTRK3* gene fusion
- Low-grade cribriform cystadenocarcinoma
- Mucoepidermoid carcinoma, low grade

Treatment and Prognosis

- Complete surgical resection is preferred treatment.
- Efficacy of radiotherapy (preoperative or postoperative) uncertain
- In a limited number of studies with long-term follow-up to date, overall indolent clinical course reported:
 - Mean disease-free survival of 92 months
 - Majority of cases reported without evidence of disease from 27 months to 10 years
 - Minority of cases with recurrent and/or metastatic disease

ADENOCARCINOMA, NOT OTHERWISE SPECIFIED (NOS) (Figs. 20-67 through 20-71)

Definition: Malignant epithelial salivary gland neoplasm with glandular or ductal differentiation but without other specific histologic features allowing for a more definitive classification.

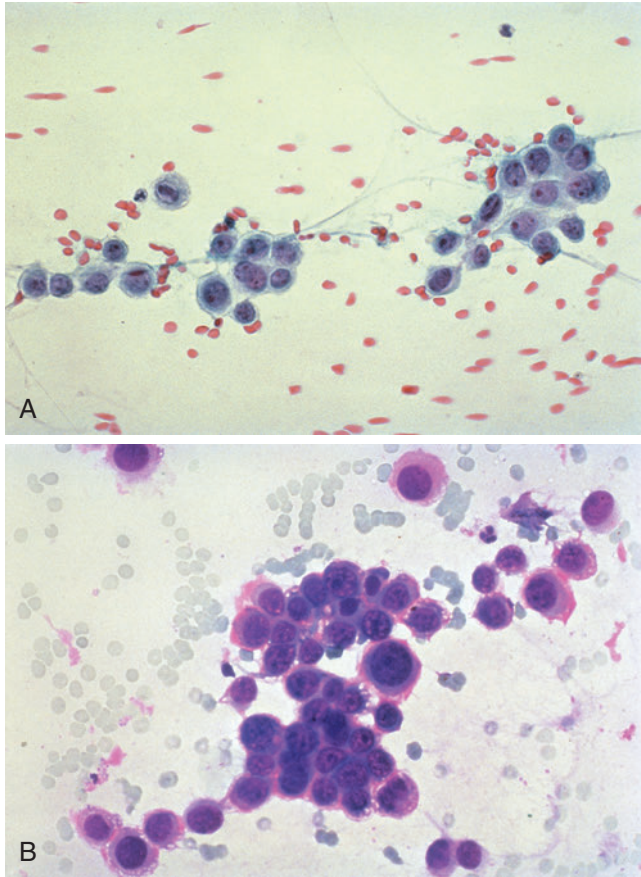


Fig. 20-67. Adenocarcinoma, NOS.

Parotid gland adenocarcinoma, NOS, high-grade, fine-needle aspiration biopsy. Cell clusters showing high-grade cytologic features and formation of gland- or duct-like structures.

Clinical

- Shrinking category of salivary gland neoplasms given identification of more specific tumor types but still considered among more common malignant salivary gland neoplasms
- More common in women than in men; occurs over a wide age range but is most frequently seen in the fifth to eighth decades of life; rarely occurs in children and adolescents
- Occurs in major and minor salivary glands:
 - In major glands, most common site of occurrence is parotid gland, representing single most common site of occurrence; may also occur in submandibular and rarely in the sublingual glands
 - Among minor salivary gland sites, most commonly occur in intraoral sites particularly palate followed by buccal mucosa, tongue, and lips (upper greater than lower)

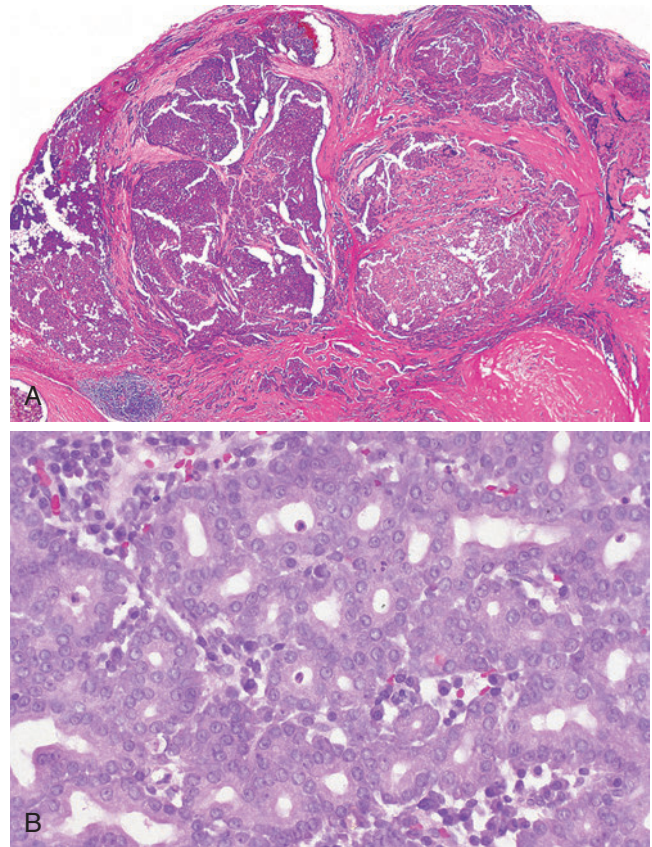


Fig. 20-68. Parotid gland adenocarcinoma, low-grade, NOS.

A, At low magnification the tumor is infiltrative with solid and cribriform growth. **B**, At higher magnification there is back-to-back glandular (cribriform) growth composed of a uniform single cell type characterized by cuboidal to round vesicular nuclei, minimal nuclear pleomorphism, and absence of increased mitotic activity. There are no features diagnostic for a more specific salivary gland tumor, hence the designation "not otherwise specified (NOS)."

- Symptoms relate to site of occurrence:
 - In major glands symptoms vary and may include:
 - Solitary, asymptomatic mass
 - Pain, cranial nerve paralysis occurs in minority of patients (approximately 20%)
 - Pain more common in submandibular gland tumors
 - Cutaneous involvement (fixation) may occur.
 - In minor glands:
 - Asymptomatic submucosal mass with ulceration and/or osseous involvement in a minority of cases
 - Duration of symptoms varies from months to years.
- Etiology:
 - No known causes

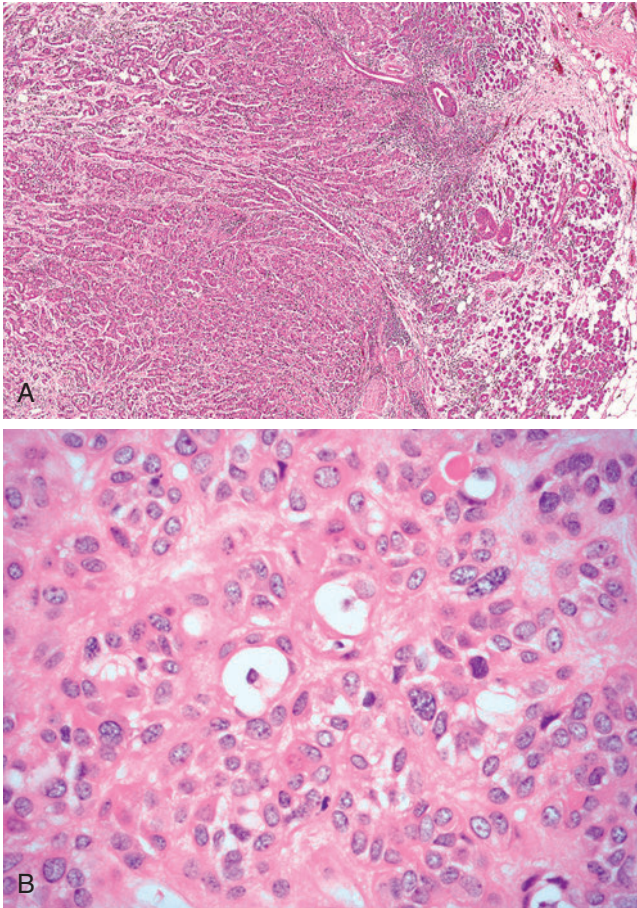


Fig. 20-69. Parotid gland adenocarcinoma, intermediate-grade, NOS.

A, Parotid tumor with invasion into the adjacent salivary gland parenchyma (*right*) showing trabecular and glandular growth. **B,** At higher magnification the glands are composed of cells with greater nuclear pleomorphism and more solid growth as compared with low-grade tumors but lacking the marked nuclear pleomorphism, increased mitotic activity, atypical mitoses, and necrosis seen in higher-grade tumors.

Pathology

Gross

- Varies from delineated and/or circumscribed to poorly demarcated and infiltrative
- Firm to hard, tan-white mass measuring from 2 to 10 cm in diameter
- Hemorrhage, necrosis, and cystic change may be seen.

Histology

- Display histologic heterogeneity but common to all growth patterns and cytologic appearances is the presence of an infiltrative neoplasm showing evidence of glandular or ductular features and an



Fig. 20-70. Parotid gland adenocarcinoma, high-grade, NOS.

Large parotid mass that was clinically painful involving the facial nerve causing facial nerve paralysis and facial distortion/asymmetry.

absence of epidermoid differentiation or other differentiation that may be indicative of another tumor type:

- Polymorphous growth patterns, including glandular or ductular structures, as well as solid, sheetlike, tubular, cribriform, lobular, cell nests, islands, and cord-like growth:
 - Multiple growth patterns seen from case to case and even within same case
- Cystic and papillary growth may be focally present but is limited in extent as more extensive cystic and papillary growth likely would be indicative of another tumor (e.g., cystadenocarcinoma).
- In higher grade neoplasms, glandular features may require diligent searching or may be represented by primitive attempts at gland or duct formation.
- Cytomorphologic diversification also seen ranging from cells having uniform appearance and distinct cell borders to cells with marked nuclear pleomorphism and indistinct cell borders.

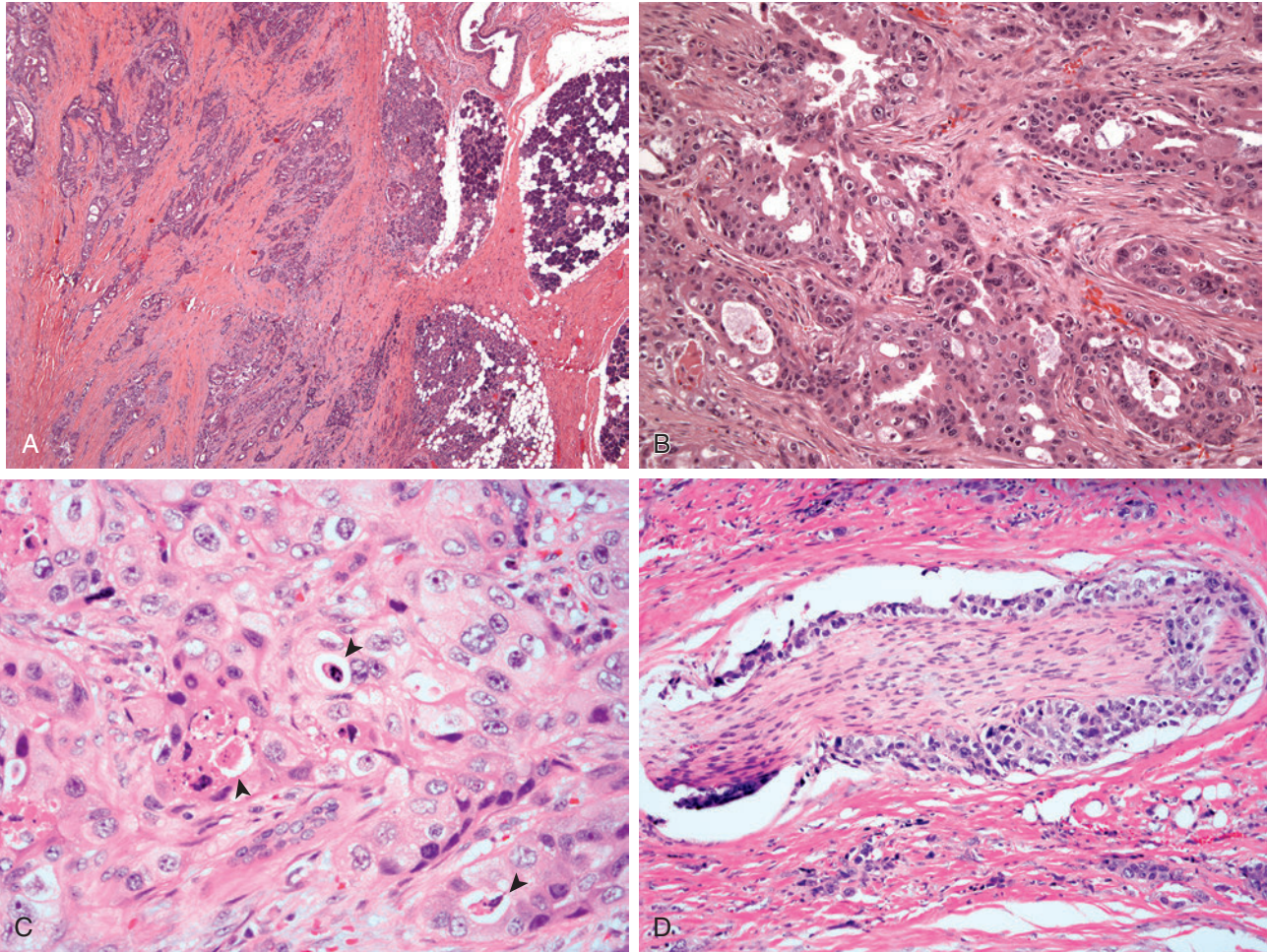


Fig. 20-71. Parotid gland adenocarcinoma, high-grade, NOS.

A, Parotid tumor that is unencapsulated and infiltrative into parotid gland parenchyma; there was also extensive extraglandular invasion with infiltrative growth into subcutaneous tissue and dermis (not shown); **(B)** complex glandular growth; **(C)** at higher magnification residual gland formation is present (*arrowheads*) with neoplastic cells characterized by enlarged and pleomorphic nuclei, prominent nucleoli, mitotic figures, and necrosis; **(D)** peri- and intraneural invasion.

- Cell types that can be seen include:
 - Cells with clear cytoplasm
 - Cells with oncocytic cytoplasm
 - Plasmacytoid-appearing cells
 - Sebaceous cells
 - Absence of mucocytes and epidermoid cells
- Histologic grading into low, intermediate, and high is based on degree of gland formation (differentiation), cellular pleomorphism, and mitotic activity:
 - Low grade:
 - Well circumscribed but at least focally invasive
 - Numerous gland or duct-like structures
 - Relatively uniform cytomorphologic features composed of a single cell type characterized by cuboidal to round tumor cells with small nucleoli, abundant cytoplasm, distinct cell borders, and little nuclear pleomorphism with few mitotic figures
 - Intermediate grade:
 - Glands or duct-like structures are readily seen.
 - In comparison to low-grade tumors there are greater cellular pleomorphism and more mitoses but usually atypical mitoses are not identified.
 - High grade:
 - Generally grow in solid sheets
 - Cells marked by anaplastic cytologic features, including enlarged, hyperchromatic and pleomorphic nuclei, small to prominent nucleoli, numerous mitoses, including atypical forms, necrosis, and hemorrhage

- Presence of glandular differentiation may require extensive searching or the use of special stains (e.g., mucicarmine).
- Stroma may be collagenized and occasionally may appear myxoid or mucinous.
- Extensive infiltrative growth generally seen in higher grade lesions and may include neurotropism, lymph-vascular invasion, invasion into fibroconnective tissue, and extraparenchymal invasion into soft tissues
- Some tumors may contain areas with focal features of other tumor types (e.g., adenoid cystic carcinoma, acinic cell adenocarcinoma, epithelial-myoepithelial tumor); however, these foci are very limited and do not justify exclusion from classification as adenocarcinoma, NOS.
- Histochemistry:
 - Intraluminal mucicarmine and diastase-resistant, PAS-positive material
 - Intracytoplasmic mucin generally not identified
 - Diastase-sensitive, PAS-positive intracytoplasmic material indicative of glycogen may be present.
- Immunohistochemistry:
 - Epithelial markers positive including cytokeratins (e.g., AE1/AE3, CAM5.2, CK7), CEA, and EMA
 - Myoepithelial-related markers generally negative including p63, calponin
 - May be positive for mammaglobin and GCDFP-15
- Metastatic tumor more common in histologically higher-grade tumor and in patients previously treated
- Most accurate factor in predicting survival is clinical stage:
 - 15-year survival rates include:
 - 54% for stage I
 - 31% for stage II
 - 3% for stage III
 - Histologically higher grade tumors tend to be clinically stage III tumors.
 - Histologically lower grade tumors tend to be clinically stage I tumors.
 - Other factors correlating with prognosis include:
 - Histologic grade:
 - Lower histologic grade lower rate of local recurrence(s) or metastatic (regional or distant) disease and the longer disease-free survival
 - Higher histologic grade the higher the rate of local recurrence(s) or metastatic (regional or distant) disease and the shorter the disease-free survival
 - Site of involvement:
 - Intraoral tumors more favorable prognosis than parotid gland and submandibular gland tumors
 - ◻ A higher percentage of submandibular gland adenocarcinomas are high-grade neoplasms as compared with parotid-based neoplasms accounting for greater likelihood of submandibular adenocarcinomas metastasizing to regional lymph nodes than lesions of parotid gland or intraoral minor salivary glands.

Differential Diagnosis

- Pleomorphic adenoma
- Monomorphic adenomas
- Epithelial-myoepithelial carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Cystadenocarcinomas
- High-grade mucoepidermoid carcinoma
- Metastatic adenocarcinoma

Treatment and Prognosis

- Complete surgical excision is preferred treatment:
 - Extent of the surgery dependent on location and clinical stage of disease (subtotal versus total glandectomy)
- Neck dissection dependent on presence of overt neck disease or clinical suspicion of nodal involvement
- Postoperative adjuvant radiotherapy used in advanced clinical stage neoplasms
- Local recurrence not uncommon, especially in high-grade neoplasms
- Metastatic disease occurs in approximately 26% of patients with cervical lymph nodes and lungs most commonly affected sites:
 - Other metastatic sites may include bone, skin, and abdominal sites.

ADENOID CYSTIC CARCINOMA

(Figs. 20-72 through 20-81)

Definition: Malignant epithelial salivary gland neoplasm predominantly composed of modified myoepithelial or basal (abluminal) cells with a minor component composed of ductal (luminal) structures characterized by its histologic appearance, tendency to invade nerves, and protracted but nonetheless relentless clinical course.

Synonyms: Cyndroma (old term used for cribriform type)

Clinical

- Represent approximately 10% to 12% of all malignant salivary gland neoplasms
- Slightly more common in women than in men; occurs over wide age range but most commonly occurs in the fifth through seventh decades of life:

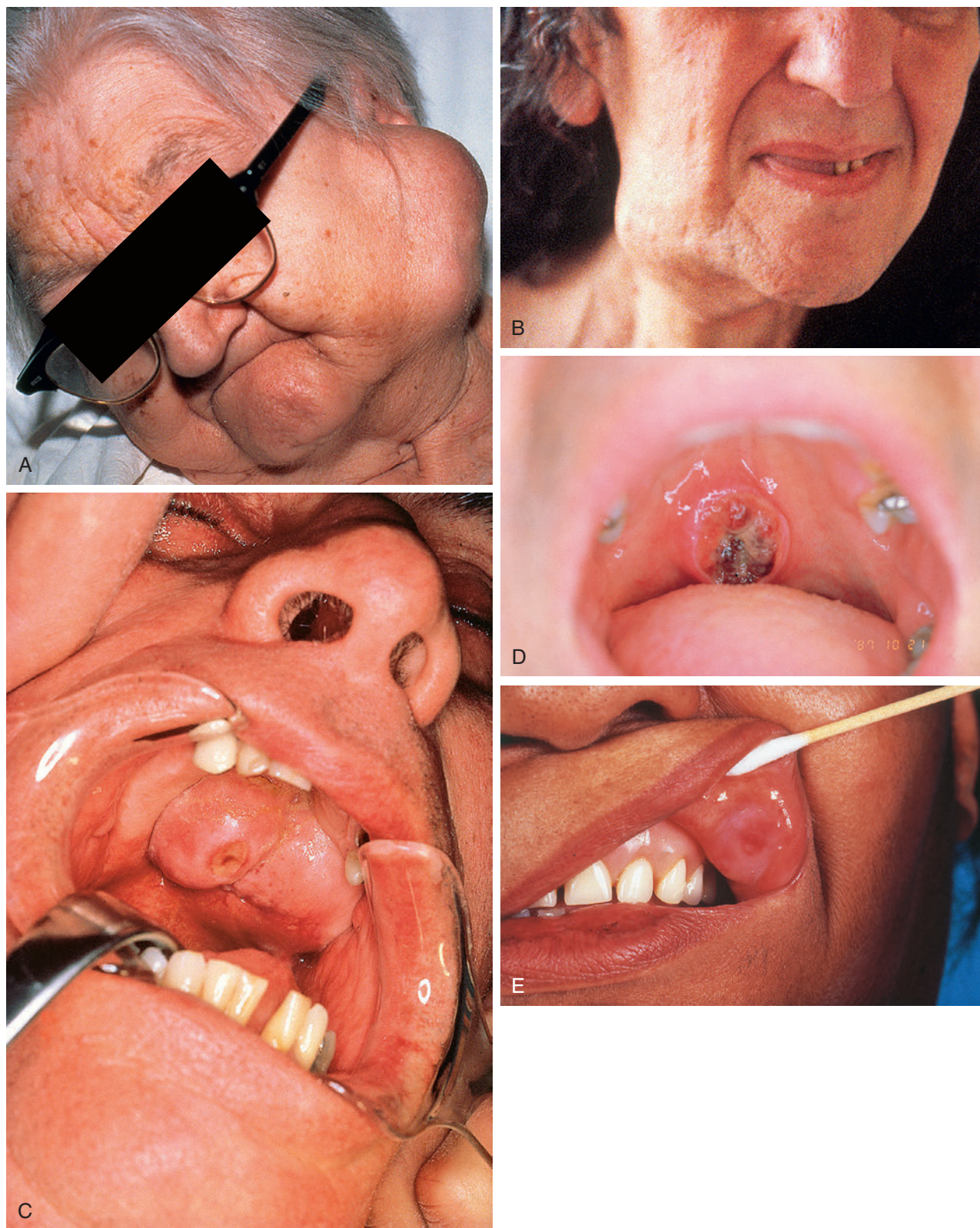


Fig. 20-72. Adenoid cystic carcinoma.

Adenoid cystic carcinoma may originate anywhere in the upper aerodigestive tract, including (A) parotid gland; (B) submandibular gland; (C) hard palate; (D) soft palate; and (E) lip.

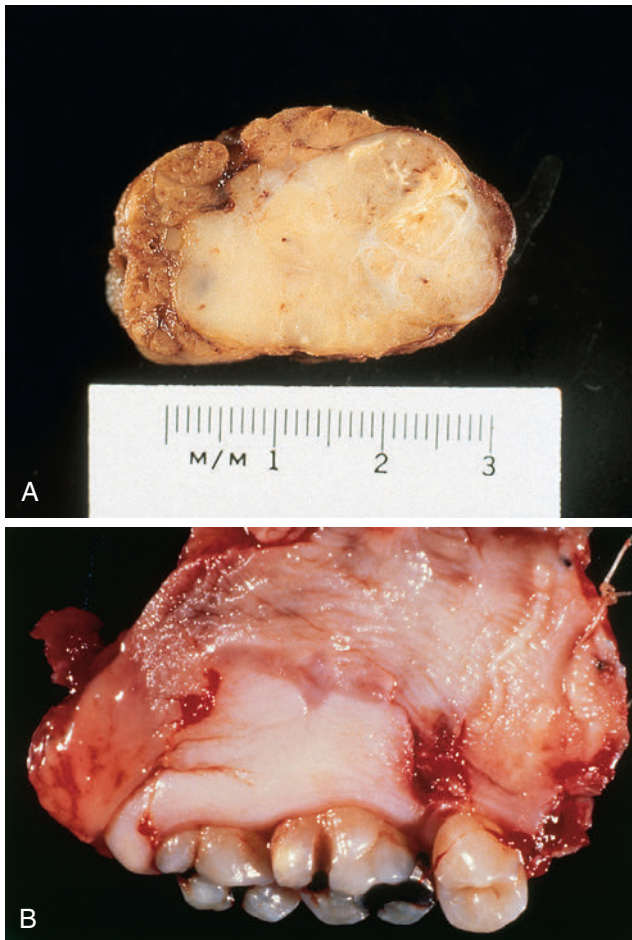


Fig. 20-73. Adenoid cystic carcinoma, resection specimens.

A, Submandibular gland replaced by a solid neoplasm replacing most of the gland; the tumor in part appears circumscribed but has infiltrative borders. **B**, Maxillary sinus neoplasm that invaded through the palate with involvement of the oral cavity.

- Generally uncommonly encountered prior to the third decade of life
- In major salivary glands, primarily involves parotid and submandibular glands:
- Nearly half arise in minor salivary glands:
 - May involve minor salivary glands throughout upper respiratory tract but most commonly involves intraoral sites:
 - Palate most common intraoral site
 - Second only to parotid gland as most common site of occurrence
 - Other minor salivary gland sites of involvement include:
 - Tongue, sinonasal tract, ceruminous glands of external auditory canal, and lacrimal gland:
 - More common tumor type of lacrimal glands
- Symptoms vary according to site involved but most common complaint is a slow-growing mass with or

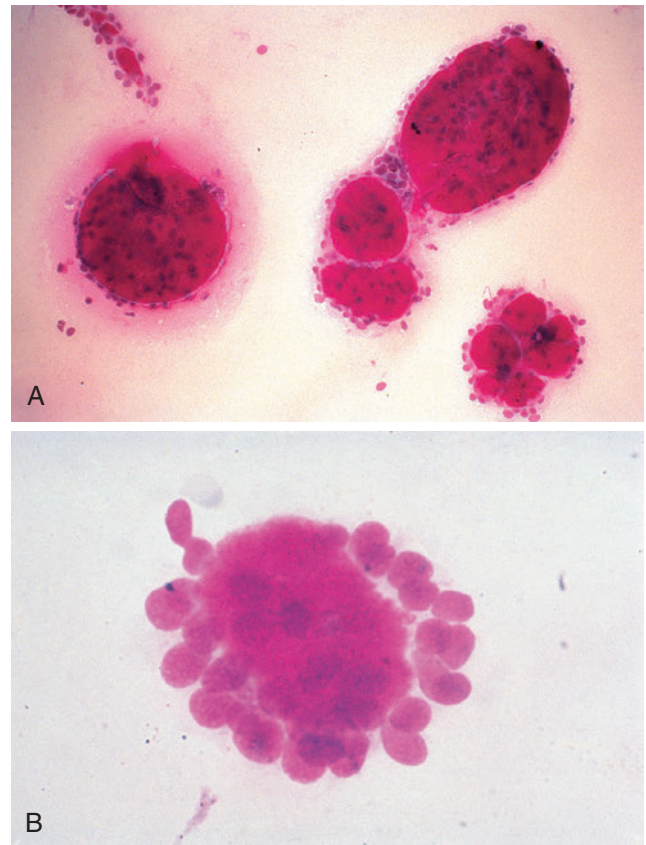


Fig. 20-74. Adenoid cystic carcinoma, fine-needle aspiration biopsy.

The aspirate is characterized by the presence of spheres, globules, and elongated cylinders of acellular stroma surrounded by uniform-appearing basaloid cells.

without associated pain or cranial nerve (e.g., facial nerve) paralysis:

- Other symptoms include:
 - Airway obstruction, epistaxis, otalgia, and hoarseness
 - Rarely, may present as a rapidly enlarging mass
 - Ulceration is often present in mucosal-based tumors.
 - Fixation to surrounding tissues is often present.
- Etiology:
 - No known cause

Pathology

Gross

- Circumscribed, unencapsulated, partly encapsulated, poorly circumscribed to infiltrative, solid, rubbery to firm, tan-white to gray-pink mass measuring from 2 to 4 cm in greatest dimension

Fine-Needle Aspiration Biopsy

- Aspirates are characterized by presence of relatively uniform cells associated with (surrounded by or

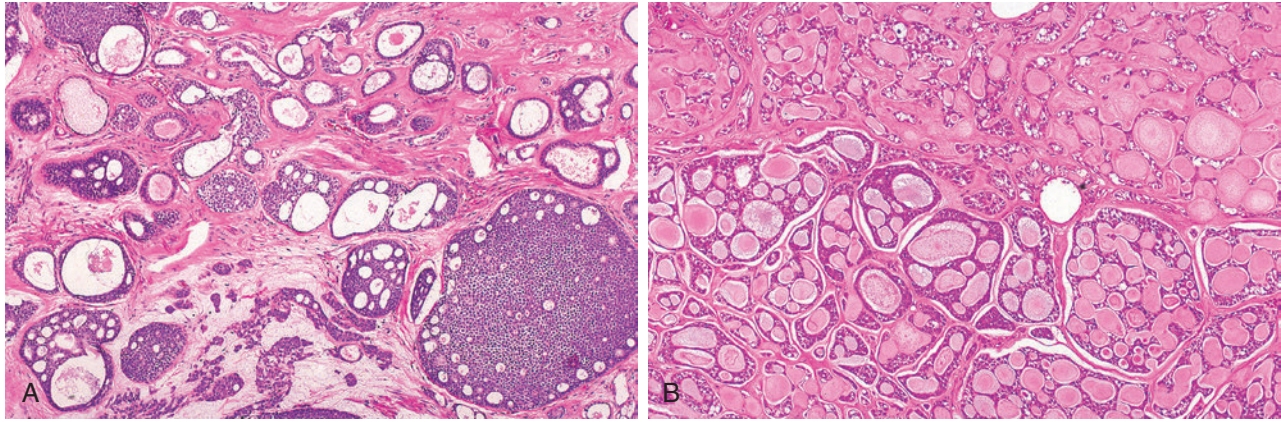


Fig. 20-75. Adenoid cystic carcinoma.

A, Infiltrating neoplasm with multiple (polymorphous) growth patterns including cribriform, solid, tubular/ductular and trabecular. **B**, “Classic” cribriform growth is present (lower portion of the illustration) with prominent intracystic and extracellular hyalinized eosinophilic (reduplicated basement membrane-like) material.

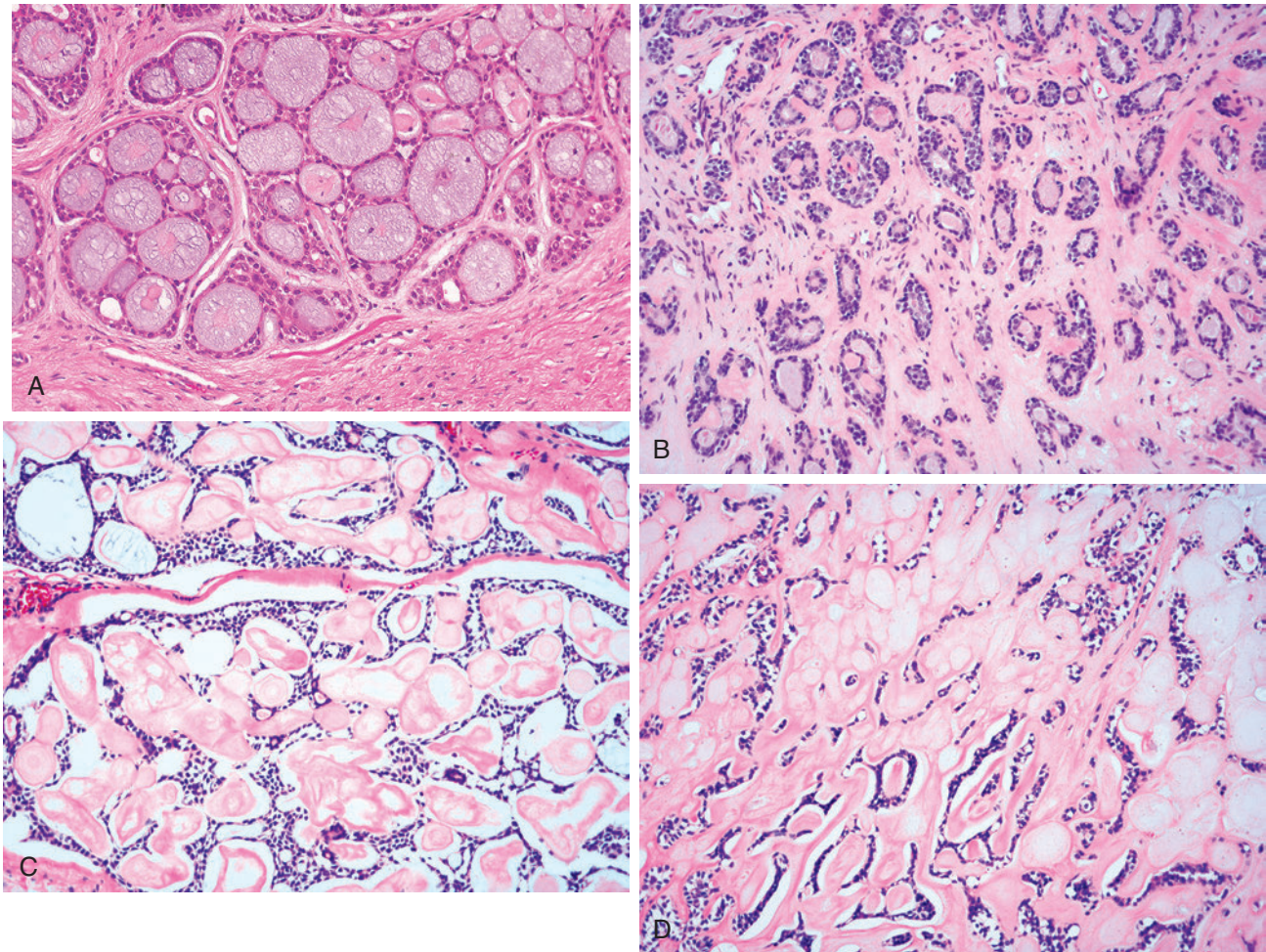


Fig. 20-76. Adenoid cystic carcinoma.

A, Cribriform pattern creating a “Swiss cheese” configuration includes pseudocysts lined by abluminal (modified myoepithelial) cells containing basophilic mucinous material. **B**, Tubular growth pattern with intraluminal eosinophilic to basophilic-appearing material. **C**, Cystic spaces filled with eosinophilic hyaline (basement membrane-like) material. **D**, Extracellular eosinophilic hyaline (basement membrane-like) material resulting in trabecular and cord-like growth.

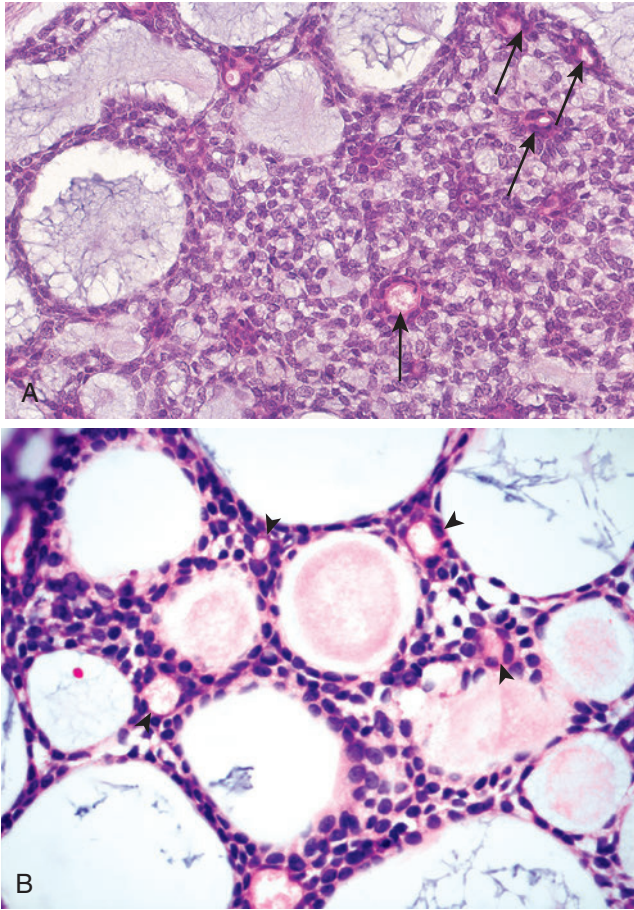


Fig. 20-77. Adenoid cystic carcinoma.

A and **B**, The abluminal (modified myoepithelial) cells dominate in any given tumor but true luminal (epithelial) cells can be seen forming glandular spaces (arrows in **A**; arrowheads in **B**) but may be limited in extent and difficult to identify.

clinging to) spheres, globules, and elongated cylinders of acellular stroma:

- Diagnosis often can be made by FNAB.
- Matrix globules appear metachromatic by Romanowsky staining, purple to pink by Giemsa staining, and pale green or light orange by Papanicolaou staining.
- Similar to pleomorphic adenoma, the diagnosis is based on the presence of characteristic extracellular matrix material.
- Matrix of pleomorphic adenomas tends to be fibrillar and less well defined as compared to the extracellular matrix material associated with adenoid cystic carcinoma. However, overlapping features between the extracellular matrix material of adenoid cystic carcinoma, pleomorphic adenoma, basal cell adenoma, acinic cell adenocarcinoma, and other tumors may create difficulties in the cytologic diagnosis.

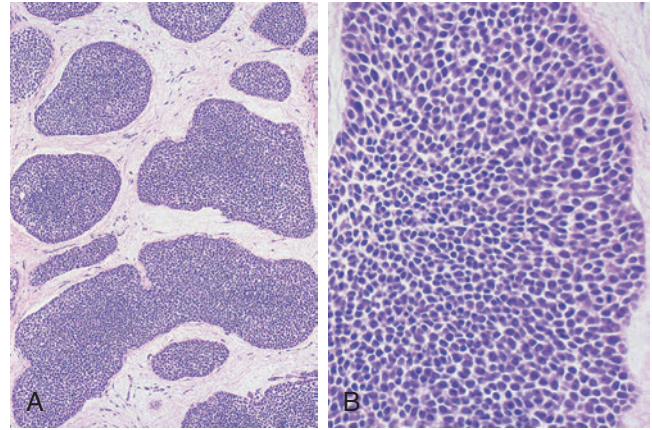


Fig. 20-78. Adenoid cystic carcinoma, solid variant.

A, Tumor cells arranged in solid nests and present in at least 30% of a given tumor. **B**, The cellular component in the solid variant tends to include larger more pleomorphic nuclei with increased mitotic activity.

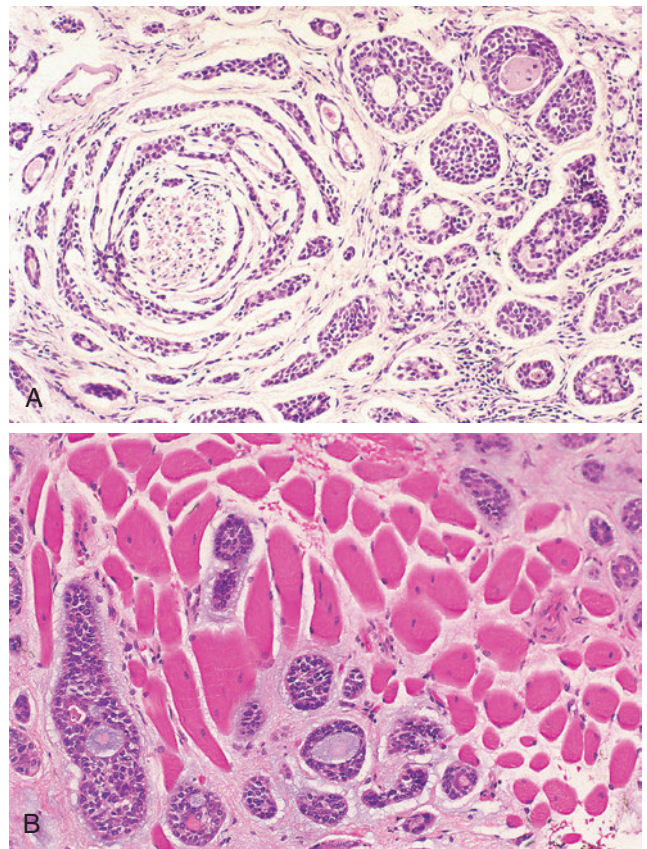


Fig. 20-79. Adenoid cystic carcinoma.

A, Characteristically perineural invasion (neurotropism) is identified. **B**, Less frequently invasion into soft tissues, including skeletal muscle, may be identified.

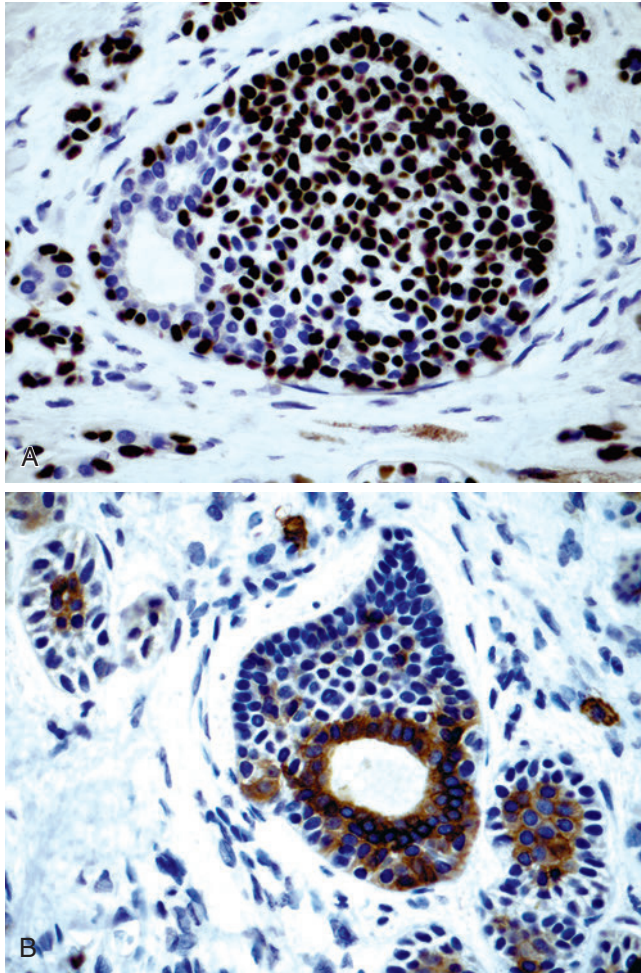


Fig. 20-80. Adenoid cystic carcinoma.

Immunohistochemical staining is not typically required in diagnosing adenoid cystic carcinoma but among the markers and staining patterns seen include (A) p63 dedicated to the abluminal (myoepithelial) cells but not luminal lining cells; (B) CD117 dedicated to luminal lining cells but not abluminal (myoepithelial) cells. NOTE: CD117 is not uniquely identified in adenoid cystic carcinoma but can be seen in other salivary gland neoplasms, including benign and malignant neoplasms.

- Cells of adenoid cystic carcinoma are small with uniform, hyperchromatic nuclei, limited cytoplasm, high nuclear-to-cytoplasmic ratio, and indistinct cell borders.
- Cells may be arranged individually or in loose syncytial fragments.
- In solid variant of adenoid cystic carcinoma:
 - Cells may be larger with greater variability in the size and shape of the nuclei.
 - Nucleoli may be identifiable.
 - There is often loss of cellular cohesion with overlapping of cells.
 - Necrosis and mitoses may be seen.

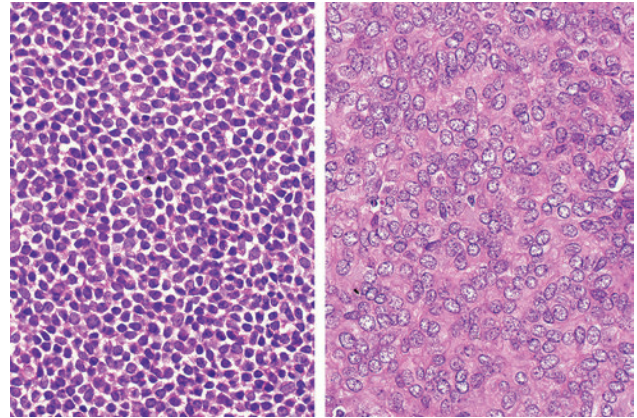


Fig. 20-81. Adenoid cystic carcinoma vs PLGA.

The differentiation between adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma (PLGA) can be extremely challenging. Although there is suggestion that staining patterns of p63 and p40 may contrast between these two lesions, thereby allowing for differentiation, such findings are not consistently identified. Differentiation may be predicated on the cytomorphologic findings. *Left*, In adenoid cystic carcinoma the lesional cells are composed of smaller isomorphic hyperchromatic nuclei lacking significant pleomorphism and mitotic activity; *right*, in PLGA the lesional cells are comprised of larger isomorphic vesicular nuclei lacking significant pleomorphism and mitotic activity.

- MYB immunohistochemical staining in FNAB specimens potentially useful in diagnosis of adenoid cystic carcinoma (positive nuclear staining) and in differential diagnosis from pleomorphic adenoma (negative staining)
 - Reported sensitivity of MYB on FNAB of 80% and specificity of 100% relative to pleomorphic adenoma

Histology

- Typically unencapsulated and infiltrative with varied growth patterns (i.e., polymorphic) including cribriform, tubular/ductular, and solid:
 - Individual neoplasms may have single growth but characteristically are composed of multiple patterns of which any one may predominate.
 - Some cases may be encapsulated without invasive growth with diagnosis predicated on characteristic light microscopic features.
 - Common to all histologic patterns (see below) is proclivity to peri- and, less often, intraneural invasion:
 - Not pathognomonic for adenoid cystic carcinoma

- Seen in a variety of other salivary gland and non-salivary gland tumors
- In adenoid cystic carcinoma tendency for infiltration along nerves beyond main tumor
- In addition to neurotropism, invasion into adjacent structures including salivary gland parenchyma, fibroconnective tissues (e.g., fat, skeletal muscle) and lymph-vascular or angioinvasion
- Generally tend to be resistant to presence of squamous differentiation:
 - Identification of squamous component (cells with intercellular bridges, keratinization, squamous eddies) supports an alternative diagnosis rather than adenoid cystic carcinoma
- Cellular components:
 - Basaloid-appearing (abluminal) cells:
 - Represent modified myoepithelial or basal cells
 - Dominant cell type
 - Surround pseudocysts
 - Composed of uniform angular to oval, hyperchromatic nuclei with absent nucleoli and scanty cytoplasm with indistinct cell borders:
 - Occasional cells with small nucleoli may be seen
 - Eosinophilic to clear-appearing cytoplasm may be present
 - Nuclear pleomorphism and mitotic activity are typically not present.
 - Low or 1:1 nuclear-to-cytoplasmic ratio.
 - Ductal (luminal) structures:
 - True glandular spaces
 - Scattered among basaloid cells and may be difficult to identify
 - Characterized by presence of cells with round nuclei and eosinophilic-appearing cytoplasm
- Interstitial stroma, from which the epithelial component is sharply demarcated, varies in appearance from myxoid to mucinous to hyalinized

Cribriform Pattern

- Most characteristic (“classic”) pattern
- Arrangement of cells in “Swiss cheese” or sieve-like configuration with many oval or circular microcystic (pseudocystic) spaces
- Microcysts are pseudocysts (not true epithelial lined glandular lumens) contiguous with stromal connective tissue and contain basophilic mucinous substance and/or hyalinized eosinophilic material:
 - Cystic spaces are pseudocysts, which are extracellular and lined by replicated basement membrane.
 - Basophilic mucinous substance is alcian blue positive.
 - Hyalinized eosinophilic material is PAS positive.

Tubular Pattern

- Often seen in association with cribriform pattern
- Cells are arranged in ducts or tubules.
- Dual cell differentiation (i.e., ductal and myoepithelial cells) present with readily identifiable epithelial-lined true ducts surrounded by myoepithelial (abluminal) cells.
- Ducts or tubules may be empty or contain faintly eosinophilic mucinous material.

Solid Pattern

- Least common pattern
- Neoplastic cells arranged in sheets or nests of varying size and shape
- Little tendency to form cystic spaces, tubules, or ducts
- Cytomorphology similar to cribriform and tubular patterns but findings in solid pattern may include:
 - Tendency for cells to be larger with larger nuclei
 - Greater nuclear pleomorphism
 - Increased mitotic activity (5 or more mitoses per 10 high-power fields)
 - Necrosis (confluent foci and individual cell)
- Histologic grading:
 - Grade I:
 - Mostly tubular with some cribriform patterns
 - Absence of solid pattern
 - Absence of nuclear pleomorphism and increased mitotic activity
 - Grade II:
 - Pure cribriform pattern or mixed tubular/cribriform; solid patterns may be present but not >30%
 - Slightly greater degree of nuclear pleomorphism and mitotic activity than Grade I
 - Grade III:
 - >30% solid pattern
 - More significant nuclear pleomorphism and increased mitotic activity over Grade II:
 - Larger cells with larger nuclei
 - 5 or more mitoses per 10 high-power fields
 - Necrosis often present:
 - Confluent foci and individual cell
- Histochemistry:
 - Pseudocysts contain diastase-resistant, PAS-positive, and mucicarmine-positive material.
- Immunohistochemistry:
 - Myoepithelial or basal (abluminal) cells:
 - Cytokeratins, p63, p40, S100 protein, calponin, smooth muscle actin, smooth muscle myosin heavy chain, and vimentin positive
 - Cytokeratin tends to be less intensely reactive as compared to ductal cells
 - Glial fibrillary acidic protein may be focally positive.

- Ductal (luminal) cells:
 - Cytokeratins (pancytokeratin, CK7, CK14, CK17, CK19), S100 protein, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) and c-kit (CD117) positive:
 - Cytokeratin tends to be more intensely reactive as compared to myoepithelial or basal cells.
- IHC findings including pairing p63 and p40 reported to assist in differentiating pleomorphic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC) include:
 - PA: p63+/p40+
 - Cellular PA: concordant p63+/p40+ or p63–/p40–
 - PLGA: consistent p63+/p40–
 - AdCC: p63+/p40+

CAUTIONARY NOTE: While p63/p40 IHC panel can be a valuable tool for making distinction between PA, PLGA, and AdCC it is not infallible and any given example may demonstrate divergence from the reported p63/p40 immunophenotype.
- Additional immunohistochemical findings may include:
 - Expression of MYB protein (see below under Cytogenetics):
 - Identified in translocation-positive and translocation-negative adenoid cystic carcinomas
 - More than 80% of adenoid cystic carcinomas reported to stain positive for MYB protein
 - 14% of nonadenoid cystic carcinoma neoplasms also reported to express MYB protein
 - MYB immunostaining may be useful for diagnosis of adenoid cystic carcinoma, but neoplasms in differential diagnosis may also express MYB protein.
 - Ki67 (MIB1) staining:
 - Proliferative indices reported to be significantly higher in adenoid cystic carcinoma (21%) as compared with polymorphous low-grade adenocarcinoma (2%)
 - Increased proliferation index may not be present in all cases of adenoid cystic carcinoma and by itself does not unequivocally differentiate it from polymorphous low-grade adenocarcinoma.
 - Reactivity for mammaglobin may be present, including cases with positive staining and cases with negative staining.
 - May be DOG-1 positive, showing distinctive combined apical ductal and membranous/cytoplasmic myoepithelial staining profile

- GATA-3 staining may be present but not diffusely as seen in salivary duct carcinoma and mammary analogue secretory carcinoma.
- Sox10 variably positive in abluminal and luminal cells
- No immunoreactivity for neuroendocrine markers (e.g., synaptophysin, chromogranin), GDCP15, and PLAG1
- Ultrastructure:
 - Ductal (luminal) cells:
 - Microvilli, desmosomes, tonofilaments, and rough endoplasmic reticulum
 - Myoepithelial (abluminal) cells:
 - Variable findings including cytoplasmic processes, cytoplasmic filaments, dense bodies, desmosomes, tonofilaments
 - Pseudocysts contain reduplicated basal lamina.
 - Basal lamina surround epithelial islands.
- Cytogenetic and molecular genetics:
 - Specific chromosomal translocation t(6;9)(q22-23;p23-24) involving the v-myb avian myeloblastosis viral oncogene homolog (MYB) and nuclear factor I/B (NFIB) genes results in *MYB-NFIB* gene fusion identified in adenoid cystic carcinomas:
 - Identified in adenoid cystic carcinomas irrespective of site of occurrence, including salivary glands, sinonasal tract, larynx, tracheobronchial tree, lacrimal gland, as well as non-head and neck sites (e.g., breast, vulva)
 - Gene fusion found in 30% to 50% of cases with increase to 86% when performed on frozen specimen
 - *MYB-NFIB* gene fusion in dermal cylindromas strengthening evidence for common molecular pathways for development of benign and malignant salivary, adnexal, and breast tumors
 - Not detected in other salivary gland neoplasms:
 - 1 purported case of polymorphous low-grade adenocarcinoma reported to express adenoid cystic carcinoma-associated *MYB-NFIB* by RT-PCR analysis
 - Molecular consequences of this alteration incompletely understood but suggest important role in development of adenoid cystic carcinoma
 - Dysregulated microRNAs (miRNA) found in adenoid cystic carcinomas:
 - No significant differences in miRNA expression between *MYB-NFIB* fusion-positive and fusion-negative cases
 - Of highly dysregulated miRNA in adenoid cystic carcinoma, overexpression of miR-17

and miR-20a was significantly associated with poor outcome.

- Upregulation of miR-17-92 may play a role in biology of ACC and could potentially be targeted in future therapeutic studies.
- Additional mutations identified in adenoid cystic carcinoma include:
 - PIK3CA, ATM, CDKN2A, SF3B1, SUFU, TSC1, and CYLD
 - Mutations in SPEN (split ends, homolog of *Drosophila*), which encodes an RNA-binding coregulatory protein, suggest that other changes in transcriptional regulation may involve NOTCH, FGFR, or other signaling pathways in which SPEN participates.
 - Mutations in genes encoding chromatin-state regulators, such as SMARCA2, CREBBP, and KDM6A, reported suggesting aberrant epigenetic regulation in adenoid cystic carcinoma oncogenesis.
 - Mutations in genes central to DNA damage response and protein kinase A signaling also implicated
 - Recurrent mutations in FGF-IGF-PI3K pathway (30% of tumors)
 - Might represent new avenues for therapy

Hybrid Tumors

- Rare occurrence of neoplasm composed of two or more histologic distinct types, each of which conforms with an exactly defined tumor category having an identical origin within same topographic area
 - In contrast, biphasically differentiated tumors are a mixture of two cellular patterns corresponding to a specific classification (e.g., epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, others)
- Most common tumor types include:
 - Adenoid cystic carcinoma
 - Salivary duct carcinoma
 - Epithelial-myoepithelial carcinoma
- Other tumor types that may be seen in hybrid tumors include:
 - Basal cell adenoma
 - Warthin tumor
 - Canalicular adenoma
 - Acinic cell carcinoma
 - Basal cell adenocarcinoma
 - Myoepithelial carcinoma
- Combinations may include multiple malignant tumor types, multiple benign tumor types, and admixture of benign and malignant tumor types.
- May occur in initial clinical presentation or in recurrent tumor
- Prognosis predicated on highest histologic grade malignancy (e.g., salivary duct carcinoma)

High-Grade Transformation (“Dedifferentiation”) in Adenoid Cystic Carcinoma

- Unusual occurrence of a histologically low-grade adenoid cystic carcinoma transforming to a high-grade carcinoma and/or progression from solid adenoid cystic carcinoma to a high-grade carcinoma:
 - Male predominance
 - Age range of fourth to eighth decades with median age in seventh decade (61 years)
 - Occurs most often in association with sinonasal and submandibular adenoid cystic carcinomas
 - Most common morphologies for high-grade component include poorly differentiated cribriform adenocarcinoma and solid undifferentiated carcinoma
 - Micropapillary and squamoid patterns occasionally identified
 - Histologically high-grade transformation distinguished from conventional adenoid cystic carcinoma by presence of:
 - Nuclear pleomorphism with enlargement and irregularity
 - Higher mitotic counts
 - Loss of the biphasic ductal-myoepithelial differentiation
 - Prominent comedonecrosis
 - Fibrocellular desmoplasia
 - Ki-67 and p53 labeling indices elevated in high-grade components
 - Loss or diminished p63 and calponin staining in high-grade components
 - Behavior follows that of less differentiated component and often characterized by:
 - Aggressive growth
 - Nodal metastases
 - Distant metastases
 - Poor prognosis with increased mortality:
 - Death often occurring within 5 years of diagnosis with median overall survival of 12 months

Differential Diagnosis (Table 20-8)

- Pleomorphic adenoma
- Basal cell adenoma:
 - May show cribriform growth
 - Absence of infiltrative growth:
 - Occasional cases of adenoid cystic carcinoma may not be invasive.
 - Cell types, including cells with larger more vesicular nuclei with identifiable nucleoli combined with basaloid hyperchromatic nuclei and squamous differentiation, should allow distinction from adenoid cystic carcinoma.

TABLE 20-8 Adenoid Cystic Carcinoma: Differential Diagnosis

Tumor	Growth Characteristics	Histology	Squamous Differentiation	Neurotropism	Cytogenetics
AdCC, cribriform/tubular	Invasive, polymorphous including “Swiss cheese,” microcysts, tubules, and ductules; reduplicated basement membrane material present	Predominantly composed of uniform basaloid cells surrounding pseudocysts with angular to oval, hyperchromatic nuclei (myoepithelial cells) with admixed epithelial cells lining glandular spaces with round nuclei and eosinophil-appearing cytoplasm (ductal cells); nuclear palisading typically absent	Absent	Yes, as well as invasive into other structures	MYB-NFIB
AdCC, solid	Invasive; sheets and nests of varying size and shape with little tendency to form cystic spaces, tubules or ducts; reduplicated basement membrane material uncommon	Similar to cribriform tubular but cells are larger with larger nuclei, greater nuclear pleomorphism, increased mitotic activity (5 or more mitoses per 10 high-power fields) and necrosis (confluent foci and individual cell); nuclear palisading typically absent	Absent	Yes, as well as invasive into other structures	MYB-NFIB
PLGA	Invasive, polymorphous with cribriform, tubular, solid, single cell, papillary, microcystic; reduplicated basement membrane material present	Isomorphic single-cell type with vesicular nuclei, minimal pleomorphism and absent mitotic activity; nuclear palisading typically absent	May be present typically as metaplastic foci following FNAB or biopsy	Yes, as well as invasive into other structures	None known, although PRKD2 rearrangement reported in a single case
CPA	Encapsulated, may be polymorphous; reduplicated basement membrane material present	Irrespective of cell type (ductal or myoepithelial) or degree of cellularity there usually is an absence of significant pleomorphism, mitotic activity, and no necrosis; nuclear palisading typically absent	May be present typically as metaplastic foci following FNAB or biopsy	No	PLAG1 HMGA2
BCA	Encapsulated, reduplicated basement membrane material present	Combination of basaloid cells, cells with larger more vesicular nuclei; peripheral nuclear palisading may be present	Present but usually limited in extent including squamous eddies	No	None known
BCACA	Invasive reduplicated basement membrane material present	Basaloid cells with variable nuclear pleomorphism and increased mitotic activity; peripheral nuclear may be present	Present but usually limited in extent including squamous eddies	Yes, as well as invasive into other structures	None known

TABLE 20-8 Adenoid Cystic Carcinoma: Differential Diagnosis—cont'd

Tumor	Growth Characteristics	Histology	Squamous Differentiation	Neurotropism	Cytogenetics
BSCC	Invasive, lobular, solid, nested, trabecular, organoid, cribriform; reduplicated basement membrane material may be present	Predominantly basaloid cells with marked pleomorphism, high mitotic rate and necrosis; nuclear palisading typically absent	Present but usually limited in extent and may include intraepithelial dysplasia and/or abrupt keratinization and/or differentiated invasive squamous with keratinization and intercellular bridges	Yes, as well as invasive into other structures	None known
EMC	Invasive, tubular/ductular; typically lacks reduplicated basement membrane material present	Biphasic cell pattern including inner epithelial cells and outer myoepithelial cells	Absent to rare	Yes, as well as invasive into other structures	Limited cases have <i>HRAS</i> exon 3 codon 61 mutation

ACC, Adenoid cystic carcinoma; BCA, basal cell adenoma; BCACA, basal cell adenocarcinoma; BSCC, basaloid squamous cell carcinoma; CPA, cellular pleomorphic adenoma; EMC, epithelial-myoepithelial carcinoma; PLGA, polymorphous low-grade adenocarcinoma.

- Presence of squamous differentiation represents feature not typically associated with adenoid cystic carcinoma
- Absence of *MYB-NFIB* gene fusion
- Polymorphous low-grade adenocarcinoma
 - Overlapping features with adenoid cystic carcinoma
 - Purported differential staining of p63 and p40 than that seen in adenoid cystic carcinoma:
 - Consistent p63+/p40– as compared with adenoid cystic carcinoma showing consistent p63+/p40+
- Basal cell adenocarcinoma
- Basaloid squamous cell carcinoma
- Epithelial-myoepithelial carcinoma
- Recurrence rates range from 16% to 85% and high recurrence rates directly relate to inadequate surgical excision.
- Regional lymph node metastases are uncommon, ranging from 5% to 25%:
 - Neck dissection at time of surgical removal of primary tumor is generally not warranted.
 - Usually occur in association with tumors of submandibular gland origin
- Distant metastasis ranges from 25% to 55%:
 - Generally occur late in disease course following multiple local recurrences
 - Occurs primarily to lungs, bone, brain, and liver
 - Although prolonged survival may occur after metastases, death usually follows within 1 year of identification of metastatic foci.
- Short-term prognosis generally good corresponding to the slow growth leading to prolonged survivals; long-term prognosis is poor
 - 5-year overall survival ranges from 60% to 90%
 - 10-year overall ranges from 29% to 80%
 - 15-year overall survival ranges from 29% to 55%
- Factors affecting prognosis include:
 - Location of primary tumor:
 - Submandibular gland tumors have worse prognosis than parotid gland tumors.
 - Overall, major salivary gland adenoid cystic carcinomas have a better prognosis than their minor salivary gland counterparts, although palatal tumors have a better prognosis.
 - Sinonasal tract tumors have a poor prognosis.
 - Size of the primary tumor:
 - Smaller primary neoplasms that are more amenable to complete resection the better the prognosis

Treatment and Prognosis

- Wide local surgical excision is preferred treatment:
 - Problems confronting surgical removal relate to infiltrative nature with tendency to extend along nerve segments further compounded by their deceptively circumscribed macroscopic appearance
- Radiosensitive and radiotherapy particularly useful (although not curative) in:
 - Controlling microscopic disease after initial surgery
 - Treating locally recurrent disease
 - Palliation management in unresectable tumors
- Chemotherapy used as palliation in patients with advanced disease:
 - Role of chemotherapy in treatment remains unproven.
 - No proven chemotherapeutic protocols

- Tumors measuring greater than 4 cm have a worse prognosis.
- Facial nerve paralysis:
 - Symptoms of facial nerve paralysis may be associated with worse prognosis and quicker demise of patient
- Histologic grade:
 - Tumors with tubular and cribriform growth have better prognosis:
 - 15-year survival rates:
 - Grade I: 39%
 - Grade II: 26%
 - Predominantly solid tumors (i.e., more than 30% of overall pattern) have worse prognosis associated with earlier and more frequent recurrent tumor.
 - Higher incidence of metastasis:
 - May metastasize even in clinically lower stage tumors (e.g., T1, T2)
 - Earlier fatal outcomes:
 - 14% 5-year survival
 - 5% 15-year survival
- Clinical stage:
 - Advanced clinical stage associated with poorer outcome
 - Stage I: 75% 10-year survival
 - Stage II: 43% 10-year survival
 - Stages III-IV: 15% 10-year survival
- Positive surgical margins and/or failure of local disease control following initial surgery:
 - Recurrent tumor is generally a sign of incurability.
- Adverse prognosis also associated with:
 - Presence of distant metastatic disease (5-year survival rate of 20%)
 - Presence of extranodal extension in nodal metastasis
 - Presence of osseous invasion
- Higher proliferative index (greater than 10% of tumor cells) as determined by Ki67 staining correlates to more aggressive tumors.

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA OF MINOR SALIVARY GLANDS (PLGA)

(Figs. 20-82 through 20-89)

Definition: Malignant epithelial neoplasm characterized by cytologic uniformity, morphologic diversity, infiltrative growth pattern, and a low metastatic potential.

Synonyms: Terminal duct carcinoma; lobular carcinoma

- Terminology of “terminal duct” carcinoma was used to emphasize proposed histogenesis of the tumor, thought to be progenitor cell of the distal or terminal

duct portions of salivary gland unit (i.e., intercalated duct reserve cell).

- Terminology of “lobular” carcinoma was used because of presence of single cell–filling infiltrative growth pattern similar to that of lobular carcinoma of breast origin.

Clinical

- More common in women than in men; occurs over a wide age range from the second to tenth decades of life, but most frequently seen in the sixth to eighth decades of life:
 - Rarely occurs in the pediatric population
- Occurs primarily in minor salivary glands:
 - Almost exclusively identified in the oral cavity:
 - Approximately 60% to 70% involve palate (junction of hard and soft palate)
 - Other intraoral locations include buccal mucosa, upper lip, retromolar region, and base of tongue
 - Less common locations include parotid gland, lacrimal gland, nasopharynx, nasal cavity, sublingual, and submandibular glands:
 - May occur in parotid gland as malignant epithelial component in a carcinoma ex pleomorphic adenoma
- Most common symptom is that of a painless mass or swelling occasionally associated with bleeding, increase in size or discomfort; other less frequently identified symptoms include otalgia, odynophagia, tinnitus, and airway obstruction
 - Duration of symptoms is variable, ranging from as short as 2 weeks to a 20- to 30-year history of a mass lesion.
- Etiology:
 - No predisposing factors known to exist

Pathology

Gross

- Polypoid or raised, circumscribed to poorly demarcated, round to oval, mucosal-covered masses ranging in size from 1.0 to 6.0 cm in greatest dimension
- In general, overlying mucosa remains intact; however, surface ulceration may be present.

Fine-Needle Aspiration Biopsy

- Smears show high cellularity with a population of mixed epithelial and myoepithelial cells.
- Sheets and clusters of cells are seen and occasionally branching papillae may be identified.
- Epithelial cells appear cuboidal to spindle-shaped with uniform, round to ovoid nuclei with fine nuclear chromatin; absent or inconspicuous nucleoli; and a moderate amount of dense cytoplasm.

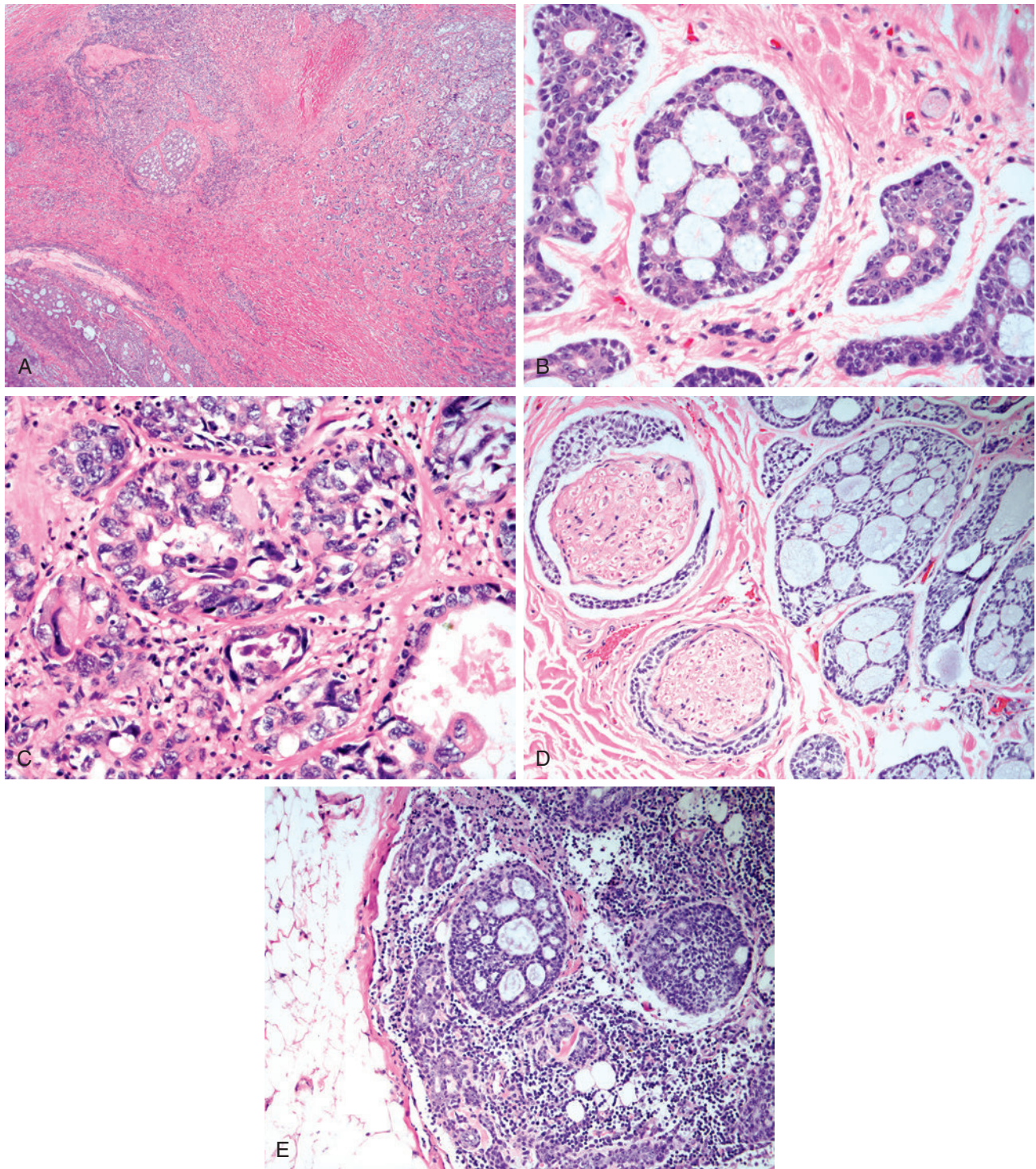


Fig. 20-82. High-grade transformation (dedifferentiation) of adenoid cystic carcinoma.

A, Transitional areas from differentiated adenoid cystic carcinoma characterized by cribriform growth and more uniform appearing cells (left of center) and areas of more disorganized growth (*right*). **B**, Higher magnification of the differentiated adenoid cystic carcinoma foci. **C**, Higher magnification of the histologically higher grade malignant component representing a high-grade adenocarcinoma. In relationship to the differentiated carcinoma there was **(D)** perineural invasion and **(E)** cervical lymph node metastasis.

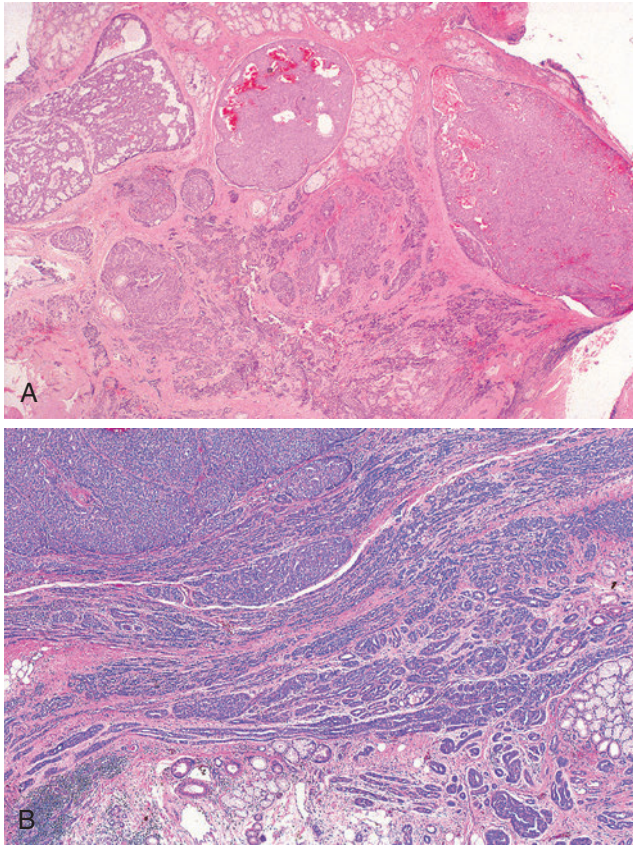


Fig. 20-83. Polymorphous low-grade adenocarcinoma.

A and **B**, At low magnification these tumors are unencapsulated and infiltrative, composed of more than one growth pattern (i.e., polymorphous). **B**, A characteristic feature is the presence of a swirling pattern often located at peripheral aspects of neoplasm.

- Occasionally cells form spheric structures containing hyaline globules.
- Myxoid matrix either dispersed in the background or interspersed with the cellular elements can also be seen.

Histology

- At low magnification appears well circumscribed, but unencapsulated and infiltrative growth may be appreciated.
- Multiple growth patterns (i.e., polymorphism) identified, including tubular (glandular, ductular), trabecular, solid nests, targetoid swirls, cribriform, fascicular, single cell filing, cystic, and/or papillary:
 - These patterns may be identified between tumors and within an individual tumor.
 - Many salivary gland tumors are polymorphous so the presence of polymorphism is not diagnostic for PLGA or for that matter any other salivary gland tumor.

- Main microscopic patterns are:
 - Tubular (glandular, ductular):
 - Identifiable central lumens
 - Seen individually or in clusters
 - Complex tubuloglandular structures common
 - Seen throughout the lesion but may be prominent at periphery where they are seen infiltrating adjacent tissues
 - Trabecular:
 - May appear in streaming pattern with identifiable lumens
 - Targetoid swirls:
 - Best appreciated at lower magnification(s)
 - Often located at peripheral aspects of neoplasm
 - Swirls, concentric whorls or targetoid arrangements
 - Characteristic although not pathognomonic
 - May envelop blood vessels or surround nerves
 - Solid or lobular:
 - Often seen in the central portions of the tumor
 - Sometimes seen with peripheral palisading of columnar cells
 - Cribriform and/or microcystic:
 - Similar to adenoid cystic carcinoma
 - Single cell filing:
 - Refers to pattern of cell growth in which the cells are arranged in a single row
 - Not a consistently common finding
 - Often located at periphery of tumor
 - Papillary or papillary-cystic foci:
 - Usually not a predominant feature
 - Consists of dilated cystic spaces with or without intraluminal papillary projections
 - Less common patterns include fascicular and canalicular
- Lesional cells characteristically:
 - Small to medium-sized cuboidal to columnar isomorphic cells with indistinct cell borders and uniform ovoid to spindle-shaped nuclei with vesicular to stippled to minimally hyperchromatic (basophilic) nuclear chromatin, small to inconspicuous nucleoli, scant to moderate amounts of eosinophilic to amphophilic cytoplasm, and indistinct cell borders
 - Spindle-shaped cells may be identified.
 - Minimal to absent nuclear pleomorphism
 - Absent to low mitotic activity
 - Atypical mitoses uncommon
 - Necrosis is not a typical feature.
 - Occasionally other cell types may be seen, including:
 - Clear cells and mucinous cells
 - Less often oncocytic, squamous, or acinic cells may be found.

- Presence of myoepithelial cells is controversial:
 - Some reports document myoepithelial cells as integral component
 - Some reports document absence of myoepithelial cells or very focal presence of myoepithelial cells.
- Tumor stroma varies from mucoid to hyaline to mucohyaline:
 - Often has a slate gray appearance
 - In some cases tumor nests are separated by a fibrovascular stroma.

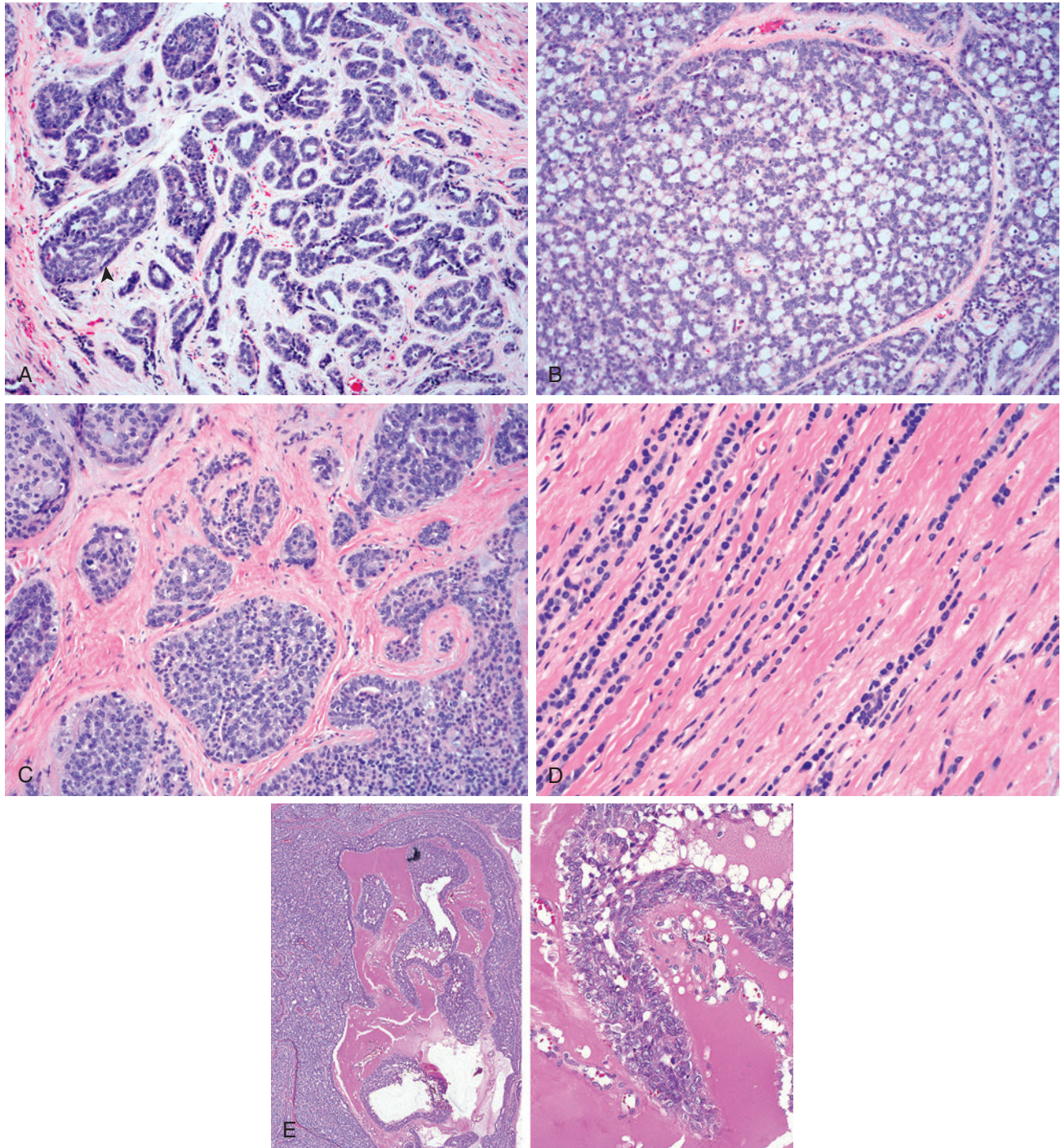


Fig. 20-84. Polymorphous low-grade adenocarcinoma.

A variety of growth patterns may be seen from case to case and even within a single case, including (A) tubular with focal cribriform (*arrowhead*); (B) microcystic; (C) solid; (D) single cell filing; (E) papillary;

Continued

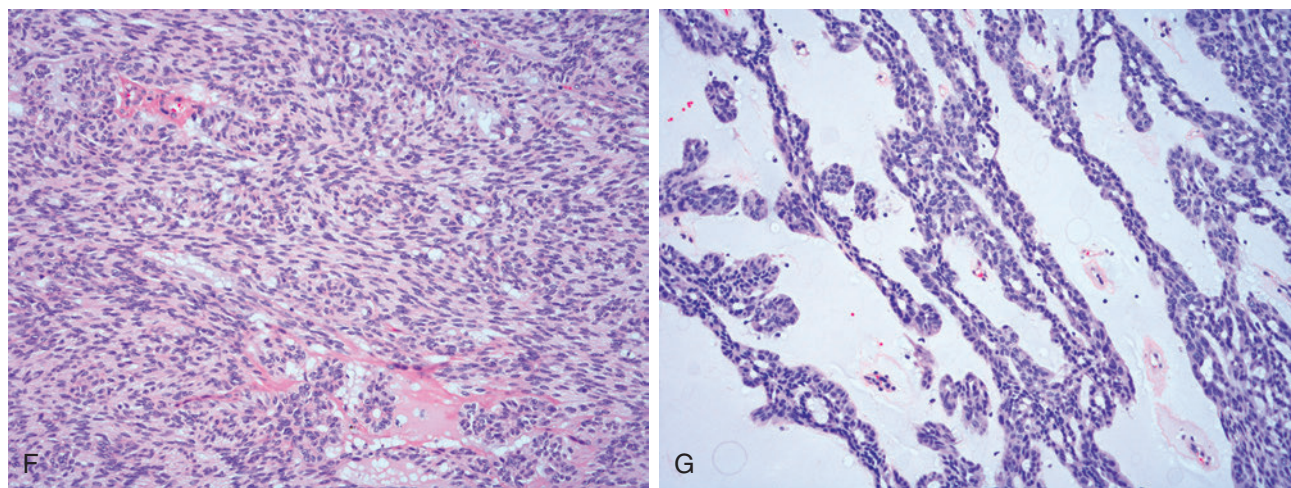


Fig. 20-84, cont'd

(F) fascicular; and (G) canalicular.

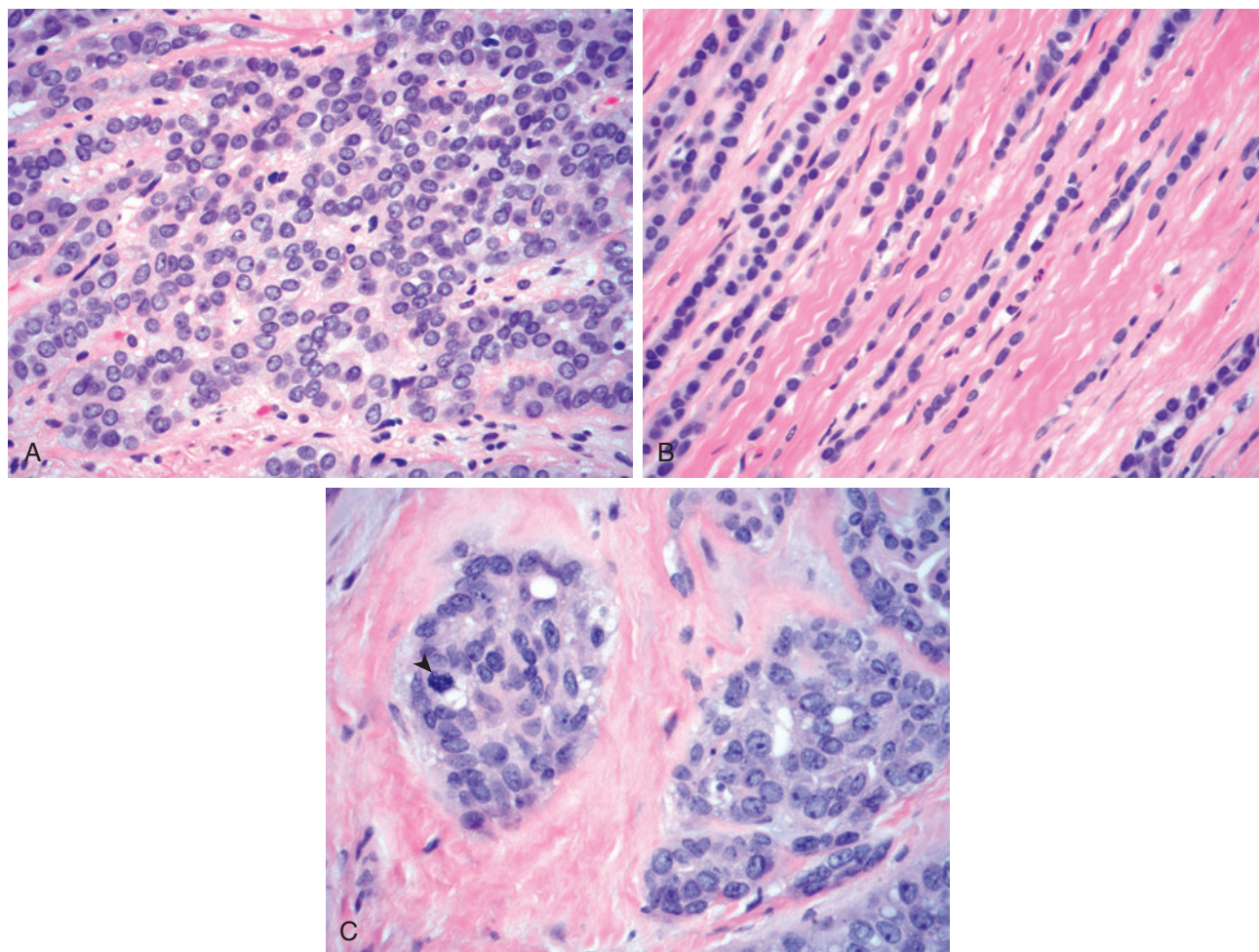


Fig. 20-85. Polymorphous low-grade adenocarcinoma.

A and **B**, Irrespective of growth pattern, the neoplastic cells are rather uniform (isomorphic), with limited variation in size and shape, vesicular-appearing nuclei, inconspicuous to small nucleoli, and absence of mitotic activity or necrosis.
C, Mitotic figures (*arrowhead*) may occasionally be identified.

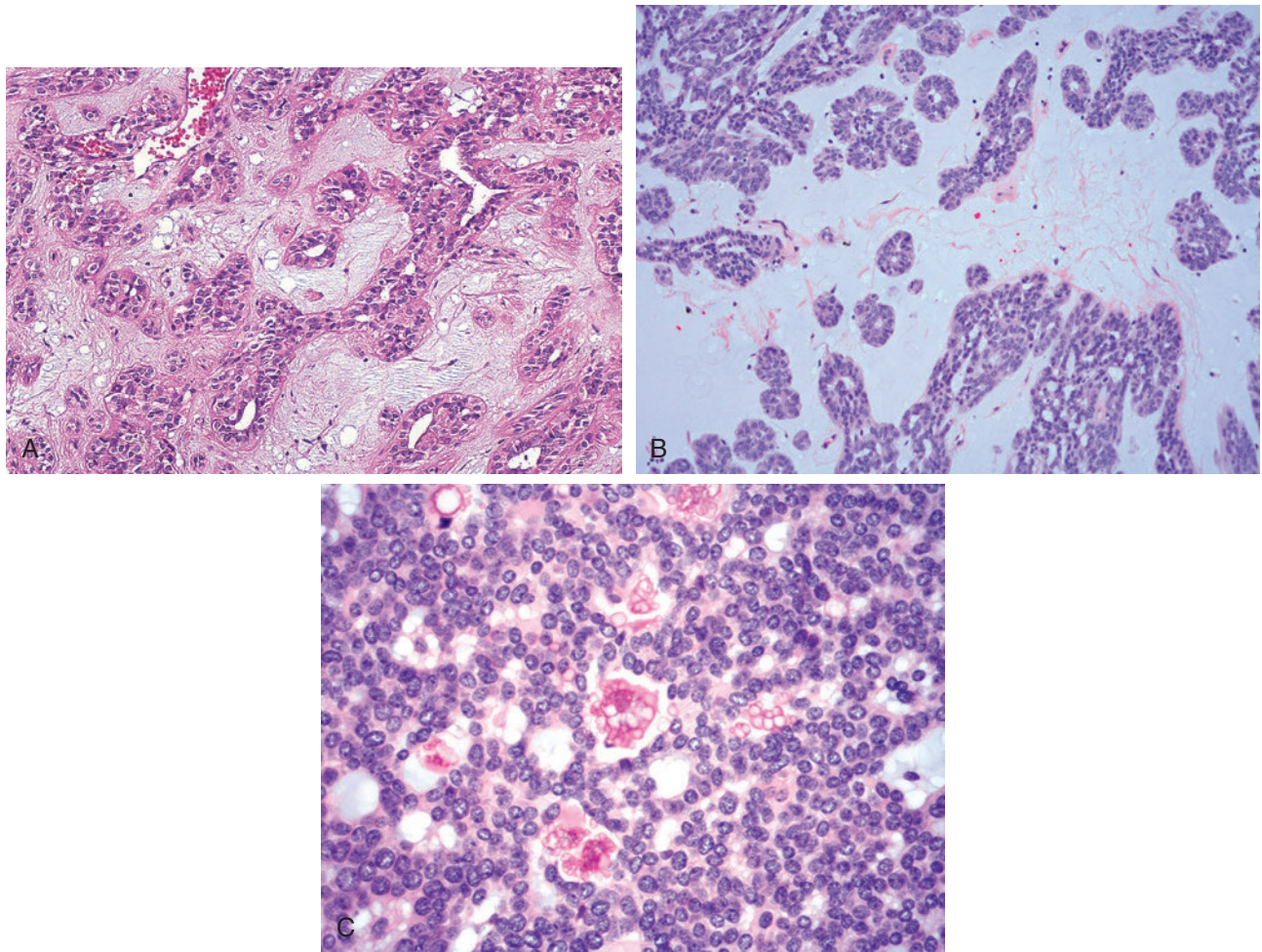


Fig. 20-86. Polymorphous low-grade adenocarcinoma.

A and **B**, The stroma tends to be myxoid or chondroid with a grayish appearance. **C**, Tyrosine-like crystals may be identified.

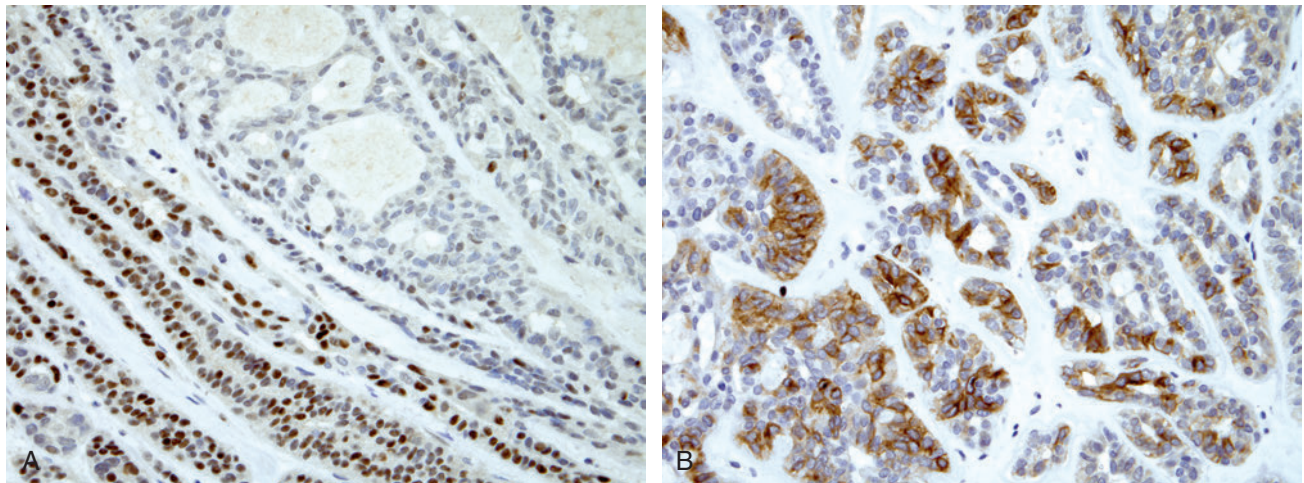


Fig. 20-87. Polymorphous low-grade adenocarcinoma.

Immunohistochemical staining is not typically required in diagnosing polymorphous low-grade adenocarcinoma. Among the markers seen include **(A)** haphazard p63 immunoreactivity including focal positive areas adjacent to negative areas; typically other myoepithelial markers are negative (not shown); **(B)** CD117 immunoreactivity may be present and is not a stain that consistently differentiates polymorphous low-grade adenocarcinoma from adenoid cystic carcinoma. A consistent marker seen in polymorphous low-grade adenocarcinoma is S100 protein (see next image).

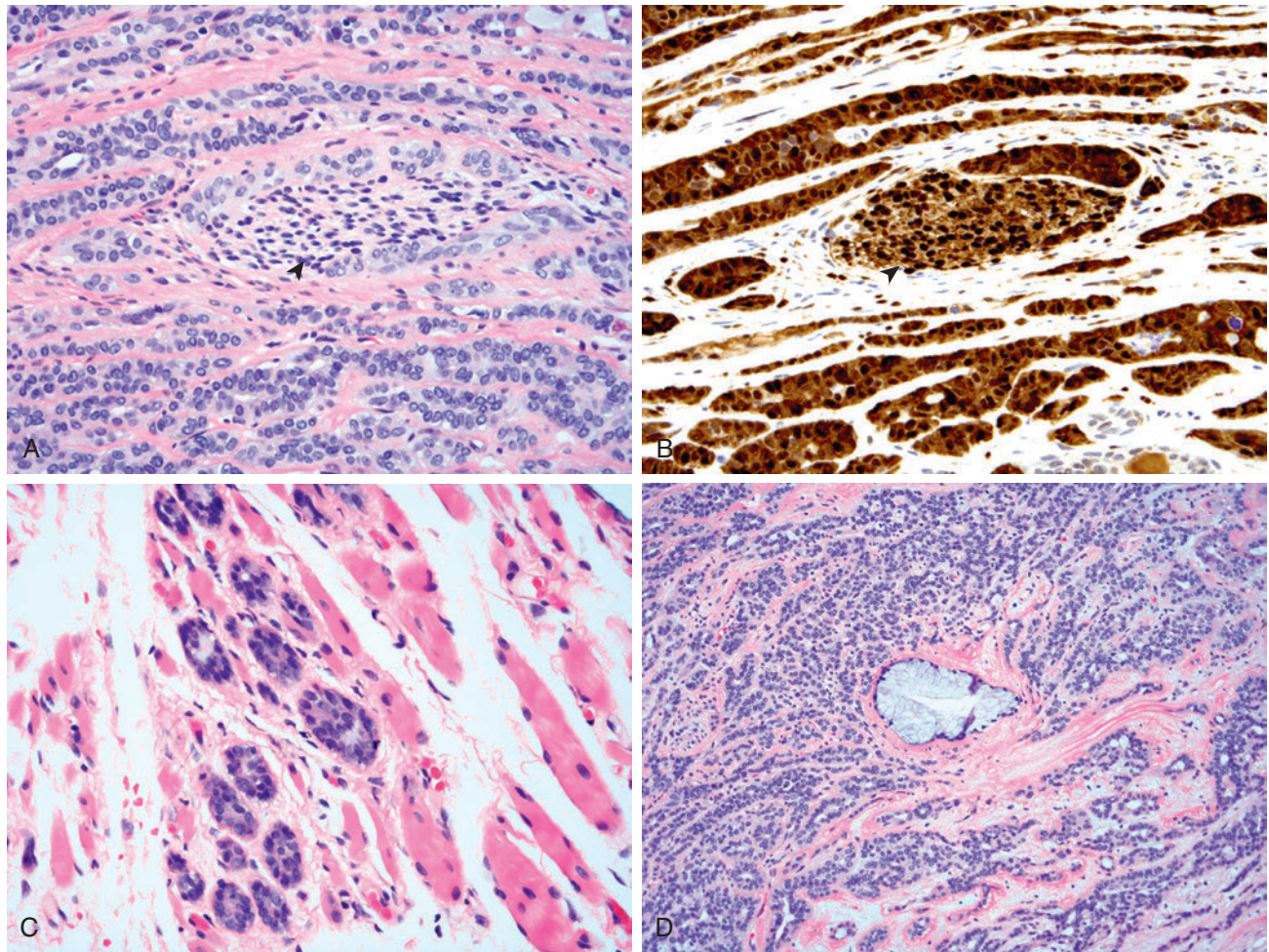


Fig. 20-88. Polymorphous low-grade adenocarcinoma.

Invasive growth is a required feature in diagnosing polymorphous low-grade adenocarcinoma, which may include (A) perineural invasion (*arrowhead*) that may be readily identified by light microscopy but may require (B) S100 protein staining to confirm the presence of a peripheral nerve (*arrowhead*); note the tumor cells are diffusely and strong S100 protein positive. In addition to neurotropism, infiltrative growth may include invasion into (C) skeletal muscle or fat (not shown). D, Another characteristic although not pathognomonic finding is entrapment rather than effacement of residual minor salivary glands. Although not shown here, extension and involvement of the surface epithelium are not indications of invasion and should not be used as evidence of malignancy.

- Areas of hemorrhage may be present.
- Despite the innocuous cytologic appearance, neoplasm always invasive:
 - Neurotropism (peri- and intraneural) found in majority of tumors usually involving small to medium-sized nerves
 - Perivascular invasion can also be seen with tumor nests often arranged in concentric fashion around these structures.
 - Invasion of seromucous glands:
 - Envelopment but not effacement typical infiltrative pattern
 - Rather characteristic although not pathognomonic
 - Invasion of mature adipose tissue and/or skeletal muscle
 - Invasion of bone:
 - May be seen in tumors of palate or mandible
 - Extension and involvement of surface (squamous) epithelium may be present, but this finding is not considered evidence of invasive growth or diagnostic for malignancy
- Other changes that may be identified include:
 - Tyrosine-type crystalloids and psammoma bodies can be seen in some cases.
 - Pseudoepitheliomatous hyperplasia of surface (squamous) epithelium

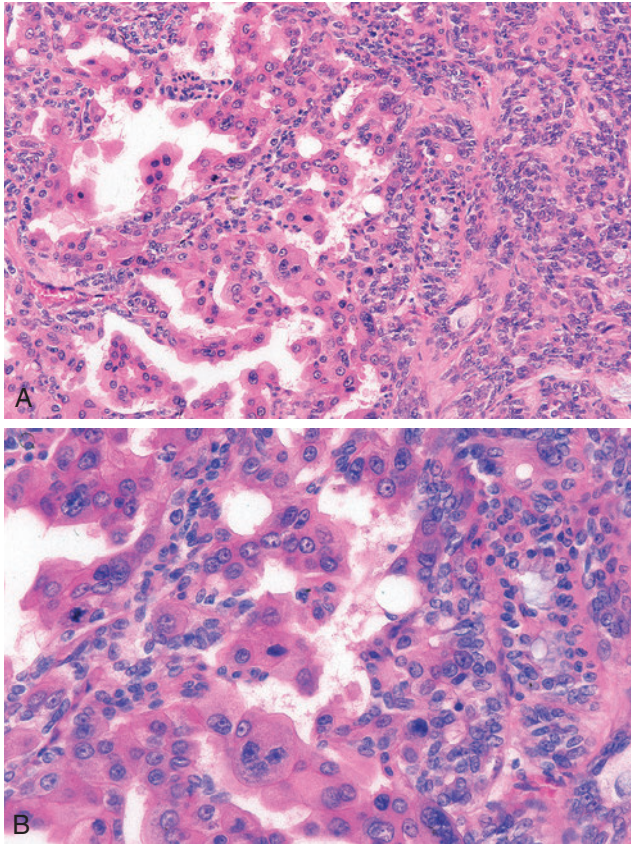


Fig. 20-89. PLGA.

Rarely, transition to a higher histologic grade tumor may be seen in PLGA. **A**, PLGA with typical histology is seen on right transitioning to an area with greater nuclear pleomorphism and mitotic activity (*center and left*).

B, Higher magnification of the higher histologic grade (less differentiated) component of the tumor.

- Squamous metaplasia:
 - A feature that can be seen following fine-needle aspiration biopsy or incisional biopsy
- Histochemistry:
 - Intraluminal mucin can be identified by diastase-resistant, PAS-positive material
 - Intracytoplasmic mucin if present is focal and weakly stained by mucicarmine or PAS with diastase.
- Immunohistochemistry:
 - Cytokeratins, EMA, S100 protein, vimentin positive
 - Variable reactivity for CEA and muscle-specific actin (MSA)
 - p63 and p40:
 - Variable p63 reactivity but usually at least focally present
 - p40 usually negative
 - IHC findings including pairing p63 and p40 reported to assist in differentiating pleomor-

phic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC) include:

- PA: p63+/p40+
- Cellular PA: concordant p63+/p40+ or p63–/p40–
- PLGA: consistent p63+/p40–
- AdCC: p63+/p40+

CAUTIONARY NOTE: While p63/p40 IHC panel can be a valuable tool for making distinction between PA, PLGA, and AdCC it is not infallible and any given example may demonstrate divergence from the reported p63/p40 immunophenotype.

- Usually negative for other markers of myoepithelial cells including calponin, actins, smooth muscle myosin heavy chain
- GFAP typically negative
- May be reactive for mammaglobin and/or GCDFP15
- May occasionally be PLAG1 positive
- Variable c-kit (CD117), bcl-2, and galectin 3
- Low proliferative rate indices (less than 5%) by Ki67 staining
- Electron microscopy:
 - Glandular or duct-like structures, junctional complexes (desmosomes, tight junctions), lumina, and microvilli
- Cytogenetics and molecular genetics:
 - Somatic *PRKD1* hotspot mutations encoding p.Glu710Asp found in 73% of PLGAs but not in other salivary gland tumors emerging as a new cancer-related gene likely constituting a driver of PLGA:
 - Morphologic and molecular overlap with cribriform adenocarcinoma of minor salivary glands (see below) including the fact that these two tumors are driven by genes in the same family suggests they are closely related
 - CGH analysis revealed:
 - PLGA genome is genetically stable, containing comparatively few copy number alterations (CNAs)
 - In line with clinical observation that PLGA is a slow-growing, low-grade carcinoma with low metastatic potential
 - Absence of *MYB-NFIB* by RT-PCR analysis
 - Single reported case expressing *MYB-NFIB*
 - Absence of ETV6 translocation

High-Grade Transformation (“Dedifferentiation”) in PLGA

- Rare occurrence of a histologically typical PLGA with high-grade carcinoma component characterized by:
 - Nuclear atypia
 - Markedly increased mitotic activity

- Increased proliferation indices (Ki67 or MIB1 index)
- Prominent zones of necrosis
- High-grade component may resemble salivary duct carcinoma including immunoreactivity for androgen receptor
- Recent identification of high-grade tumor with morphologic, immunohistochemical and molecular features of PLGA and cribriform adenocarcinoma of minor salivary glands (referred to as high-grade polymorphous/cribriform adenocarcinomas) identified characterized by greater nuclear pleomorphism, increased mitotic activity, solid growth and necrosis with more aggressive behavior

Differential Diagnosis (Table 20-9)

- Pleomorphic adenoma:
 - In minor salivary gland sites is unencapsulated similar to PLGA but noninvasive unlike PLGA
- Monomorphic adenoma
- Adenoid cystic carcinoma:
 - Differentiation is predicated on light microscopic features because both tumors may show neurotropism and have overlapping immunohistochemical findings.
 - Presence of isomorphic cells composed of small angulated hyperchromatic nuclei that characterize adenoid cystic carcinoma contrast to the isomorphic round to oval, vesicular nuclei of PLGA.
 - More pronounced cribriform component
 - Presence of *MYB-NFIB* fusion would support diagnosis of adenoid cystic carcinoma.
- Cribriform adenocarcinoma (see below):
 - Based on differences in morphology and, more importantly, biologic behavior (local recurrence, cervical lymph node and distant metastases, and mortalities directly related to neoplasm) should be considered a distinct and separate entity from PLGA.

Treatment and Prognosis

- Treatment includes complete surgical excision in as conservative a manner as to ensure tumor-free margins:
 - Invasion of bone may necessitate more extensive surgical resection that may include maxillectomy or en bloc resection of mandible.
- Limited (if any) utility for radiation or chemotherapy
- Neck dissection is not indicated unless there is evidence of cervical adenopathy.
- Overall prognosis is excellent:
 - Indolent behavior
 - 95% 10-year survival
 - Local recurrence rate between 9% and 17%:

- Due to its slow growth rate, local recurrence typically occurs several years following initial treatment.
- Regional metastatic rate from 9% to 15%:
 - Similar to local recurrence, may occur several years following initial treatment
- Distant metastases seldom reported
- Death attributed to tumor is unusual and occurs after prolonged periods
- Papillary architecture may be associated with more aggressive behavior:
 - Increased incidence of recurrence
 - Increased incidence of regional (cervical nodal) and distant metastasis
 - No increase in mortality
 - Such neoplasms may in fact be cribriform adenocarcinomas of minor salivary glands (see below)
- PLGA may occur as malignant component in carcinoma ex pleomorphic adenoma:
 - In setting of carcinoma ex pleomorphic adenoma:
 - Better prognosis than other types of carcinomas arising in pleomorphic adenoma
 - More aggressive than de novo PLGA
- Histologic high-grade transformation of an otherwise typical PLGA may rarely occur:
 - See previous discussion.
- Some consider polymorphous low-grade adenocarcinoma the low-grade variant of adenoid cystic carcinoma based on the morphologic similarities as well as common derivation from intercalated duct region; however, there is no support for this consideration.
- Cribriform adenocarcinoma of minor salivary glands previously considered a variant of PLGA but now recognized as a separate tumor type (see below)

CRIBRIFORM ADENOCARCINOMA OF MINOR SALIVARY GLANDS (CAMSG) (Fig. 20-90)

Definition: Submucosal invasive adenocarcinoma with cribriform, tubular/glandular, and papillary growth, nuclear features reminiscent of thyroid papillary carcinoma, and tendency to be associated in a high percentage of cases with nodal metastasis.

Synonyms: Cribriform adenocarcinoma of the tongue and minor salivary glands (CATSMG)

Clinical

- Slightly more common in women than in men; occurs in adults over a wide age range from 21 to 85 years with a mean of 56.8 years

TABLE 20-9 PLGA and Other Intraoral Salivary Glands Neoplasms: Selective Differential Diagnosis

Tumor	Capsule, Invasion	Growth Patterns	Cytomorphology	Stroma	IHC	Cytogenetic
PLGA	Absent and infiltrative	Polymorphic, including tubular/ductules, cribriform, solid, linear single cell, "streaming" along periphery, papillary	Isomorphic cells with minimal pleomorphism; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Slate gray myxoid; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, S100 protein, others; p40 negative*; low proliferation indices	None known although <i>PRKD2</i> rearrangement reported in a single case
PA	Absent but well circumscribed	Polymorphic, including tubules, ribbons, sheets, cords, cysts, trabeculae	Dual cell population: ducts/glands and myoepithelial cells; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Chondromyxoid; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, p40, S100 protein, others; low proliferation indices	<i>PLAG1</i> <i>HMG2A</i>
CPA (E or M)	Absent but well circumscribed	Polymorphic, including tubules, ribbons, sheets, cords, cysts, trabecular, fascicular, anastomosing cords	Dual cell population: ducts/glands and myoepithelial cells; for myoepithelial predominant tumors lesional cells include spindle-shaped and plasmacytoid cells but ducts/glands focally seen; no necrosis or increased mitotic activity; intercellular hyaline material may be present	Scanty but identifiable chondromyxoid stroma; crystalloids may be present	Positive for epithelial and myoepithelial markers: CKs, p63, S100 protein, others; low proliferation indices	<i>PLAG1</i> <i>HMG2A</i>
AdCC, tubular, cribriform	Absent and infiltrative	Polymorphic, including cribriform, tubular/ductules, islands, cysts, nests, cords, solid	Basaloid cells with uniform, angulated, hyperchromatic nuclei, scanty cytoplasm; no necrosis or increased mitotic activity; intercellular hyaline material present	Myxoid-hyaline stroma	Positive for epithelial and myoepithelial markers: CK, p63, p40, S100 protein, others; increased proliferation indices [†]	<i>MYB-NFIB</i>
CAM SG	Absent and infiltrative	Cribriform, tubular/glandular papillary and solid growth patterns; often divided into lobules by fibrous septa	Lesional cells include round to oval to elongated nuclei with irregularities in size and shape, clear to very fine-appearing nuclear chromatin; nuclear grooves and nuclear pseudoinclusions (reminiscent nuclei in papillary thyroid carcinoma); mild to focally moderate nuclear pleomorphism may be present but no substantial increase in mitotic activity and no necrosis	No specific stromal component; calcifications including psammomatoid concretions may be present	Strong reactivity for cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK18), S100 protein, and vimentin; variable reactivity for p63, calponin, CK14, smooth muscle actin, CK5/6; negative for thyroglobulin and TTF1; significant reactivity for CD117 (cytoplasmic and membranous); low proliferation	Recurrent <i>PRKD1-3</i> rearrangement

*p40 not necessarily consistently negative in PLGA or positive in the other neoplasms.

[†]Increased proliferation indices may not be present in all cases of AdCC and by itself does not definitively differentiate it from PA, cellular PA, and PLGA.

AdCC, Adenoid cystic carcinoma; CAMSG, cribriform adenocarcinoma of minor salivary glands; CKs, cytokeratins; CPA, cellular pleomorphic adenoma; E, epithelial predominant; M, myoepithelial predominant; PA, pleomorphic adenoma; PLGA, polymorphous low-grade adenocarcinoma.

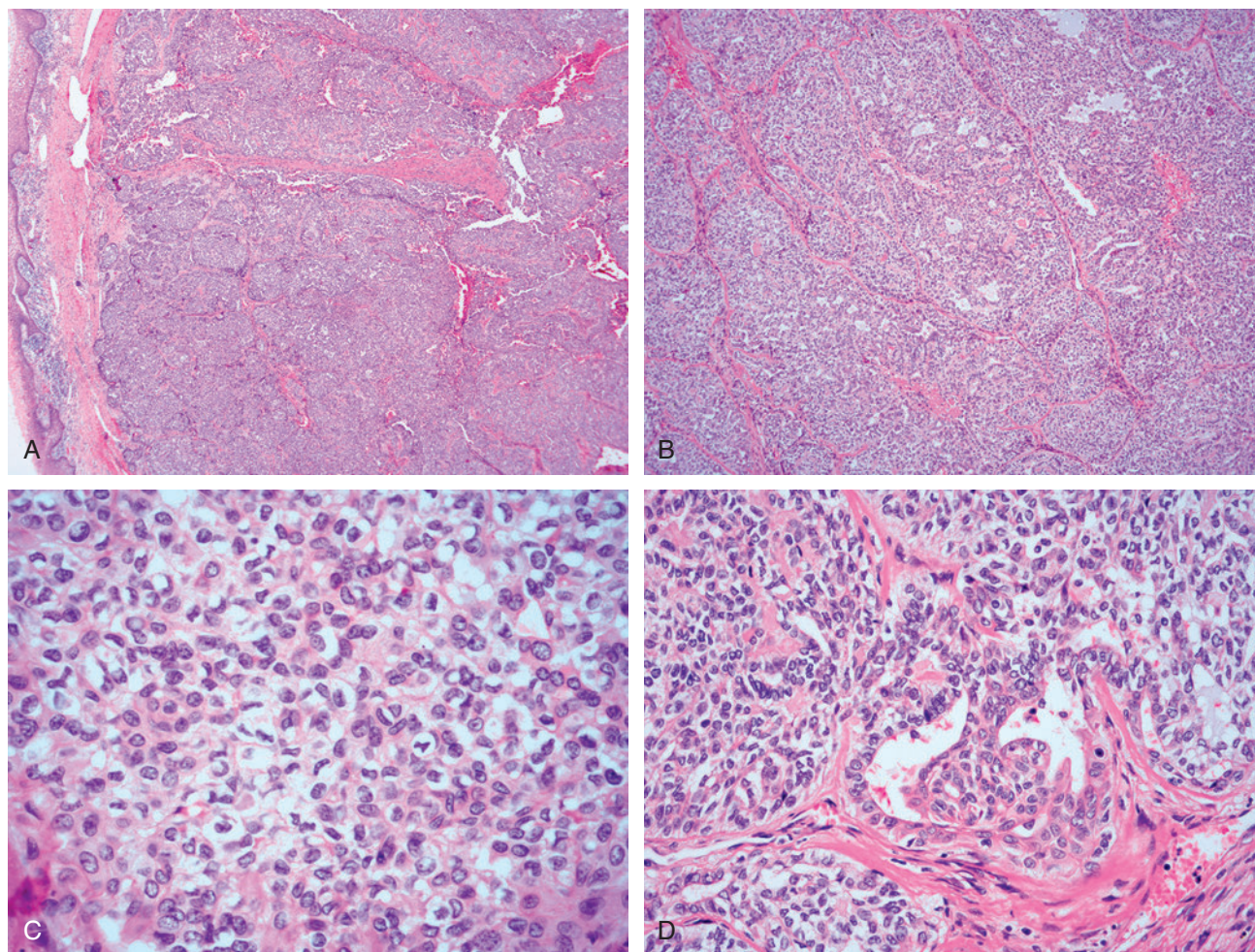


Fig. 20-90. Cribriform adenocarcinoma of minor salivary glands.

A, Submucosal unencapsulated and invasive neoplastic proliferation; intact squamous epithelium is present (*extreme left*). **B**, Neoplastic proliferation comprised of lobules separated by fibrous septa showing cribriform and solid growth patterns; intraluminal eosinophilic secretions are seen. **C**, Lesional cells show nuclear features reminiscent of those seen in papillary thyroid carcinoma (solid variant) including round to oval to elongated nuclei with irregularities in size and shape, clear to very fine-appearing nuclear chromatin. **D**, Tumor nests detached from surrounding fibrous stroma by clefts imparting a glomeruloid appearance.

- Most common site of occurrence is tongue:
 - Base of tongue a frequent location
 - Other intraoral sites of occurrence include soft palate, buccal mucosa, tonsil, lip
 - May occur outside the oral cavity including major salivary glands
- Presentation may include:
 - Intraoral mass
 - Not infrequently may present with enlarged lateral neck mass
- Etiology:
 - No known associated causes

Pathology

Gross

- Unencapsulated lesion with tan-gray to white color and firm to hard consistency

Fine-Needle Aspiration Biopsy

- Aspirates contain polymorphic fragments of epithelial cells arranged in monolayer sheets, papillary fronds and tips, and occasional cribriform configurations.
- Metachromatic stromal fragments may be identified and may be misinterpreted as colloid.
- Background myxoid/mucoid material reminiscent of colloid may be prominent.

Histology

- Submucosal unencapsulated and invasive adenocarcinoma with cribriform, tubular/glandular, papillary, and solid growth patterns:
 - Often divided into lobules by fibrous septa
- In solid areas, tumor nests may be detached from surrounding fibrous stroma by clefts (presumably

artifactual) imparting a somewhat glomeruloid appearance:

- Peripheral layer of such solid tumor nests often displays hyperchromatic nuclei in a vaguely palisaded pattern
- Lesional cells include round to oval to elongated nuclei with irregularities in size and shape, clear to very fine-appearing nuclear chromatin, and nuclear grooves:
 - Nuclear features somewhat reminiscent of those seen in papillary thyroid carcinoma (solid variant)
 - Intranuclear inclusions may be identified.
- Mild to focally moderate nuclear pleomorphism may be present but with no substantial increase in mitotic activity and no necrosis.
- Calcifications, including psammomatoid concretions, may be present.
- Intraluminal mucinous-appearing secretions may be present.
- Infiltrative growth may include perineural invasion, lymph-vascular invasion, and invasion into soft tissues including skeletal muscle.
- Intact overlying squamous epithelium often identified:
 - Typically no ulceration present
 - Pseudoepitheliomatous hyperplasia may be present.
 - No evidence of intraepithelial dysplasia and/or carcinoma in situ
- Histochemistry:
 - Intraluminal secretions diastase-resistant, PAS-positive, and weakly mucicarmine positive
- Immunohistochemistry
 - Strong reactivity for cytokeratins (AE1/AE3, CAM5.2, CK7, CK8, CK18), S100 protein, and vimentin
 - Variable reactivity for basal/myoepithelial cell markers including p63, calponin, CK14, smooth muscle actin, CK5/6
 - May be reactive for galectin-3, CK19, and HBME-1 but negative for thyroglobulin and thyroid transcription factor 1 (TTF1)
 - Significant reactivity for c-kit (CD117), including strong cytoplasmic and membranous expression, may be present in from 10% to 80% of lesional cells.
 - p16 staining (cytoplasmic and nuclear) may be present but typically with patchy pattern in majority of cases considered nonreactive; rare cases reported as diffusely reactive
 - Negative for EMA, epidermal growth factor receptor, *HER-2/neu*, estrogen receptor, and progesterone receptor negative
 - Negative mammaglobin and c-kit
 - Low proliferation indices (less than 5%) by Ki67 staining

- Cytogenetics and molecular genetics:
 - Novel and recurrent gene rearrangements in *PRKD1-3* identified, suggesting possible pathogenic dichotomy from PLGA
 - Presence of cases with similar genetic findings considered “indeterminate” for CAMSG and PLGA as well as activated E710D hotspot mutation in *PRKD1* in 73% of PLGAs suggests shared pathogenesis between CAMSG and PLGA
 - No mutations of *RET*, *BRAF*, *KRAS*, *HRAS*, *NRAS*, *c-kit*, and *PDGFRA* genes
 - Negative for high-risk/low-risk HPV types:
 - In one reported case high-risk HPV type 33 detected (this case also showed weak positivity of HPV type 18)

Differential Diagnosis

- Polymorphous low-grade adenocarcinoma
- Adenoid cystic carcinoma
- Metastatic thyroid papillary carcinoma

Treatment and Prognosis

- Complete surgical resection to include tumor-free margins is indicated.
- Regional (cervical) lymph node metastasis:
 - High frequency (65%) at presentation
 - Should necessitate neck dissection as part of initial treatment protocol
- Highly favorable prognosis:
 - Majority of patients alive without disease or alive with recurrent disease over periods ranging from 2 months to 13 years (median follow-up of 6 years 5 months)
 - Prognosis does not appear to be altered by presence of nodal metastasis.

MALIGNANT MIXED TUMORS OF SALIVARY GLANDS

- Following lesions are grouped within this category:
 - Carcinoma ex pleomorphic adenoma
 - Noninvasive or intracapsular carcinoma ex pleomorphic adenoma
 - True malignant mixed tumor or carcinosarcoma
 - Metastasizing pleomorphic adenoma

Carcinoma Ex Pleomorphic Adenoma (CEPA) (Figs. 20-91 through 20-94)

Definition: Malignant transformation of a pre- or coexisting pleomorphic adenoma with infiltrative growth:

- By definition this tumor type lacks evidence of a co-existing mesenchymal malignancy (i.e., sarcoma)



Fig. 20-91. Carcinoma ex pleomorphic adenoma.

Carcinoma ex pleomorphic adenoma, high-grade, appearing as a huge, fungating mass completely obliterating and distorting the patient's normal facial structures.

- May be identified in association with histologic evidence of a pleomorphic adenoma
- Arises in a site previously involved by a pleomorphic adenoma

Synonym: Carcinoma ex mixed tumor

Clinical

- Accounts for approximately 12% of all malignant salivary gland neoplasms, 4% to 6% of all pleomorphic adenomas, and 2% to 4% of all salivary gland neoplasms
 - Of entities included under the designation malignant mixed tumors of salivary glands, more than 90% are (invasive) carcinoma ex pleomorphic adenomas.
- No gender predilection; may be seen over a wide age range but most frequently occurs in the sixth to seventh decades of life:
 - Occur approximately one decade older than patients with pleomorphic adenomas
 - Extraordinarily rare in infants and young children
- Sites of occurrence:
 - Most commonly occurs in major salivary glands:
 - Parotid gland > submandibular gland
 - May occur less often in minor salivary glands
 - Palate most commonly involved minor salivary gland site
 - Rarely occurs in sublingual gland
- Typical clinical presentation includes sudden or rapid enlargement of a long-standing painless, non-enlarging or slowly enlarging mass over a short time period (e.g., 3- to 6-month period)
 - Associated symptoms may include pain, facial nerve paresis or paralysis, soft tissue fixation

(especially in patients with recurrent tumors), and regional lymphadenopathy.

- Time period for malignant transformation of pleomorphic adenoma (initial or recurrent) may be from 2 to 50 years but on average is approximately 20 years:
 - Risk of malignant transformation increases with duration of tumor:
 - 1.6% for tumors less than 5 years
 - 9.5% for tumor present for more than 15 years

Pathology

Gross

- Appearance may depend on histologic grade:
 - Most are histologically high grade and appear as poorly circumscribed to overtly infiltrative masses with tan-white appearance and firm to hard consistency:
 - Areas of hemorrhage, necrosis, cystic change, and softening of the tissue may be present.
 - Occasionally high-grade CEPA may be circumscribed and/or encapsulated (see intracapsular CEPA below)
 - Histologically low-grade CEPAs may appear poorly circumscribed to overtly infiltrative or may show similarities to pleomorphic adenoma, including circumscription or encapsulation.
- May range in size from 1 to 17 cm in greatest dimension
- Residual foci of pleomorphic adenoma may be identified, appearing as glistening to fibrotic (nodular) foci

Fine-Needle Aspiration Biopsy

- Unequivocal malignant epithelial cells admixed with benign epithelial and stromal components of pleomorphic adenoma are considered diagnostic by FNAB:
 - In most aspirates epithelial cells predominate over stromal components.
 - Necrosis and mitotic figures, including atypical forms, may be seen.
- Aspirates may be cellular and include epithelial cells with atypia characterized by mild to moderate degree of pleomorphism, absence of unequivocal malignant cells, and a variable proportion of benign epithelial and stromal components.
- Sampling error is important cause of diagnostic pitfalls:
 - Correlation with clinical findings is essential in FNAB diagnosis.
 - In appropriate clinical setting (i.e., rapid enlargement of a long-standing salivary gland tumor), any degree of nuclear atypia should be documented and should raise concern for a possible

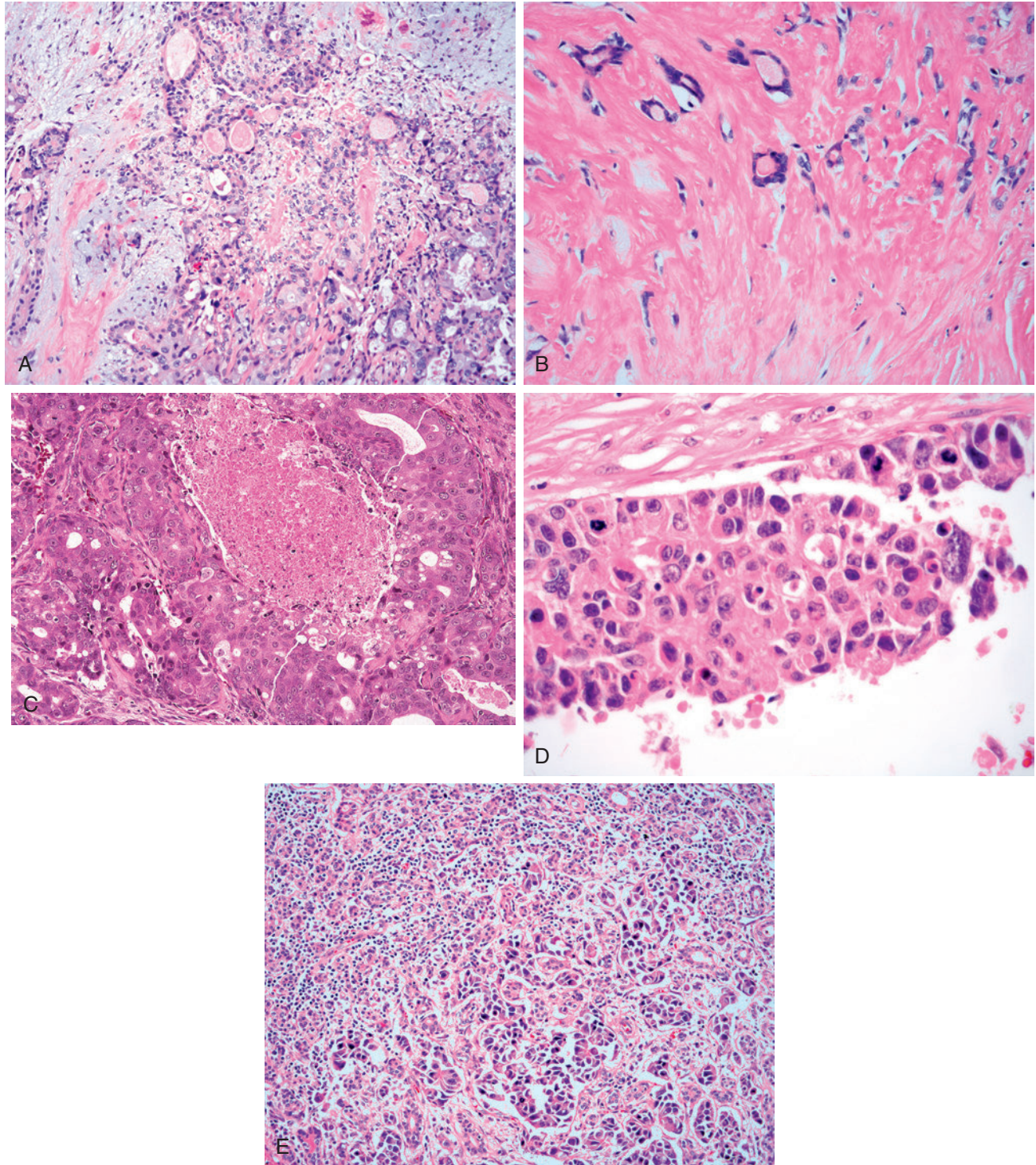


Fig. 20-92. Carcinoma ex pleomorphic adenoma, high-grade.

A, Transition between residual pleomorphic adenoma (*top*) characterized by benign glandular structures and chondromyxoid stroma to areas with more complex glandular growth pattern and marked nuclear pleomorphism (*lower*). **B**, Area of residual pleomorphic adenoma characterized by acellular hyalinization with benign tubules. **C** and **D**, The malignant component often is a high-grade adenocarcinoma with features similar to those of salivary duct carcinoma including cribriform growth with comedotype necrosis and cells with marked nuclear pleomorphism and increased mitotic activity; lesional cells were androgen receptor positive (not shown). Typically there is extensive invasive growth including (**E**) into adjacent salivary gland parenchyma, *Continued*

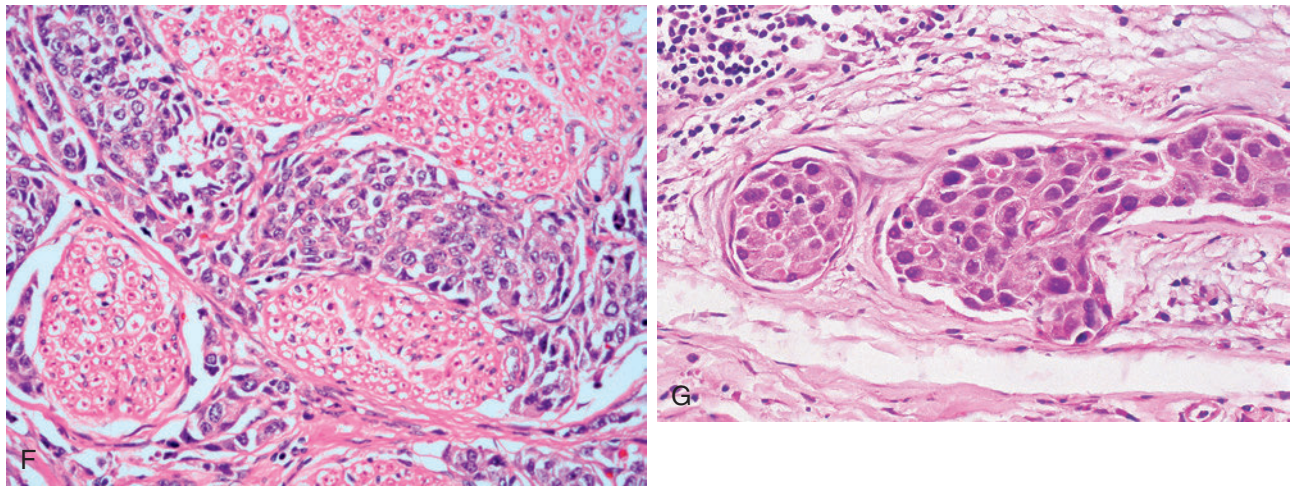


Fig. 20-92, cont'd

(F) perineural invasion, and (G) lymph-vascular invasion (note the features of squamous cell carcinoma).

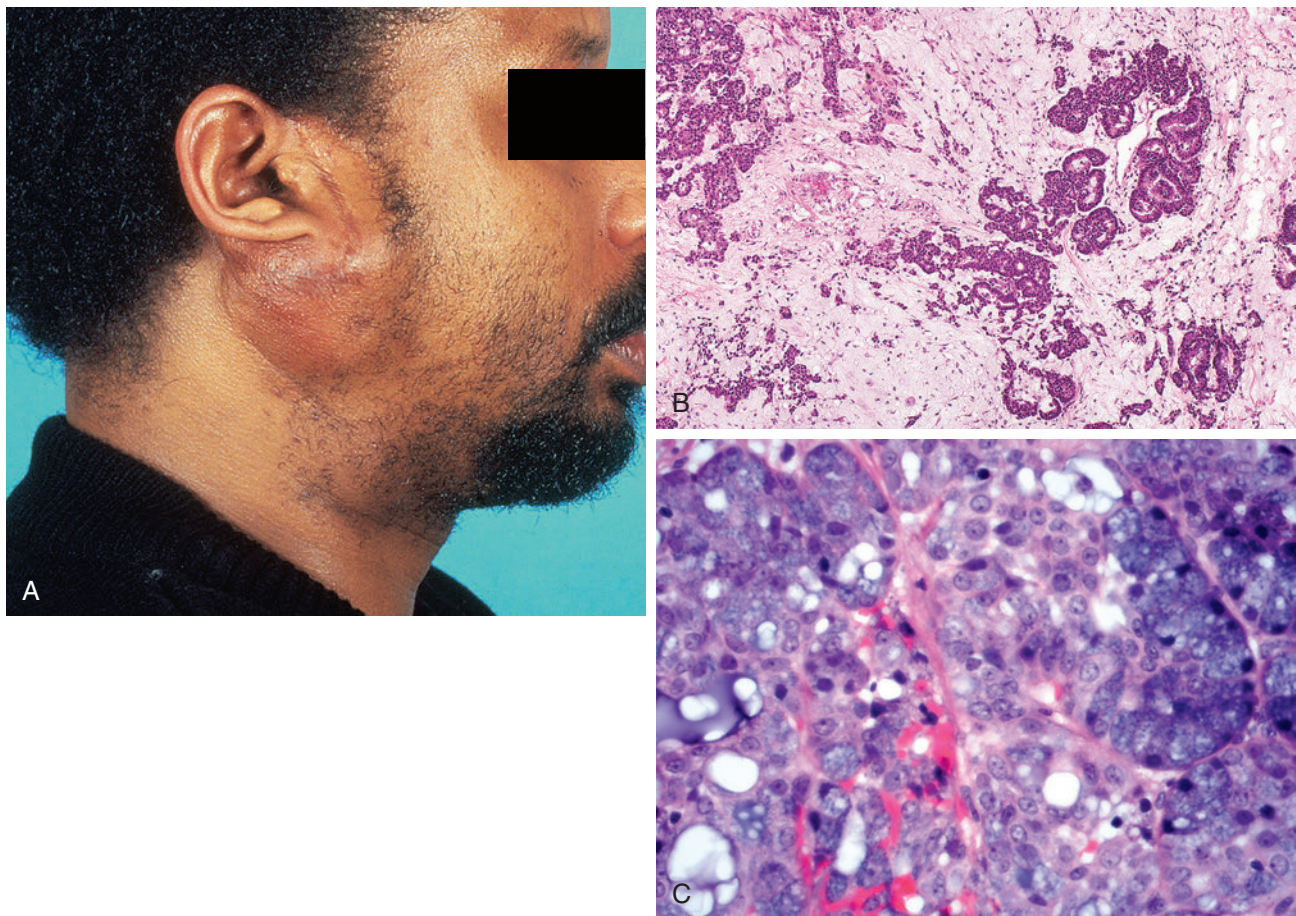


Fig. 20-93. Carcinoma ex pleomorphic adenoma, low-grade.

A, This man had previous excision of a pleomorphic adenoma (note scar anterior to the ear) with recurrence and recent enlargement of the recurrent tumor. **B** and **C**, The recurrence was a myxoid-predominant pleomorphic adenoma within which was another type of neoplastic proliferation characterized by tubular growth and cells with prominent basophilic cytoplasmic granules and vacuolated cells; these cells were DOG1 positive (not shown). The findings are those of an acinar cell carcinoma ex pleomorphic adenoma.

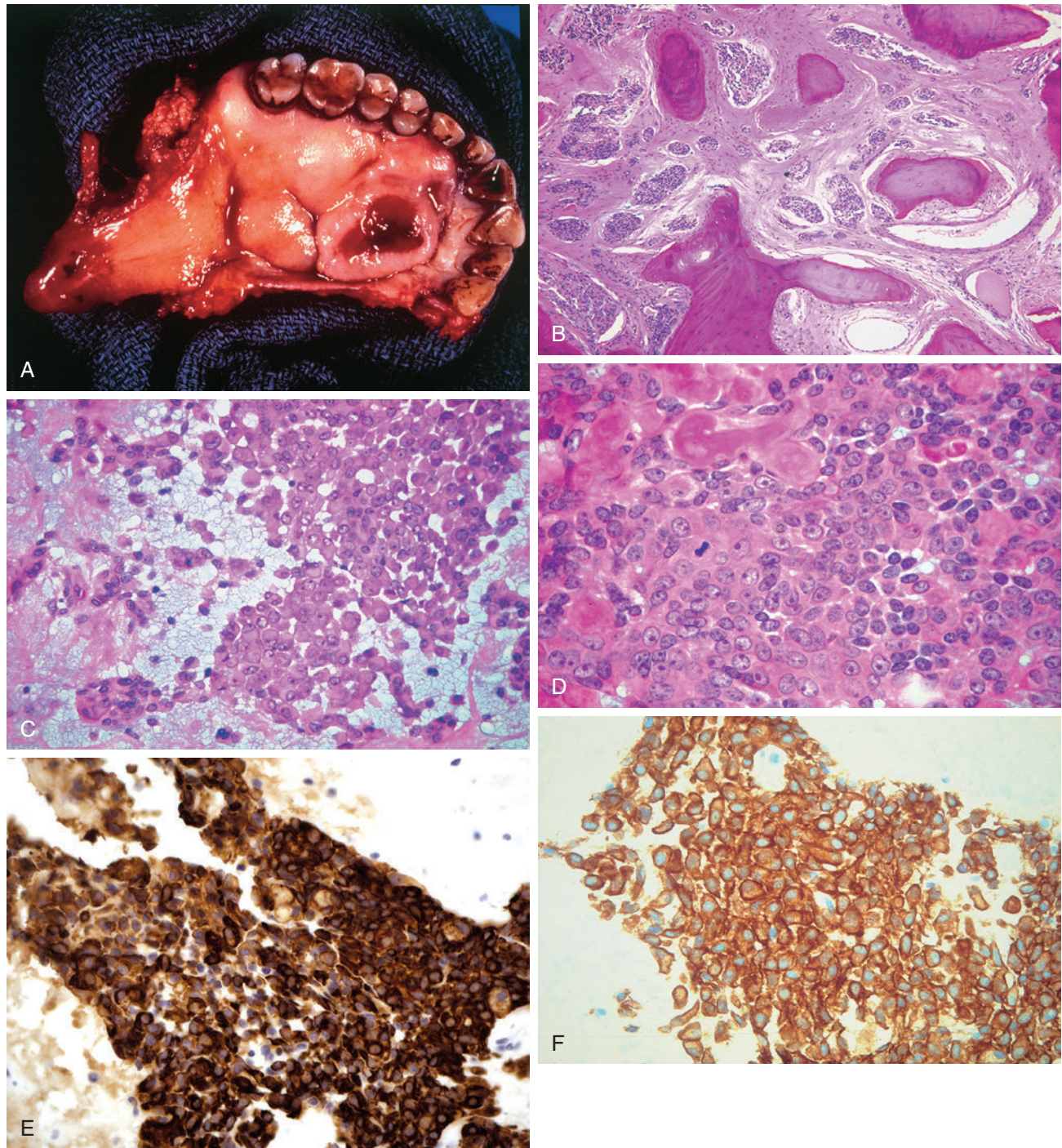


Fig. 20-94. Carcinoma ex pleomorphic adenoma, low to intermediate grade.

A, This patient had multiple recurrences of a palatal mass most recently with rapid increase in size and evidence of bone invasion by radiologic imaging; a biopsy (not shown) confirmed the presence of tumor in bone, necessitating radical excision. **B**, At low magnification the tumor is extensively infiltrative into palatal bone. **C**, Residual foci of a myoepithelial-predominant (plasmacytoid) pleomorphic adenoma were present. **D**, Areas of the tumor showed increased nuclear pleomorphism with prominent nucleoli, scattered mitoses, and stromal hyalinization. Immunohistochemical staining showed the neoplastic cells to be reactive for **(E)** cytokeratin (AE1/AE3), **(F)** calponin,

Continued

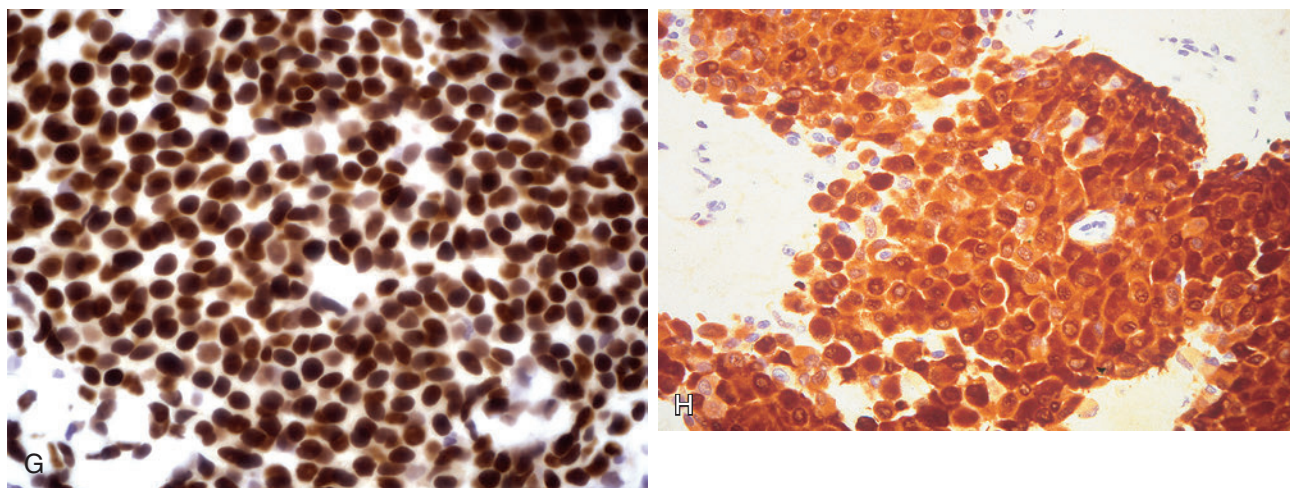


Fig. 20-94, cont'd

(G) p63, and (H) S100 protein. The findings in this case are those of a myoepithelial carcinoma ex pleomorphic adenoma.

diagnosis that may necessitate additional FNAB.

Histology

- Carcinomatous component may be histologically high grade or lower grade:
 - Carcinoma in most cases is histologically high grade, characterized by enlarged cells with marked nuclear pleomorphism, nuclear hyperchromasia, prominent nucleoli, increased mitotic activity with atypical mitoses and necrosis.
 - High-grade carcinomas are most often:
 - Salivary duct carcinoma or high-grade adenocarcinoma, not otherwise specified
 - Less often tumor types include undifferentiated carcinoma, squamous cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, small cell carcinoma, oncocytic carcinoma
 - In a significant minority of cases the carcinoma is histologically low grade with carcinoma defined on basis of recognition into a specific type of salivary gland carcinoma and/or evidence of infiltrative growth.
 - Histologically lower-grade carcinomas include:
 - Low- to intermediate-grade adenocarcinoma, NOS, myoepithelial carcinoma, mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma, acinic cell adenocarcinoma, epithelial-myoepithelial carcinoma, adenoid cystic carcinoma
 - Rare example of melanoma arising in carcinoma ex pleomorphic adenoma reported
- Invasive growth is present, including invasion into adjacent salivary gland parenchyma, fibroconnective tissue (e.g., skeletal muscle, adipose tissue, others), neurotropism (peri- and intraneural), and lymphovascular angioinvasion.
- Evidence of pleomorphic adenoma:
 - Proportion of pleomorphic adenoma in any given case varies from being readily identifiable to cases in which it is difficult to identify appearing hypocellular or hyalinized without cellularity.
 - Foci of pleomorphic adenoma and carcinoma may be demarcated from one another or two components may be intimately admixed.
 - Transition areas between benign and malignant foci may be present.
 - Evidence of (residual) pleomorphic adenoma may include presence of:
 - Classic foci including combination of benign tubular or ductular structures, myoepithelial cells, and chondromyxoid stroma
 - Hyalinized (nodular) stroma:
 - May contain identifiable benign tubular or ductular structures with bland cytomorphology and dual cell (epithelial and myoepithelial) differentiation by light microscopy and/or immunohistochemical staining
 - May be acellular:
 - Extensive hyalinization in a pleomorphic adenoma has been shown to be associated with increased risk for malignant transformation, and presence of hyalinized focus/nodule near to a malignancy is evidence of residual pleomorphic adenoma supporting diagnosis of CEPA.
 - Numerous sections may be required to identify foci of residual pleomorphic adenoma.

- Immunohistochemistry:
 - *HER-2* expression, p53 expression, androgen receptor, and Ki67 labeling index higher in carcinomatous component
 - S100 protein overexpression reported to be significantly more prevalent in carcinomatous component than in pleomorphic adenoma with or without atypical features
 - Results suggest that S100 protein immunohistochemical staining may be useful diagnostic marker for identifying the early phase of carcinoma ex pleomorphic adenoma in combination with *HER-2*, p53, androgen receptor, and Ki67
 - *PLAG1* staining may be present but FISH appears to be more sensitive than IHC staining in detecting *PLAG1* abnormalities.
- Cytogenetics and molecular genetics:
 - Most CEPAs regardless of morphologic subtype carry altered *PLAG1* or *HMGA2* genes
 - FISH for *PLAG1* and *HMGA2*:
 - CEPAs reported positive for *PLAG1* or *HMGA2* rearrangements/amplifications
 - Represent the most common genetic events in CEPA regardless of histologic subtype
 - Rearrangements of *PLAG1/HMGA2* identified in most hypocellular PAs but only in a small subset of cellular PAs
 - De novo carcinomas reported negative for *PLAG1* and *HMGA2*
 - *HER2* gene amplification found in up to 82% of cases
 - More common in presence of cases with extracapsular invasion than without invasion
 - Alterations in *TP53* gene and p53 protein overexpression identified in up to 67% and 75% of cases, respectively:
 - Involved in the early stages of malignant transformation of PA
 - LOH at microsatellite loci on 8q and 12q in benign and malignant components and 17p in the malignant component
 - Rearrangements of 8q12 and 12q13-15 frequently identified
- Major glands:
 - Usually radical extirpation with sacrifice of facial nerve
- Minor glands:
 - Complete excision with tumor-free margins, which may necessitate removal of a portion of the mandible or maxilla.
- Due to a high rate of nodal metastasis, cervical lymph node dissection usually performed
- Adjunctive radiotherapy used for extensively invasive tumors, as well as in conjunction with surgery:
 - Radiotherapy in conjunction with surgery plays a beneficial role in preventing local recurrence.
- Chemotherapy is of questionable benefit.
- Associated with high recurrence and metastatic rates:
 - Recurrence rates (one or more) vary from 23% to 53%
 - Majority of recurrences develop within 5 years from the diagnosis, although recurrences decades later may occur.
 - Palatal CEPA tends to recur less often than CEPA of major salivary glands.
 - Metastatic rates (local and metastatic) vary and have been reported as high as 70%.
 - Metastases most frequently occur to regional lymph nodes, lungs, brain, and bone (vertebral column).
- In general, prognosis is poor especially in patients with local recurrence, regional metastasis, or distant metastasis:
 - Following the discovery of metastatic disease, death usually follows within 1 year.
- Survival rates include:
 - 5-year range from 25% to 65%
 - 10-year range from 24% to 50%
 - 15-year range from 10% to 35%
 - 20-year range from 0 to 38%
- Low-grade CEPA:
 - Wide surgical excision is the preferred treatment.
 - Unless there is clinical evidence supporting nodal metastases, then neck dissection may not be necessary.
 - Adjunctive radiotherapy in combination with surgery may be beneficial if the tumor is extensively invasive.
 - Prognosis for these tumors is considered to be much better than for histologically high-grade CEPA.
- Factors adversely affecting prognosis include:
 - Origin in major salivary gland
 - Recurrent and/or metastatic disease (locoregional, distant)

Differential Diagnosis

- Cellular pleomorphic adenoma
- Atypical pleomorphic adenoma
- Intracapsular CEPA (see below)
- Salivary duct carcinoma
- True malignant mixed tumor (see below)

Treatment and Prognosis

- For high-grade CEPA:
 - Wide surgical excision is the preferred treatment:

- Higher T stage
- Presence of neurotropism
- Histologic grade:
 - High-grade CEPAs have worse prognosis than low-grade CEPAs.
- Presence of *HER-2* gene amplification
- Surgical margins:
 - Presence of tumor-positive margins associated with higher recurrence rates and tumor-associated mortality rates than tumor-free margins; presence of tumor-free margins does not exclude the possibility of recurrence, metastasis, or tumor-related death.
- Extent of invasion:
 - Arguably most important prognostic factor
 - Discrepant findings in literature relative to distance defining better or worse prognosis including:
 - Invasion beyond 8 mm from the capsule associated with a poor outcome (i.e., died of disease)
 - Invasion greater than 1.5 mm portended worse outcome (e.g., shorter survival) than invasion less than 1.5 mm from capsule
 - Threshold for distinguishing minor extracapsular invasion with good prognosis from wide extracapsular invasion with poor prognosis is 5 mm
 - Patients with minimally invasive tumor have more favorable outcome than patients with widely invasive neoplasm.
 - Minimally invasive carcinoma ex pleomorphic adenoma can recur and can cause death.
- Presence of myoepithelial carcinoma subtype reported to increase risk of recurrence in carcinoma ex pleomorphic adenoma, especially within the group of minimally invasive tumors

Noninvasive or Intracapsular Carcinoma Ex Pleomorphic Adenoma (Fig. 20-95)

Definition: Salivary gland tumor showing histologic evidence of pleomorphic adenoma with unequivocal evidence of cytologic malignancy entirely confined to within the capsule without invasive growth.

Synonyms: Early carcinoma ex pleomorphic adenoma; intratubular carcinoma ex pleomorphic adenoma; carcinoma in situ ex pleomorphic adenoma

- Carcinoma in situ represents earliest phase of malignant transformation, characterized by carcinoma within ductal luminal cells, retention of myoepithelial cell layer, and absence of stromal invasion.

- Findings akin to ductal carcinoma in situ (DCIS) of the breast

Clinical

- Uncommon lesion with greater recognition in literature
- Demographics, including gender and age, are similar to pleomorphic adenoma.
- Clinical features at the initial diagnosis that may indicate a greater likelihood of malignant transformation include:
 - Occurrence in the submandibular gland
 - Older patient age
 - Larger tumor size
- Generally thought to represent early stage development in malignant transformation of a pleomorphic adenoma

Pathology

Gross

- Similar to pleomorphic adenoma

Histology

- Residual foci indicative of a pleomorphic adenoma are present, which may include benign glands or ducts, myoepithelial cells, chondromyxoid stroma, and/or hyalinized areas.
- Carcinomatous element composed of overtly malignant cells with enlarged, pleomorphic, and hyperchromatic nuclei with increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and high mitotic rate.
 - To date, no reported instances of low-grade intracapsular CEPA
 - In theory such tumor types may occur composed of residual pleomorphic adenoma and identifiable malignancy purely based on cell type(s); examples could include:
 - Adenoid cystic carcinoma, acinic cell carcinoma, low-grade mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma
 - May also include examples of carcinoma in situ
- By definition there is no evidence of invasion beyond the capsule of the tumor.
- Extensive sampling of the tumor, which may require submission of the entire tumor, should be performed to ensure that extracapsular involvement has not occurred.
- Immunohistochemistry:
 - Carcinomatous component strongly positive for *HER-2*
 - Cells of the maternal PA negative for *HER-2*
- Cytogenetics and molecular biology
 - Amplification of *HER-2/neu* gene signals in non-invasive carcinoma cells:

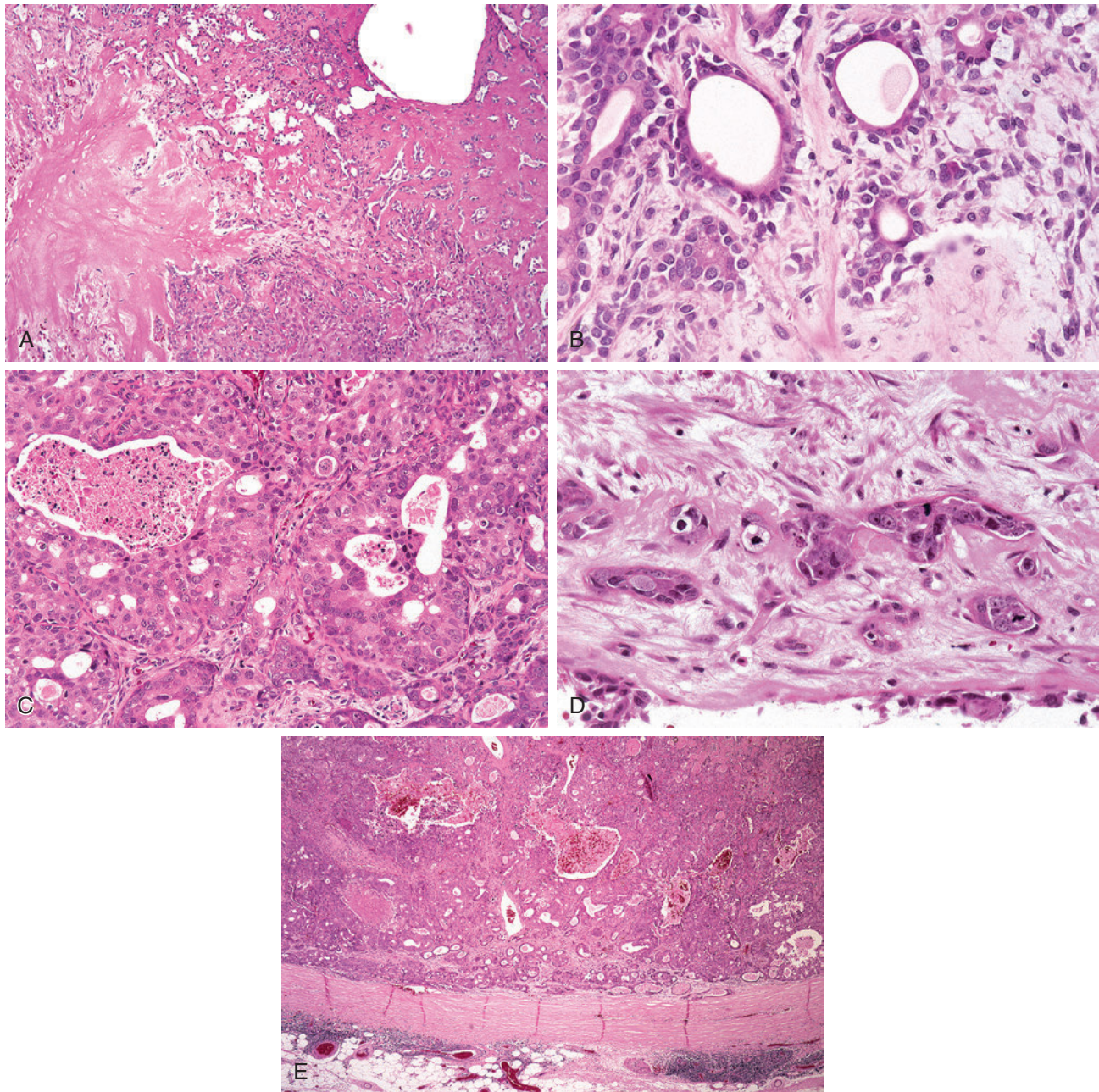


Fig. 20-95. Noninvasive carcinoma ex pleomorphic adenoma.

Noninvasive (intracapsular) carcinoma ex pleomorphic adenoma. **A** and **B**, Areas of this encapsulated parotid tumor showed foci of pleomorphic adenoma characterized by benign tubules with dual cell population within a variable appearing stroma including acellular hyalinization (**A**) and chondromyxoid appearing (**B**). **C** and **D**, Elsewhere in this neoplasm there were foci of high-grade carcinoma with features of salivary duct carcinoma (**C**) and squamous cell carcinoma (**D**). **E**, The entire tumor was submitted for histologic evaluation, showing it to be completely encapsulated without evidence of invasive growth.

- Less common than in cases with extracapsular invasion
- Alterations in *TP53* gene and p53 protein overexpression
- Involved in the early stages of malignant transformation of PA

Differential Diagnosis

- Atypical pleomorphic adenoma:
- Recurrent pleomorphic adenoma:
 - May be multinodular and/or include one or more nodules in the soft tissues of the neck



Fig. 20-96. Carcinosarcoma.

Carcinosarcoma appearing as huge parotid tumor completely distorting this patient's face.

- Nodules usually discrete and circumscribed without cytologic atypia

Treatment and Prognosis

- Treatment includes complete surgical excision.
- Adjunctive therapy likely unnecessary.
- Prognosis appears to be good.
 - Typically without metastatic potential
 - Single reported case with cervical lymph node metastasis
 - Another case reported of parotid gland neoplasm that recurred after interval of 8 years composed solely of pleomorphic adenoma that 5 years later recurred in the same site as myoepithelial carcinoma without evidence of ductal carcinoma as was reported in the initial intracapsular carcinoma ex pleomorphic adenoma

Carcinosarcoma (Figs. 20-96 and 20-97)

Definition: Malignant salivary gland neoplasm consisting of an admixture of malignant epithelial (carcinomatous) and malignant mesenchymal (sarcomatous) components.

Synonym: True malignant mixed tumor

Clinical

- Rare salivary gland neoplasm
- No gender predilection; most commonly seen in the sixth decade of life
- May occur in major and minor salivary glands:
 - Majority (two thirds of cases) occurs in parotid gland
 - Remainder of cases arise in submandibular gland and minor salivary glands:

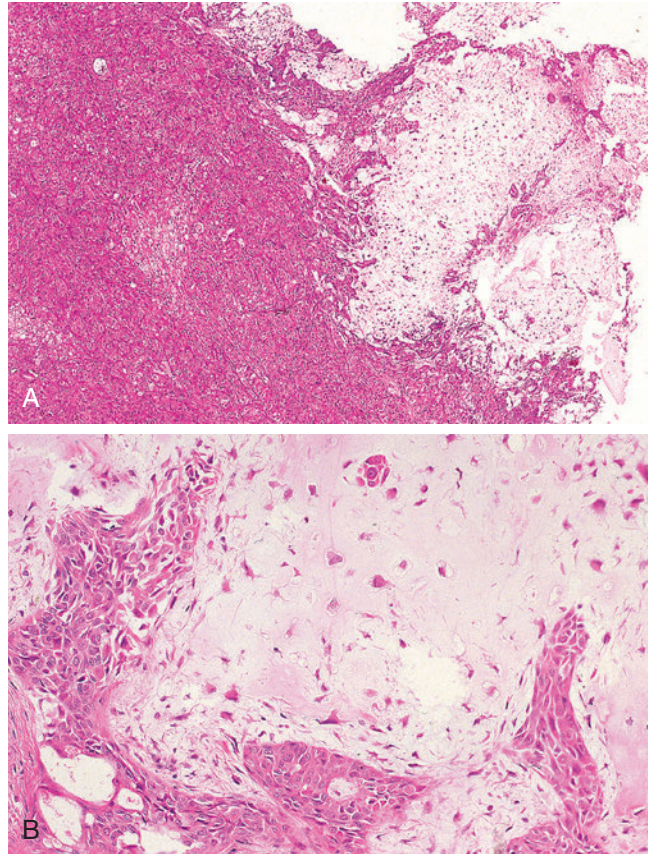


Fig. 20-97. Carcinosarcoma.

A, At low magnification there are two histologically distinct areas including solid-appearing (*left*) and more lightly staining nodular/lobular area (*right*). **B,** At higher magnification there is an admixture of carcinomatous and sarcomatous components, including carcinoma with squamous and glandular features (*left and bottom*) and chondrosarcoma (*center and upper right*).

- Among minor salivary glands, palate is most frequent site of occurrence
- Most common symptoms relate to an enlarging mass with recent increase in size with or without associated pain and/or facial nerve paralysis.
- In general, these tumors arise *de novo*; however, some arise in association with a pleomorphic adenoma and are termed carcinosarcoma ex pleomorphic adenoma:
 - In association with a pleomorphic adenoma, clinical situation may include a long-standing mass lesion with recent/sudden rapid increase in growth.
 - May develop decades following radiation therapy for benign pleomorphic adenoma, but no clear link between radiotherapy and development of carcinosarcoma
- Histogenesis subject of controversy, but most authorities consider it to be of epithelial cell and

myoepithelial cell origin, the latter giving rise to the sarcomatous component:

- Pleomorphic adenomas consisting of an admixture of epithelial and mesenchymal-appearing tissue originate from epithelial and myoepithelial cells.
- Sarcomatous component derived from modulation of modified myoepithelial cells in similar manner to modulation of myoepithelial cells in benign pleomorphic adenomas producing chondromyxoid stroma

Pathology

Gross

- Unencapsulated to poorly circumscribed to infiltrative lesion measuring from 2 to 13 cm in greatest dimension
- Cut section may show a tan-gray to yellow, predominantly solid lesion with hemorrhage, necrosis, and calcification; cystic areas may be present.

Histology

- Biphasic appearance composed of carcinomatous and sarcomatous elements; sarcomatous component usually is dominant component
- Sarcomatous component:
 - Usually chondrosarcoma
 - Other malignant mesenchymal elements may include osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, myxosarcoma, and malignant giant cell tumor.
 - Rarely, nonmalignant osteoid may be seen.
- Carcinomatous component:
 - Epithelial component is usually adenocarcinoma or squamous cell carcinoma.
 - Other malignant epithelial elements may include salivary duct carcinoma, undifferentiated carcinoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, and papillary cystadenocarcinoma.
- Cases occurring in association with a pleomorphic adenoma or in a site of previously excised pleomorphic adenoma show histologic evidence of coexisting pleomorphic adenoma or evidence of a pleomorphic adenoma in prior resection material.
- Immunohistochemistry:
 - Sarcomatous components:
 - Vimentin reactivity
 - Depending on the cell type, immunoreactivity may be present for:
 - Myogenic markers (desmin, myoglobin, myogenin, actins) for tumors with muscle (skeletal or smooth muscle) differentiation
 - S100 protein in chondrosarcoma
 - Carcinomatous components:
 - Cytokeratin positive

– Myoepithelial differentiation:

- p63, calponin, S100 protein, vimentin, smooth muscle actin, glial fibrillary acidic protein

Differential Diagnosis

- Carcinoma ex pleomorphic adenoma
- Spindle cell squamous carcinoma
- Salivary duct carcinoma, sarcomatous variant
- Synovial sarcoma
- Sarcoma, primary or metastatic

Treatment and Prognosis

- Complete surgical excision is preferred treatment:
 - Due to locally infiltrative and destructive growth radical surgery is usually necessary.
- Lymph node dissection is used for palpable disease.
- Adjunct radiotherapy is used to control local disease.
- Role of chemotherapy unproven but used in cases with metastatic disease
- Prognosis is poor:
 - Highly lethal neoplasms with mean survival of less than 30 months
 - Majority of patients die from disease.
 - Recurrent disease occurs in a majority of patients:
 - Recurrences include both histologic components.
 - Metastases occur in half the patients:
 - Metastases including both histologic components or may be restricted to the carcinomatous or sarcomatous component
 - Hematogenous spread most common with metastases most frequently to the lungs; other sites of metastases occur to liver, bone, brain, and lymph nodes (cervical and hilar)

Metastasizing Pleomorphic Adenoma (Fig. 20-98)

Definition: Salivary gland neoplasm with histomorphologic features of a pleomorphic adenoma but that metastasizes:

- Metastatic foci are histologically similar (i.e., benign) to the primary and/or recurrent neoplasms
- Due to potential for increased mortality designation “benign” has been eliminated.

Clinical

- Extremely rare
- No gender predilection; wide age range but the age at the time of primary tumor is in the third decade and in the seventh decade for metastatic tumor
- Primary neoplasm most frequently originates in parotid gland:
 - Other sites include the submandibular gland, intraoral minor salivary glands (most often the palate), and sinonasal seromucous glands.

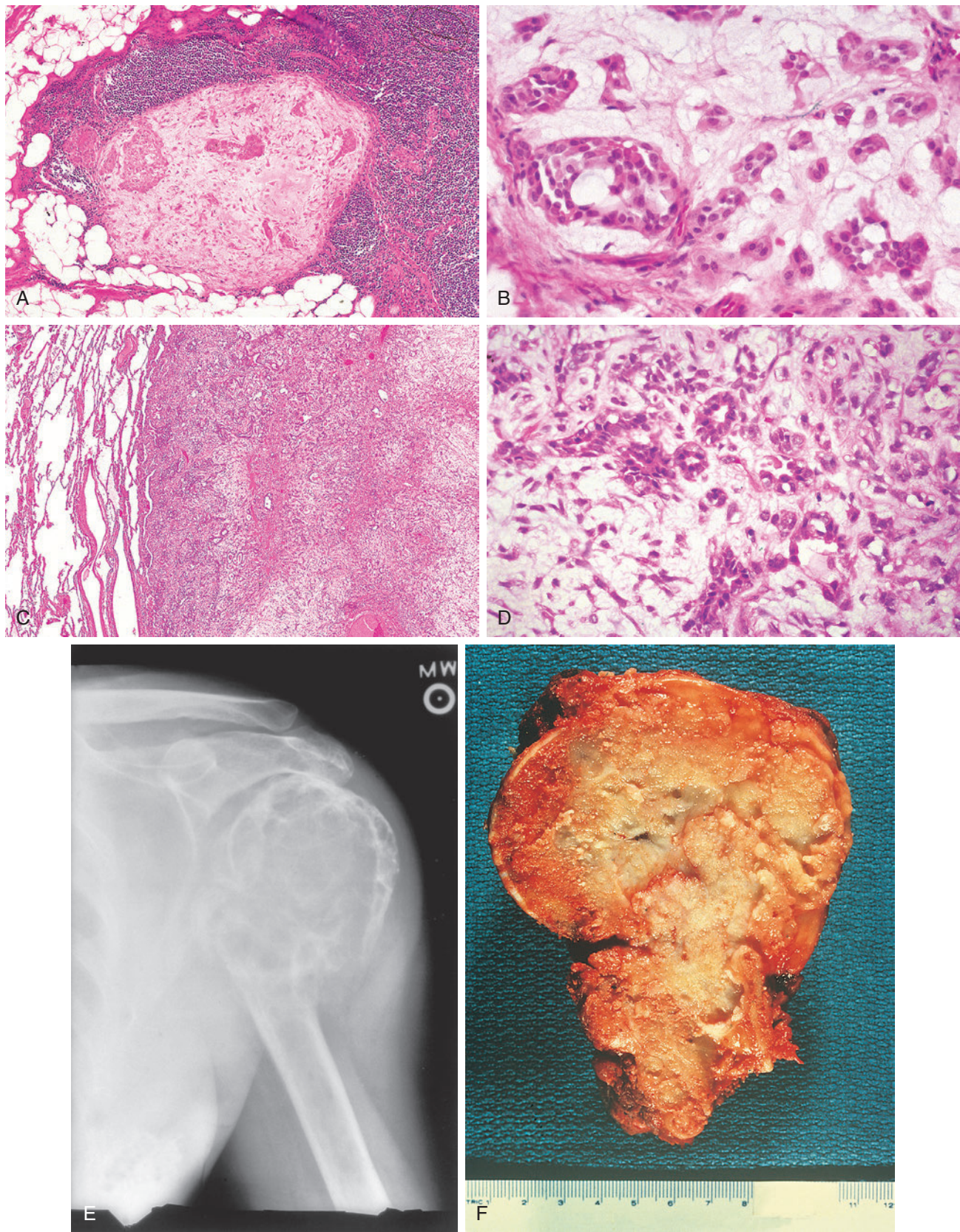
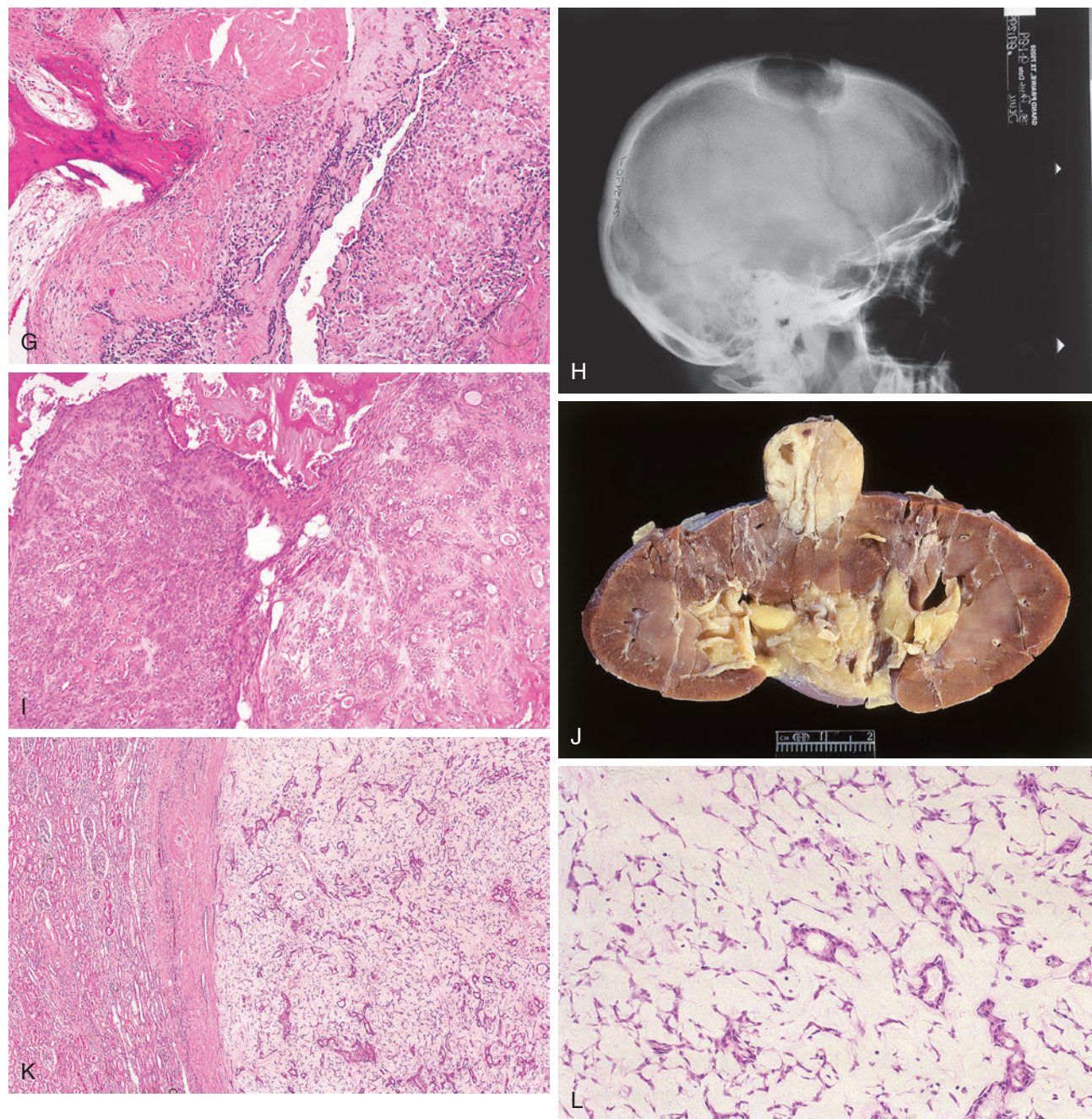


Fig. 20-98. Metastasizing pleomorphic adenoma.

All these examples occurred in different patients all with tumor recurrence (at least one but usually multiple) of major or minor salivary gland pleomorphic adenomas, in which the primary tumor, recurrent tumor, and metastatic foci retained histologic features of usual pleomorphic adenoma without cytomorphic evidence of malignant transformation. **A** and **B**, Cervical lymph node metastasis; **C** and **D**, metastasis to the lung; **E** through **G**, metastasis to the humerus,

**Fig. 20-98, cont'd**

H and **I**, metastasis to the skull; and **J** through **L**, metastasis to the kidney.

- Clinical presentation of primary salivary gland tumor is that associated with pleomorphic adenomas:
 - Absence of clinical presentation/scenario associated with carcinoma ex pleomorphic adenoma (i.e., rapid enlargement in tumor size, pain, neuropathies)
- Typically, multiple recurrent pleomorphic adenomas are seen within the area of the primary tumor prior to development of metastases:
 - Rarely metastatic foci may represent initial clinical manifestation.
- Clinical presentation of metastasis dependent on site of metastatic disease and may include:
 - Neck mass or swelling, pain, pathologic fracture, space-occupying lesion
 - Metastasis may occur at the time of initial salivary gland tumor, but more often occur at the time of the recurrent tumor(s) and/or from years to decades later.

- Metastatic spread is by hematogenous and lymphatic routes with metastatic foci seen in bone (femur, humerus, pelvis, ribs, calvarium), lung, kidney, retroperitoneum, skin, and lymph nodes.
- Reasons for metastases remains unproven, but repeated surgical manipulation(s) may represent a primary factor in introducing neoplastic foci into vascular channels (iatrogenic implantation) resulting in metastatic disease; however, arguments against this postulation include:
 - Intravascular tumor foci not identified in reported cases of metastasizing pleomorphic adenoma
 - Vascular permeation in pleomorphic adenomas does not result in metastasis.

Pathology

Fine-Needle Aspiration Biopsy

- Identical to the aspiration of a nonmetastasizing pleomorphic adenoma (see previous):
 - Metastatic lesions contained benign epithelial, myoepithelial, and stromal components.
- Cells may be slightly atypical but the cytologic findings are not those of a carcinoma.

Gross

- Primary tumors are conventional pleomorphic adenoma including well-circumscribed to encapsulated solitary mass.
- Recurrent tumors may be a single mass or, as often occurs in recurrent pleomorphic adenomas, may be multinodular.
- Metastatic tumors may be a single mass lesion or multiple lesions and often appear well circumscribed or delineated and may even be encapsulated.
- Cut surface, particularly in recurrent tumor but also in primary or metastatic tumor, may show a prominently glistening appearance due to predominant chondromyxoid stroma.
- Tumor size, whether primary, recurrent, or metastatic tumor, ranges from less than 1 cm to as large as 15 cm.

Histology

- Identical to that of pleomorphic adenoma including admixture of epithelial, myoepithelial, and chondromyxoid stroma:
 - In any given tumor any of these histologic components may predominate such that the histologic spectrum includes:
 - Epithelial predominant
 - Myoepithelial predominant
 - Stromal predominant
- Metastatic foci histologically similar to primary and/or recurrent tumor(s)
- All tumor foci whether primary, recurrent, or metastasis lack evidence of malignancy, including an

absence of anaplasia, increased mitotic activity with atypical mitoses, necrosis, invasive growth; the presence of these features would exclude the diagnosis of metastasizing pleomorphic adenoma:

- Rare examples reported of carcinoma developing in:
 - Primary pleomorphic adenoma at some point subsequent to metastases
 - Metastatic pleomorphic adenoma
- Immunohistochemistry:
 - Primary and metastatic foci share similar immunostaining as nonmetastasizing pleomorphic adenoma (see previous discussion on [pleomorphic adenoma](#)).
- Cytogenetics and molecular genetics:
 - No difference in DNA ploidy analysis between primary, recurrent, or metastatic tumors
 - FISH analysis in a small number of cases has identified the presence of two related hypodiploid clones in skeletal metastases that differ from cytogenetic profile of “conventional” pleomorphic adenoma, suggesting presence of tumor suppressor genes in metastasizing pleomorphic adenoma.

Differential Diagnosis

- Other categories of malignant mixed tumors
- In osseous and less so in nonosseous locations, diagnostic considerations may include primary chondroid and chondroid-related tumors, including chondrosarcoma and chordoma.
- Chondroid hamartoma of the lung:
 - Cartilaginous nests surrounded by cellular fibrous tissue and presence of adjacent alveoli and bronchioles assist in identifying chondroid hamartoma.

Treatment and Prognosis

- Preferred treatment is complete surgical excision of all tumor foci (primary, recurrent, metastases).
- Adjunct radiotherapy has been used, but its efficacy in treatment of metastatic tumor is questionable.
- High recurrence rate with approximately 90% of patients experiencing one or more recurrence of their pleomorphic adenoma at primary site of occurrence
- Prognosis is generally good even with metastatic disease; however, death may occur from metastatic disease:
 - Mortality rates range from 20% to 37%.
 - Death reported from as early as 6 months after discovery of metastasis to years later
 - More aggressive clinical course reported in immunocompromised patients (e.g., cardiac transplantation)

BASAL CELL ADENOCARCINOMA

(Figs. 20-99 and 20-100)

Definition: Low-grade malignant epithelial salivary glands neoplasm with features of basal cell adenoma but with infiltrative growth and potential for metastatic disease

- Considered malignant counterpart of basal cell adenoma.

Synonyms: Malignant basal cell adenoma; basal cell carcinoma; basaloid salivary carcinoma; carcinoma ex monomorphous adenoma

Clinical

- Uncommon salivary gland neoplasm
- No gender predilection; occurs over a wide age range but most frequently seen in fourth to ninth decades of life; rarely occurs in children
- Most commonly occurs in parotid gland (superficial lobe):
 - Approximately 90% occur in parotid gland
 - Less common sites of occurrence include submandibular gland and minor salivary glands.
- Symptoms relate to mass with or without associated pain or tenderness; duration of symptoms may be from months to years.

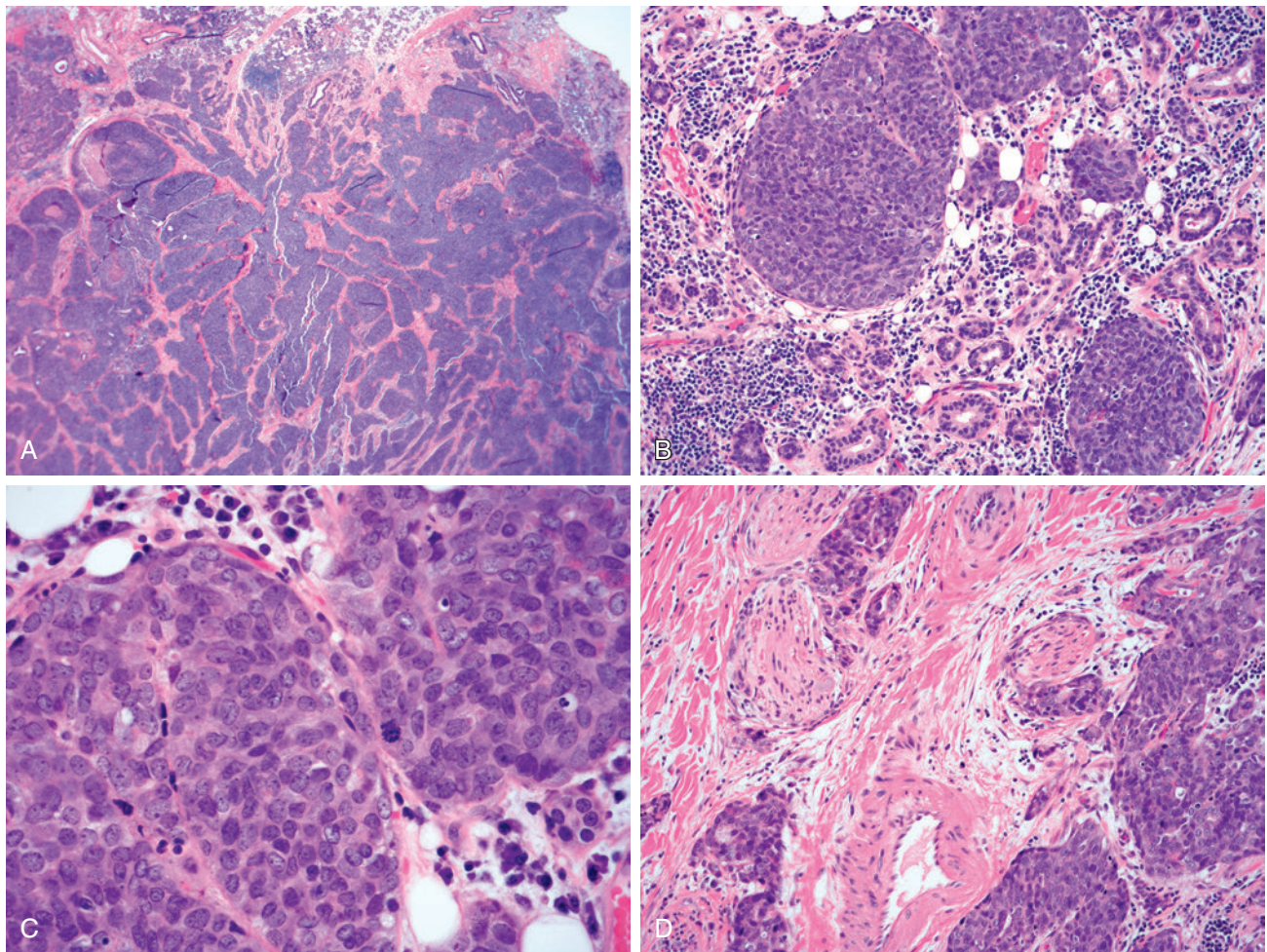


Fig. 20-99. Basal cell adenocarcinoma of the parotid gland.

A, At low magnification the tumor is unencapsulated, infiltrative into the parotid parenchyma (*top*), and composed of solid and trabecular growth. **B,** Higher magnification shows tumor nests infiltrating parotid parenchyma. **C,** Basaloid cell proliferation composed of pleomorphic nuclei and increased mitotic activity. **D,** Perineural and perivascular invasion. The cytologic atypia contrast to basal cell adenoma, which typically are composed of cytologically bland-appearing nuclei. In some examples of basal cell adenocarcinoma there may be an absence of cytologic atypia (see next illustration).

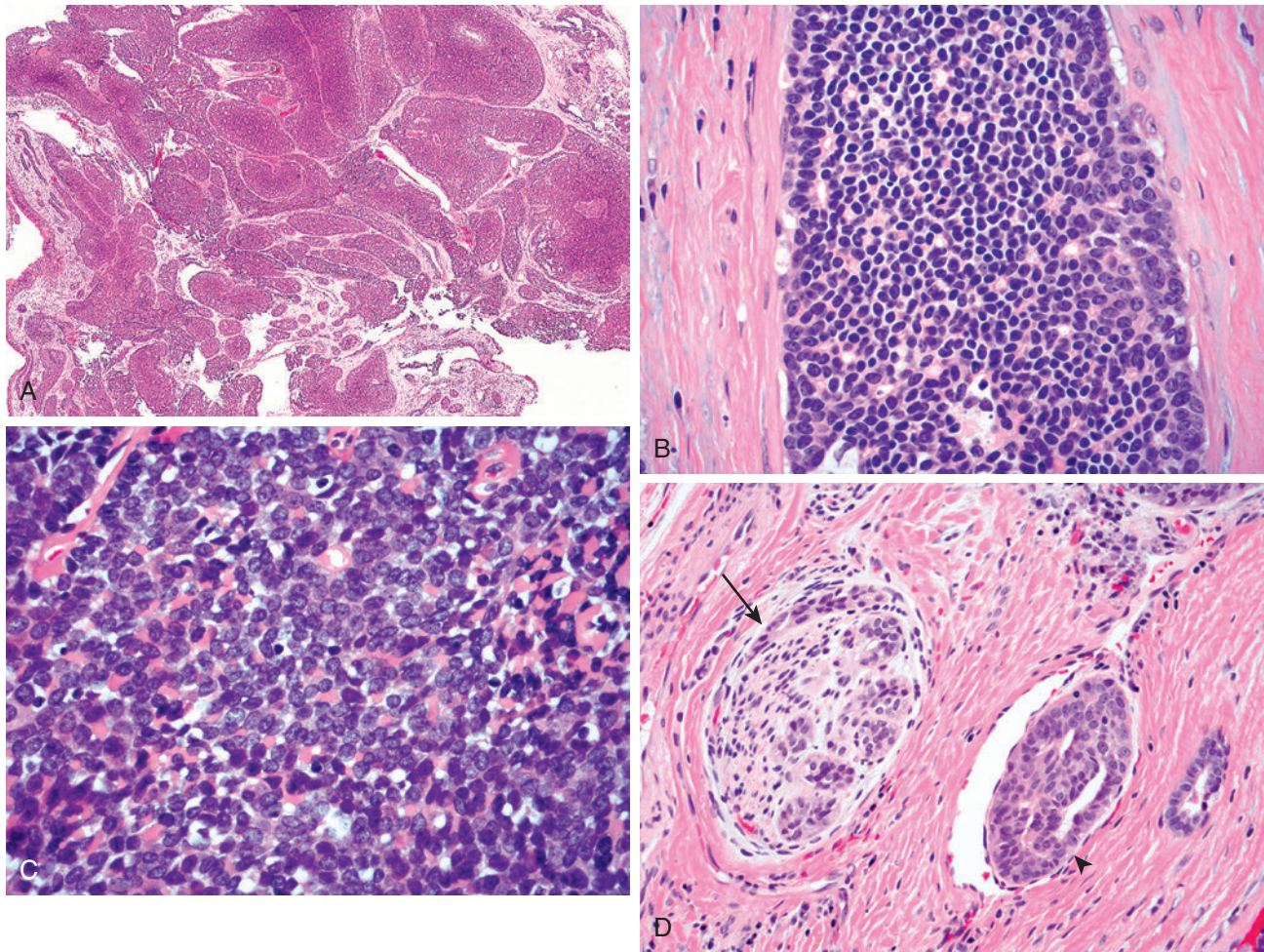


Fig. 20-100. Basal cell adenocarcinoma of minor salivary glands.

A, Submucosal infiltrative tumor characterized by trabecular and lobular growth; note the intact surface epithelium to the extreme left. **B**, Neoplastic cells include admixture of smaller cells with hyperchromatic nuclei and larger cells with vesicular nuclei; note the bland-appearing cells lacking significant nuclear pleomorphism and mitotic activity. **C**, Solid area composed of uniform basaloid-appearing cells. The cytomorphic features seen in **B** and **C** could be those of a basal cell adenoma. However, in contrast to basal cell adenoma, there is infiltrative growth in basal cell adenocarcinoma, including (**D**) peri- and intraneural invasion (*arrow*) and lymphovascular invasion (*arrowhead*). Although not illustrated here invasion of salivary gland parenchyma would also support a diagnosis of basal cell adenocarcinoma rather than basal cell adenoma in those cases with shared bland cytomorphic findings.

- Most arise de novo but may occur in association with or develop from a basal cell adenoma:
 - Most often membranous type of basal cell adenoma
 - Reported to occur in 23% of cases
- Concomitant dermal eccrine cylindroma may be identified, suggesting a salivary gland-skin adnexal diathesis.
- Suggestion that basal cell adenocarcinoma represents the solid variant of adenoid cystic carcinoma, but differences in histology and biology support separate classification.

- In infants presence of hybrid basal cell adenoma and adenoid cystic carcinoma represents sialoblastoma (see [Sialoblastoma](#)).

Pathology

Gross

- Circumscribed but unencapsulated, solid, tan-white mass varying in size from 0.7 to 4 cm in diameter; cystic foci may be focally identified.

Fine-Needle Aspiration Biopsy

- Aspiration findings are essentially identical to those of basal cell adenoma (see previous).

- Histology of many basal cell adenocarcinomas is similar to basal cell adenoma but features of malignancy may be present and identifiable by FNAB, including:
 - Marked nuclear pleomorphism with increased nuclear-to-cytoplasmic ratio
 - Increased mitotic activity
 - Necrosis

Histology

- Morphologic similarity to basal cell adenoma including:
 - Variably sized nodules or islands of tumor cells growing in solid, trabecular, membranous, and/or tubular patterns
 - Variety of morphologic patterns can be seen in any given neoplasm.
 - Solid growth with tumor nests separated by eosinophilic basal lamina (i.e., membranous pattern) or trabecular pattern is most frequent
- Lesional cells composed of uniform, basaloid epithelial cells consisting of two cell types:
 - Large round to polygonal to elongated cell with pale staining basophilic nuclei, eosinophilic to amphophilic cytoplasm, and indistinct cell borders
 - Small, round cell with dark (basophilic) nuclei, scant cytoplasm and indistinct cell borders:
 - Tend to be located peripheral to the larger cells
 - Peripheral palisading of nuclei may be seen but tends to be less prominent as compared with basal cell adenoma.
 - Of the two cellular components larger cells tend to be more common, although in any given tumor they may be seen in equal proportion.
 - Overall cytomorphology may be predominantly bland, lacking significant nuclear pleomorphism, increased mitotic activity, or necrosis.
 - Nuclear pleomorphism, increased mitotic activity, and necrosis may be seen but not consistently identified or diagnostic for carcinoma.
- Eosinophilic, hyalinized, PAS-positive basal lamina can be seen either as intercellular droplets or perinodule membranes.
- Additional findings may include presence of:
 - Tubular structures may focally be present.
 - Squamous differentiation:
 - Identified in approximately 25% of cases
 - Spindle-shaped cells
 - Cystic or cribriform patterns may be present.
- A stromal benign lymphoplasmacytic cell infiltrate may be present.
- Histologic hallmark for diagnosis of basal cell adenocarcinoma rests on the identification of infiltration as manifested by:
 - Invasion of adjacent structures (e.g., salivary gland parenchyma, soft tissue structures)
 - Lymph-vascular invasion
 - Neurotropism (e.g., perineural or intraneural invasion)
- Histochemistry:
 - In general, PAS- and mucicarmine-positive material is absent or minimally present within the basal cell adenocarcinoma; PAS-positive material may be seen within tubular lumens.
- Immunohistochemistry:
 - Consistent and diffuse pan-cytokeratin (AE1/AE3) positive
 - Most are reactive for CK14 with variable reactivity for CK7, 8, 18, 19
 - Vimentin positive
 - Focal reactivity for S100 protein, smooth muscle actin (usually peripherally located cells), carcinoembryonic antigen, epithelial membrane antigen
 - c-kit (CD117) immunoreactivity reported
 - Low proliferation rate (<5%) as seen by Ki67 staining
- Electron microscopy:
 - Similar to basal cell adenoma with evidence of differentiation along basal, myoepithelial, and ductal cell lines:
 - Basal cells: rough endoplasmic reticulum, mitochondria, tonofilaments, and desmosomes
 - Myoepithelial cells: cytoplasmic myofilaments, plasmalemmal extensions, and desmosomes
 - Ductal cells: microvilli, tight junctions, and desmosomes
- Cytogenetics and molecular genetics:
 - Chromosomal gains and losses, including:
 - Gains: 9p21.1-pter, 18q21.1-q22.3, 22q11.23-q13.31
 - Losses: 2q24.2, 4q25-q27
 - Loss of heterozygosity with high frequency at 16q12-13 regions:
 - Seen in sporadic cases and in cases of familial basaloid tumors and dermal cylindroma cases
 - Absence of *MYB-NFIB* fusion transcript
- Hybrid tumor:
 - May occur as part of a hybrid salivary gland tumor in association with other salivary gland tumors (e.g., adenoid cystic carcinoma)

Differential Diagnosis

- Basal cell adenoma:
 - Presence of invasive growth distinguishes basal cell adenocarcinoma from basal cell adenoma
- Cellular pleomorphic adenoma
- Adenoid cystic carcinoma:
 - In contrast to basal cell adenocarcinoma, adenoid cystic carcinomas:

- Have prominent cribriform pattern of growth with pseudocyst formation (features usually not present in basal cell adenocarcinoma)
- Lack dual cell population (mixture of small and large cells seen in basal cell adenocarcinoma)
- Lack peripheral nuclear palisading
- Lack squamous differentiation
- Presence of *MYB-NFIB* fusion transcript
- Myoepithelial carcinoma
- Basaloid squamous cell carcinoma
- Adamantinoma-like Ewing sarcoma (AES):
 - Rare variant of the Ewing family of tumors that resembles classic adamantinoma of bone
 - AES shows epithelial differentiation and complex immunohistochemical expression profile with keratin and basal marker immunoreactivity and can resemble a variety of carcinomas.
 - May rarely occur in parotid gland histologically simulating basal cell adenocarcinoma including:
 - Nested basaloid proliferation with peripheral palisading in tumor nests
 - “Basaloid” epithelial differentiation by cytokeratin (AE1/AE3) and p40 positivity
 - Unlike most basal cell adenocarcinomas, AES demonstrate:
 - High grade morphology
 - Absence of true ductal or myoepithelial component
 - Tendency toward neuroectodermal phenotype with focal rosette formation, CD99, and weak synaptophysin immunoreactivity
 - Presence of EWSR1 and FLI1 fluorescence in situ hybridization confirms presence of translocation supporting diagnosis.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - For parotid gland, superficial parotidectomy
 - For submandibular gland, complete glandectomy
 - For minor salivary gland, wide excision to include tumor-free margins
- Unless lymph node involvement is clinically evident, neck dissection would not appear warranted.
- Local recurrences frequent especially for tumors of minor salivary glands:
 - 71% for minor salivary gland tumors
 - 37% for major salivary gland tumors
- Metastatic disease is uncommon:
 - Occurs in 21% of minor salivary gland cases
 - Occurs in 11% of minor salivary gland cases
 - Involves regional lymph nodes and rarely lungs
- Prognosis is generally excellent:
 - Death due to disease is uncommon.

EPITHELIAL-MYOEPITHELIAL CARCINOMA (EMC)

(Figs. 20-101 through 20-105)

Definition: Low-grade malignant epithelial salivary gland neoplasm characterized by presence of ductal structures composed of two cell types, including inner (luminal) epithelial cells and outer (abluminal) myoepithelial cells.

Synonyms: Clear cell adenoma/carcinoma; glycogen-rich clear cell adenoma/carcinoma; clear cell carcinoma; tubular carcinoma; adenomyoepithelioma

Clinical

- Uncommon salivary gland neoplasm
- Slightly more common in women than in men; may occur over a wide age range but is most frequently encountered in the sixth to seventh decades of life
- Approximately 75% to 80% occur in parotid gland:
 - Other sites of involvement include submandibular gland and minor salivary glands throughout the upper aerodigestive tract including:
 - Oral cavity (palate)
 - Sinonasal tract
- Symptoms usually relate to asymptomatic, slow-growing mass:
 - Associated pain and/or facial nerve paralysis occur infrequently
 - Ulceration of a mucosal-based lesion may be present
 - Duration of symptoms ranges from months to years

Pathology

Gross

- Well-circumscribed but unencapsulated, solid, firm, tan-white to yellow mass measuring from 1 to 12 cm in greatest dimension
- Hemorrhage and necrosis may occasionally be identified.
- Minor salivary gland involvement may be associated with mucosal ulceration.

Fine-Needle Aspiration Biopsy

- Smears generally cellular with no specific architectural pattern
- Biphasic pattern including epithelial (small cell) and myoepithelial (large/clear cell) may be identified:
 - Epithelial cells are small.
 - Myoepithelial cells are large with abundant clear cytoplasm, distinct cell borders, and uniform, small nuclei.
 - Biphasic pattern may be subtle or absent since the clear cells have a fragile cytoplasm and often appear as naked nuclei.

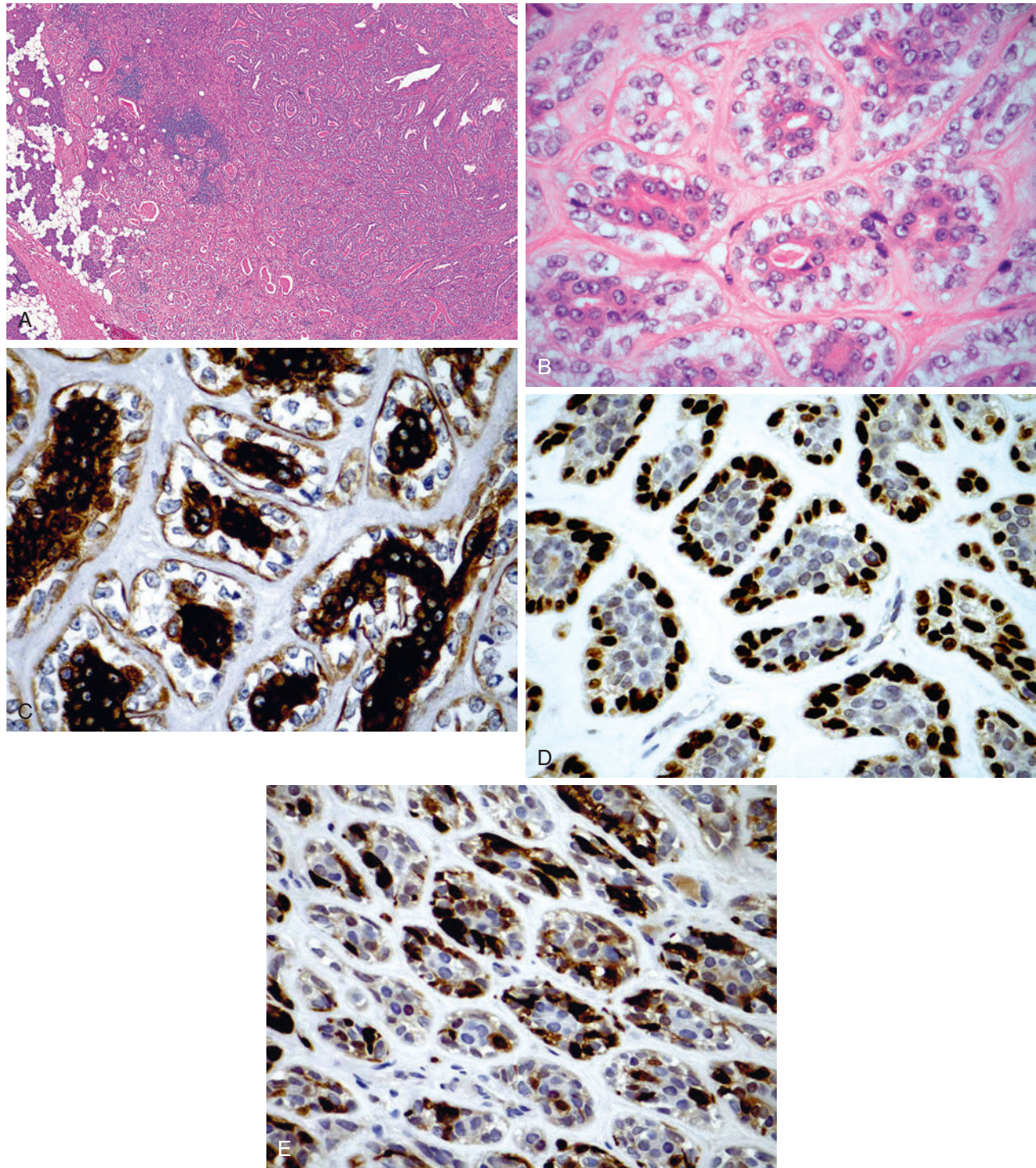


Fig. 20-101. Epithelial-myoepithelial carcinoma.

Epithelial-myoepithelial carcinoma of the parotid gland. **A**, Unencapsulated tumor invading into the parotid gland parenchyma (*lower left*). **B**, Characteristic tubular growth composed of a dual cell population with luminal or inner epithelial cell layer appearing as dark staining cuboidal to columnar cells with central or basally placed nuclei and eosinophilic cytoplasm and outer abluminal or outer myoepithelial cell layer appearing as polyhedral-shaped cells with eccentrically placed nuclei, abundant clear cytoplasm, and distinct cell borders; **C** through **E**, cytokeratin (CAM5.2) shows dedicated reactivity of the luminal cells while dedicated staining of the outer myoepithelial cells by **(D)** p63 (nuclear) and **(E)** S100 protein (nuclear and cytoplasmic).

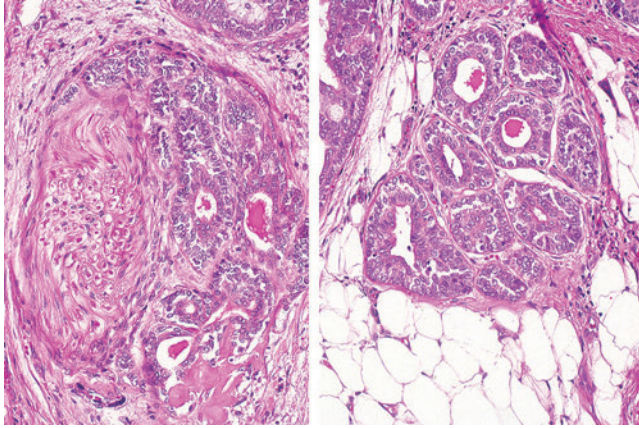


Fig. 20-102. Epithelial-myoepithelial carcinoma.

Often these tumors are infiltrative including neurotropism (*left*) and invasion into adipose tissue (*right*).

- Single cells and naked nuclei were prominent in all cases.
- Globules of hyalinized basal lamina may occasionally be seen.

Histology

- Circumscribed but unencapsulated tumors:
 - Often multinodular or multilobulated
- Infiltration present and includes invasion into adjacent/surrounding salivary gland parenchyma, neurotropism, perivascular invasion, angioinvasion, and osseous invasion.
- Tumor nests frequently have an organoid arrangement but may also have a cystic, papillary, and/or solid growth.
- Histologic hallmark is presence of two cell types identified in varying proportions in any given tumor:
 - Luminal or inner epithelial cell layer:
 - Dark staining cuboidal to columnar cells with central or basally placed nuclei and scant eosinophilic cytoplasm

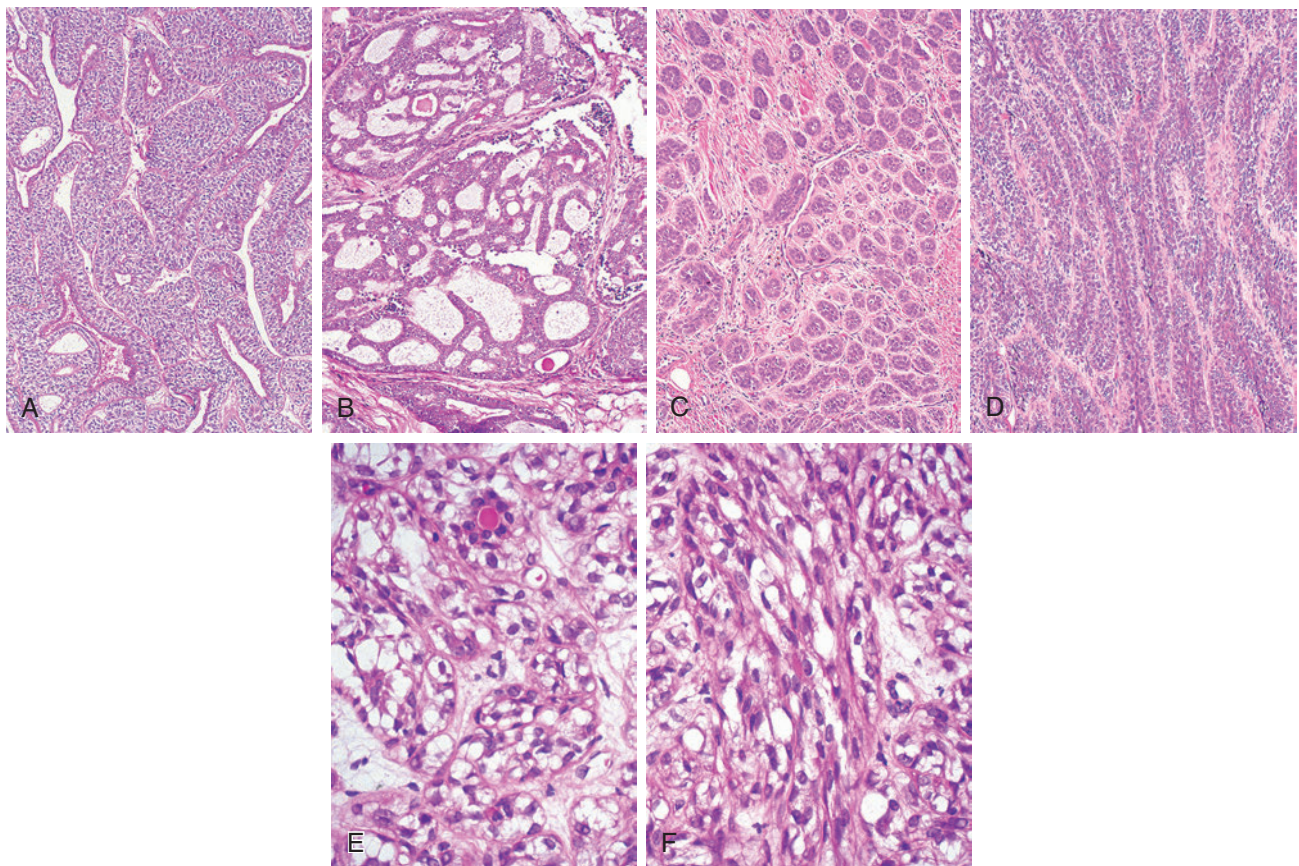


Fig. 20-103. Epithelial-myoepithelial carcinoma.

Variant growth patterns and cell types may include (A) solid and trabecular; (B) cribriform; (C) small tubules; (D) cordlike; (E) solid; and (F) fascicular composed of spindle-shaped cells. In some of these examples there is overgrowth of the myoepithelial cell component obscuring the epithelial cell component.

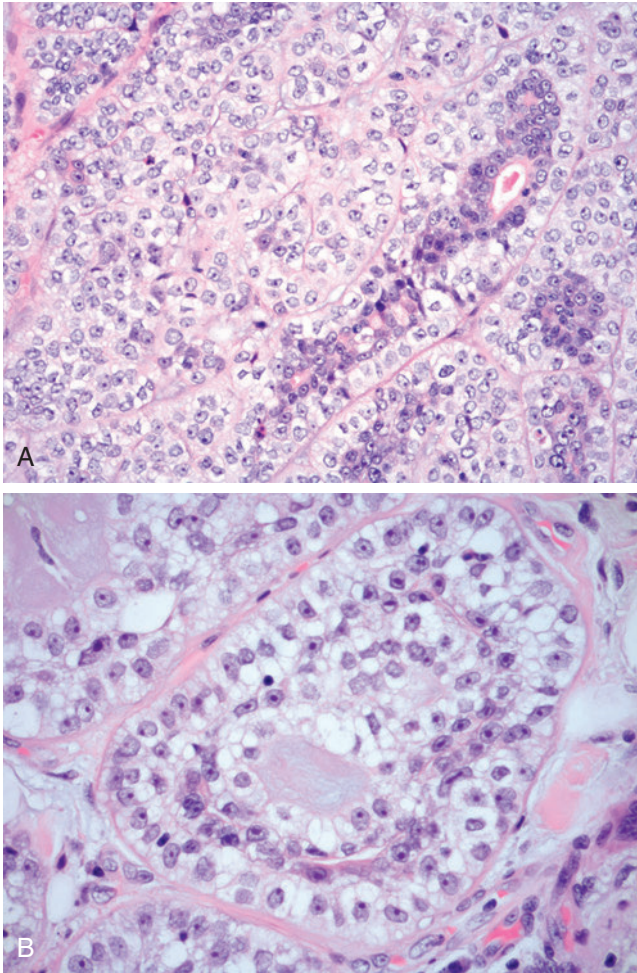


Fig. 20-104. Epithelial-myoepithelial carcinoma.

Additional variant findings in epithelial-myoepithelial carcinoma may include (A) tumors with myoepithelial cell overgrowth predominated by cells with clear cytoplasm with limited but identifiable epithelial component characterized by tubular growth composed of luminal cells with eosinophilic cytoplasm; (B) double clear cell variant in which both luminal and abluminal cells are composed of cells with clear cytoplasm.

- Surround small lumens, which may appear cystic and contain eosinophilic proteinaceous material
- Abluminal or outer myoepithelial cell layer:
 - Polygonal cells with eccentrically placed nuclei, abundant clear cytoplasm, and distinct cell borders
 - Variant myoepithelial morphologies may include:
 - Predominance of myoepithelial cells especially in tumors with solid growth that may obscure epithelial cell layer: referred to as *EMC with myoepithelial overgrowth*;

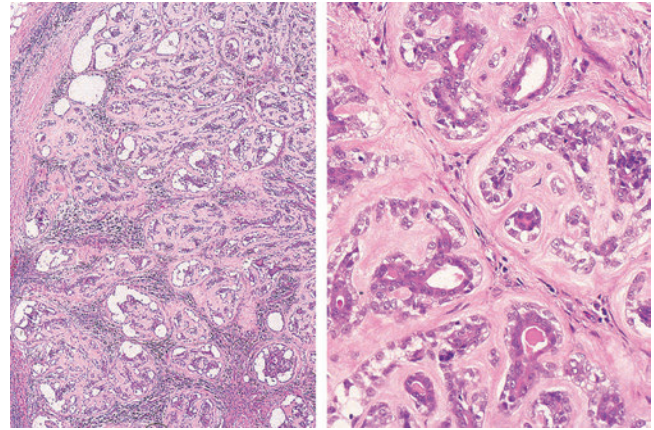


Fig. 20-105. Epithelial-myoepithelial carcinoma.

Prominent hyalinization may be present.

- “Verocay”-like nuclear palisading may be identified
 - Spindle shaped or elongated
- Lesional cells show mild to moderate pleomorphism but marked cytomorphic atypia not typically seen:
 - Mitotic activity is absent to low (2 mitoses or fewer per 10 high-power fields)
 - Necrosis usually absent but may be present within the center of tumor lobules
 - “Ancient” changes in form of focal marked nuclear pleomorphism (similar to “monster” cells in pleomorphic adenomas) may be present
- Tumor nests variably separated by thin fibrovascular stroma to loose myxoid stroma to basement membrane-like material that may be thickened appearing as eosinophilic, hyalinized membrane that is PAS positive.
- Histologic variants include:
 - Oncocytic variant
 - Uncommon variant constitute up to 8% of all EMCs
 - Oncocytic EMC:
 - Occurs in patients decades older than conventional EMC
 - Often papillary with calcification and associated sebaceous components
 - Apocrine variant
 - Named for its apocrine ductal component
 - May be mistaken for salivary duct carcinoma.
 - Epithelial component often shows overgrowth in a cribriform or even solid pattern.
 - Immunophenotypically defined by androgen receptor and gross cystic disease fluid protein

- 15 positivity. The most important aspect of differentiating oncocytic and apocrine EMC from other salivary oncocytic tumors is recognition of the biphasic nature of these variants and confirmation that the abluminal outer layer consists of plump, “activated” myoepithelial cells, regardless of tinctorial characteristics.
- Oncocytic and apocrine variants have indolent biology.
 - Double clear cell variant:
 - Luminal and abluminal cells composed of cells with clear cytoplasm
 - Usually predominated by clear-appearing epithelial cells often columnar and stratified containing large-caliber tubules
 - Surrounding myoepithelial cells also typically clear appearing
 - Sebaceous variant:
 - Rare occurrence
 - Histologically show areas of sebaceous differentiation admixed with features of bilayered ductal structures typical of EMC
 - Sebaceous differentiation may be diffusely or focally identified.
 - Generally lack cytologic atypia
 - Positive immunoreactivity for EMA confirmed sebaceous differentiation
 - Low-grade malignancy similar to conventional EMC
 - EMC ex pleomorphic adenoma
 - May be malignant component in carcinoma ex pleomorphic adenoma (EMC ex pleomorphic adenoma)
 - EMC with myoepithelial anaplasia
 - Represents progression to histologically higher-grade EMC
 - Characterized by solid growth, increased nuclear atypia in more than 20% of myoepithelial cells, and increased mitotic activity
 - Transition to severe nuclear atypia in myoepithelial cells gradual rather than abrupt with intervening areas of moderate nuclear atypia
 - Anaplastic component may include transition to squamous cell carcinoma.
 - Associated with worse prognosis
 - Histochemistry:
 - Luminal or inner epithelial cells:
 - May show diastase-resistant, PAS-positive intracytoplasmic material
 - Mucicarmine negative
 - Luminal eosinophilic material is PAS positive and mucicarmine negative
 - Abluminal or outer (myoepithelial) cells:
 - May show diastase-sensitive, PAS-positive intracytoplasmic material
 - Mucicarmine negative but rarely may be positive
 - Immunohistochemistry:
 - Luminal or inner epithelial cells:
 - Cytokeratins and EMA:
 - Strongly positive
 - Dedicated CAM5.2 staining
 - S100 protein and SOX10 variably immunoreactive
 - Absence of myoepithelial markers
 - Abluminal or outer (myoepithelial) cells:
 - p63, S100 protein, calponin, smooth muscle actin, smooth muscle myosin heavy chain, muscle-specific actin and SOX10 positive
 - Cytokeratin and EMA variably and often weakly reactive:
 - Absence of CAM5.2
 - GFAP occasionally reactive
 - Low proliferation rate (<5%) as seen by Ki67 staining
 - bcl-2 and c-kit frequently positive
 - DOG1 may be positive, showing combined apical ductal and membranous/cytoplasmic myoepithelial staining profile
 - Renal cell carcinoma marker, CD10, PAX2, PAX8, and CAIX negative
 - Electron microscopy:
 - Luminal or inner epithelial cells:
 - Lumina, microvilli, junctional complexes, desmosomes
 - Golgi complexes, dilated endoplasmic reticulum, dense core secretory granules, tonofilaments
 - Abluminal or outer (myoepithelial) cells:
 - Intracytoplasmic microfilaments with focal densities, subplasmalemmal plaques, and multilayered basal lamina
 - Fewer organelles as compared with epithelial cells
 - Cytogenetics and molecular genetics:
 - To date, no translocation has been identified but a limited number of cases evaluated found *HRAS* exon 3, codon 61 mutation.
 - Classic (low-grade) EMC lack *MYB* translocation
 - Hybrid tumor:
 - May occur as part of a hybrid salivary gland tumor in association with other salivary gland tumors (e.g., adenoid cystic carcinoma [AdCC], salivary duct carcinoma, others)
 - Hybrid EMC-AdCC may harbor *MYB* translocation.
 - High-grade transformation (“dedifferentiation”) of EMC:
 - Rare occurrence
 - Transition from foci of EMC to histologic high-grade carcinoma characterized by nuclear

- pleomorphism, increased mitotic activity, and necrosis
- Ki67 labeling index significantly increased in high-grade carcinoma component as compared with foci of EMC
- Associated with worse prognosis
- May harbor *MYB* translocation suggesting close relationship (or possibly a variant) to adenoid cystic carcinoma

Differential Diagnosis (Table 20-10)

- Clear cell oncocytoma
- Clear cell myoepithelioma
- Mucoepidermoid carcinoma, clear cell variant
- Acinic cell adenocarcinoma, clear cell variant
- Primary salivary gland clear cell carcinoma
- Metastatic tumors composed of clear cells, a rare phenomenon, including:
 - Renal cell carcinoma:
 - Absence of biphasic cell pattern, prominent fibrovascular stroma, and presence of CD10, renal cell carcinoma marker, PAX2, PAX8, and CAIX immunoreactivity
 - Thyroid carcinoma:
 - Absence of biphasic cell pattern and presence of thyroglobulin and thyroid transcription factor 1 (TTF-1) immunoreactivity

Treatment and Prognosis

- Complete surgical excision is preferred treatment.
- Adjunctive radiotherapy used in cases in patients whose tumors cannot be completely excised or when there is doubt as to the completeness of surgical resection
- Local recurrence is frequent occurrence seen in 30% to 50% of patients:
 - Most recurrences within 5 years of the initial resection but may also occur many years or decades after initial surgery
 - Multiple recurrences may occur

TABLE 20-10 Salivary Gland Tumors with Clear Cells: Differential Diagnosis

Tumor	Histology	Histochemistry	IHC	Cytogenetics
EMC	Dual cell population: (1) luminal or inner epithelial cell layer composed of dark staining cuboidal to columnar cells with eosinophilic cytoplasm surrounding small lumens and (2) abluminal or outer myoepithelial cell layer polyhedral cells with eccentrically placed nuclei, abundant clear cytoplasm and distinct cell borders	Epithelial cells: diastase-resistant, PAS-positive intracytoplasmic material, mucicarmine negative. Myoepithelial (clear) cells: diastase-sensitive, PAS-positive intracytoplasmic material; mucicarmine negative. Intraluminal eosinophilic material: PAS-positive and mucicarmine negative	Epithelial cells: cytokeratin (AE1/AE3, CAM5.2) and EMA positive. Myoepithelial cells: S100 protein, p63, calponin, SMA positive	Limited number of cases positive for <i>HRAS</i> exons 3, codon 61 mutations
CCC (hyalinizing and non-hyalinizing)	Dominated by cells with clear cytoplasm; cells with slightly eosinophilic appearing cytoplasm may be seen scattered throughout the tumor; stromal hyalinization may or may not be present	Diastase-sensitive, PAS-positive; mucicarmine negative	Cytokeratin and EMA positive; limited to absent reactivity for myoepithelial cell markers including S100 protein, p63, calponin, SMA	<i>EWSR1-ATF1</i> (hyalinizing CCC)
MEC, clear cell type	Pure clear cell variant of MEC likely nonexistent; clear cells are round to oval cells with clear cytoplasm, distinct cell borders, peripherally-placed, small, dark nuclei; clear cells may be seen and infrequently may predominate but areas of residual MEC including admixture of mucocytes, epidermoid cells and intermediate cells present	Diastase-resistant, PAS-positive; mucicarmine positive	Cytokeratin positive; p63 positive but other myoepithelial cell markers negative, including S100 protein, calponin, SMA	<i>CRTC1-MAML2</i>

Continued

TABLE 20-10 Salivary Gland Tumors with Clear Cells: Differential Diagnosis—cont'd

Tumor	Histology	Histochemistry	IHC	Cytogenetics
ACC, clear cell type	Clear cells round to oval, distinct cell borders, small peripherally placed dark nuclei; clear cells result from fixation and/or tissue processing; “pure” clear cell variant likely does not exist	Diastase-resistant, PAS-positive; mucicarmine negative	Cytokeratin, DOG1 positive; myoepithelial cell markers negative, including S100 protein, p63, calponin, SMA	None known
Oncocytoma, clear cell type	Partial or complete replacement of granular eosinophilic cytoplasm by cells with clear, nongranular-appearing cytoplasm; transition areas of typical oncocytes to clear cells may be present; other than the cytoplasmic appearance, the histology and histochemical staining is similar to the more conventional type of oncocytoma; clear cytoplasm is due in part to fixation and tissue processing artifact, and to accumulation of glycogen within the cytoplasm displacing the mitochondria to the periphery of the cells	Diastase-sensitive, PAS-positive granules; oncocytes show intracytoplasmic blue-black granules by PTAH staining	Cytokeratin, EMA positive; myoepithelial cell markers negative, including S100 protein, p63, calponin, SMA	None known
Myoepithelioma and myoepithelial carcinoma, clear cell type	Clear cells have defined cell membranes; one cell type among several different cell types seen in myoepithelioma with transition areas of typical myoepithelial cells to clear cells present	Clear cells are diastase-sensitive, PAS-positive; mucicarmine negative	Cytokeratins, EMA, p63, calponin, S100 protein, SMA, vimentin positive	<i>EWSR1-ATF1</i> reported in clear cell type of myoepithelial carcinoma
RCC	Cell nests separated by thin fibrovascular cores; clear cells have sharp cell membranes; red cells characteristically seen within luminal spaces	Clear cells are diastase-sensitive, PAS-positive; mucicarmine negative	Cytokeratins (AE1/AE3, CAM5.2), EMA, CD10, renal cell marker, PAX2, PAX8, CAIX, vimentin positive; HMWCK, CK7 and CK20 negative; myoepithelial cell markers, GATA3 negative	Partial or complete chromosome 3 loss or mutation on short arm chromosome 3p; alterations in chromosomes 14, 8, and 9
TC, papillary or follicular types	Metastasis from thyroid in general is rare and one entirely comprised of clear cells unlikely; in this scenario clear cells represent part of metastatic cellular composition that includes follicular epithelial cells with or without identifiable colloid, and with or without nuclear features of thyroid papillary carcinoma; clear cells have abundant clear to slightly granular appearance	Clear cells are typically PAS and mucicarmine negative; colloid is diastase-resistant, PAS-positive	Cytokeratins, thyroglobulin, TTF1, positive; myoepithelial cell markers negative	<i>RET/PTC</i> and <i>BRAF</i> mutations for more usual types of papillary carcinomas; <i>RAS</i> mutation for follicular variant papillary thyroid carcinoma, follicular adenoma, follicular carcinoma

ACA, Acinic cell adenocarcinoma; CAIX, carbonic anhydrase 9; CCC, clear cell carcinoma (nonhyalinizing and hyalinizing); EMA, epithelial membrane antigen; EMC, epithelial myoepithelial carcinoma; MEC, mucoepidermoid carcinoma; PAS, periodic acid Schiff; PTAH, phosphotungstic acid hematoxylin; RCC, renal cell carcinoma; TC, thyroid carcinoma; SMA, smooth muscle actin; TTF1, thyroid transcription factor 1.

- Metastatic tumor:
 - Metastases occur most often to regional (cervical and periparotid) lymph nodes:
 - Reported in up to 20% of cases
 - Less common, distant metastases occur primarily to lungs, kidney, and brain:
 - Reported in less than 10% of cases
 - Metastases may occur 10 years or more after the initial resection.
- In general, the prognosis is excellent:
 - 5-year survival rate reported to be 80%
 - 10-year survival rate reported to be 72%
 - Death may occur restricted to but not always seen in cases with metastatic tumor
- Factors associated with adverse prognosis include:
 - Large tumor size
 - Rapid growth
 - Occurrence in minor salivary glands (likely related to incomplete surgical resection)
 - Solid growth pattern
 - Nuclear atypia in greater than 20% of the tumor
 - DNA aneuploidy
 - High proliferative activity
- Factors affecting disease-free survival include:
 - Positive margin status
 - Presence of angiolymphatic invasion
 - Presence of necrosis
 - Presence of myoepithelial anaplasia
- Connection to surface mucosa in many cases
- Presence of consistent diffuse p63 immunoreactivity
- Ultrastructural presence of tonofilaments, well-formed desmosomes, and hemidesmosomes
- Presence of squamous and mucinous differentiation may indicate HCCC is a low-grade sclerosing adenosquamous carcinoma
- Other evidence show similarities to clear cell odontogenic carcinoma (CCOC) except by location including similar:
 - Histology
 - *EWSR1-ATF1* rearrangements (a finding not present in other clear cell neoplasms in the differential diagnosis)

• Until more clearly defined as being separate from CCC, both types of clear cell neoplasms are included under a single category with the possibility that future classification may separate these two entities.

Clinical

- Uncommon tumor
- No gender predilection; primarily identified in the fifth through eighth decades of life; rare in children
- Most frequently occur in intraoral sites:
 - Palate and base of tongue most common sites of occurrence
 - Other intraoral sites include buccal mucosa, floor of mouth, tongue, lip, retromolar area, and tonsillar region
 - Other less common sites of occurrence include:
 - Major salivary glands: parotid gland \gg submandibular gland
 - Nasopharynx, hypopharynx, larynx, lacrimal gland
- Most commonly present as an asymptomatic swelling
 - Pain and mucosal ulceration may be present; osseous invasion and fixation to surrounding tissues may occur.

Pathology

Gross

- Poorly circumscribed, solid mass with a gray-white appearance usually measuring 3 cm or less in greatest dimension
- Prominent hyalinization may be grossly appreciated, imparting a scar-like/fibrotic appearance.
- Infiltration of adjacent tissues may be identified.

Fine-Needle Aspiration Biopsy

- Aspirates contain numerous groups and sheets of cohesive small and large epithelial cells:
 - Groups and sheets, which had sharp outlines and showed focal nuclear overlapping

CLEAR CELL CARCINOMA (CCC) AND HYALINIZING VARIANT (HCCC)

(Figs. 20-106 through 20-108)

Definition: Malignant epithelial salivary gland tumor composed exclusively of monomorphic population of cells characterized by their clear-appearing cytoplasm (with or without stromal hyalinization) without evidence of myoepithelial differentiation and lacking histomorphologic features of other salivary gland neoplasms that may be dominated by a prominent population of clear cells (e.g., mucoepidermoid carcinoma, acinic cell adenocarcinoma, epithelial-myoepithelial carcinoma, myoepithelial carcinoma, others).

Synonyms: Clear cell adenocarcinoma; hyalinizing clear cell adenocarcinoma; glycogen-rich clear cell carcinoma

Classification

- Evidence suggests that HCCC may represent a squamous mucosal-derived neoplasm rather than a neoplasm of seromucous gland origin; such evidence includes:

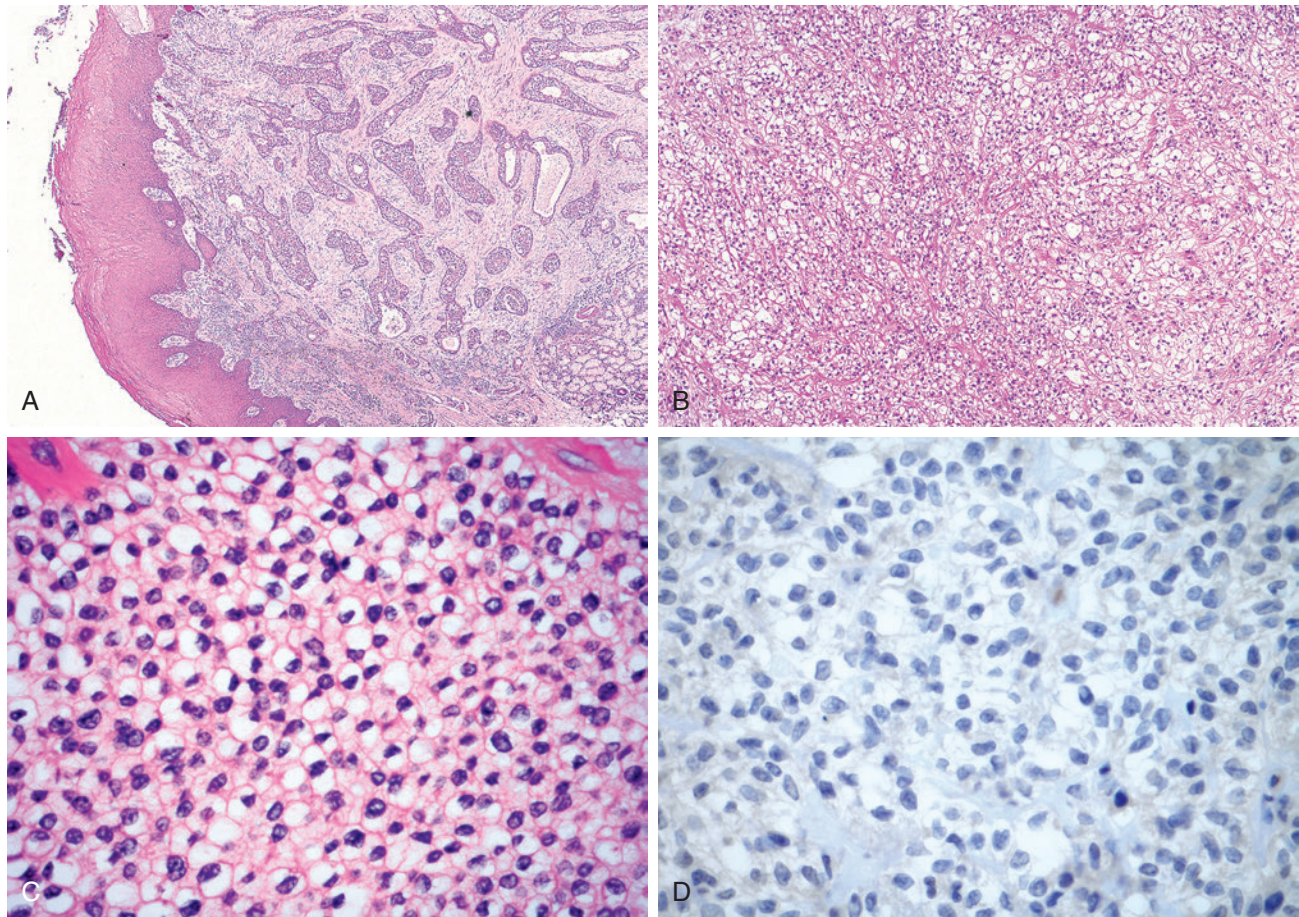


Fig. 20-106. Clear cell carcinoma of minor (oral cavity) salivary glands.

A, Submucosal unencapsulated and infiltrative tumor with trabecular solid, nested growth; the tumor is infiltrative into seromucous glands (*lower right*). **B**, Another example characterized by diffuse proliferation of cells exclusively composed of cells with clear cytoplasm. **C**, At higher magnification the entire neoplasm is comprised of cells with clear-appearing cytoplasm, distinct cell membranes, and rather bland-appearing nuclei lacking significant nuclear pleomorphism and increased mitotic activity. **D**, The lesional cells are p63 negative.

- Cells have uniform, round to ovoid nuclei, granular-appearing chromatin, small nucleoli, and abundant, well-defined clear-appearing cytoplasm.
- Myoepithelial cells or hyaline globules are absent.

Histology

- Clear cell carcinoma (CCC)
 - Unencapsulated infiltrative submucosal neoplasm with solid sheets, nests, cords, trabeculae, and single-cell growth patterns:
 - Ducts and gland-like spaces typically not identified
 - But may focally be seen although such structures may represent entrapped non-neoplastic ducts
 - Lesional cells may extend and involve overlying surface (squamous) epithelium.
- Lesional cells characterized by presence of abundant clear-appearing cytoplasm:
 - May predominate in any given lesion
 - Cells with slightly eosinophilic-appearing cytoplasm may be admixed with clear-appearing cells.
 - Nuclei are oval to round with finely granular-appearing chromatin, centrally to eccentrically located and inconspicuous to small nucleoli.
 - Cell borders/membranes are distinct.
- Cytomorphologically, cells are uniform in appearance with mild nuclear pleomorphism, although moderate pleomorphism may be present, scarce to absent mitotic figures; necrosis is not usually identified.
- Stromal findings include minimal collagen deposition, appearing as interconnecting fibrous septa.

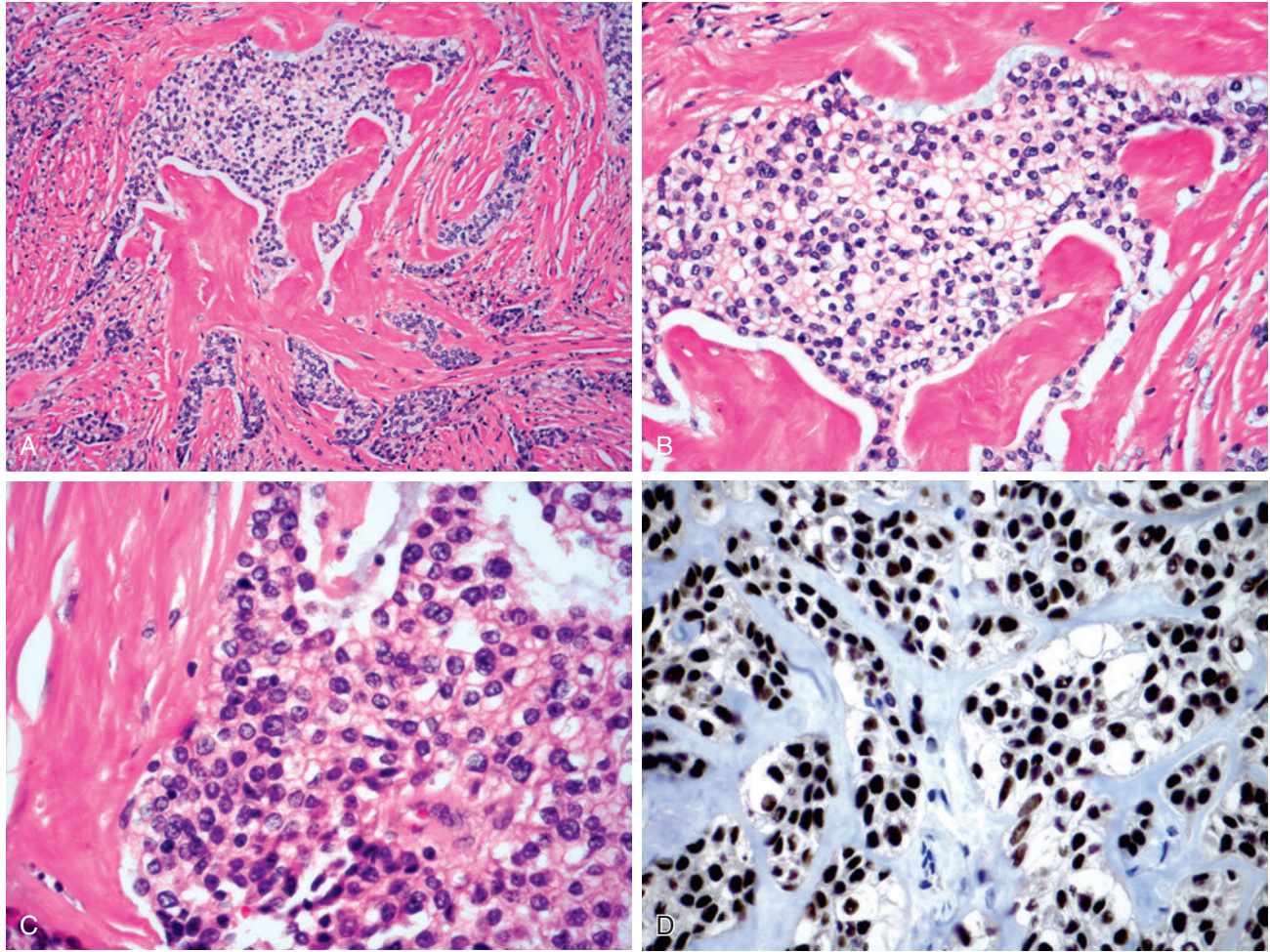


Fig. 20-107. Hyalinizing clear cell carcinoma of minor (oral cavity) salivary glands.

A, The tumor is characterized by the presence of markedly thickened bands of sclerotic or hyalinized collagen in which nests and cords of lesional cells are seen. **B**, In contrast to clear cell carcinoma without hyalinization, which is exclusively composed of clear cells, in this tumor there is an admixture of cells with pale eosinophilic cytoplasm with clear cells rather than exclusively composed of clear-appearing cells. **C**, However, a predominance of clear cells may be seen in a minority of cases. Irrespective of the nature of the cytoplasm the cells are rather uniform with round to oval nuclei lacking significant pleomorphism and distinct cell membranes. **D**, The lesional cells are diffusely p63 immunoreactive.

- Histochemistry:
 - Intracytoplasmic diastase-sensitive, PAS-positive material indicative of glycogen
 - Mucicarmine staining usually negative
- Immunohistochemistry
 - Cytokeratins including high molecular weight focally to diffusely positive
 - CEA positive
 - Myoepithelial markers typically negative including S100 protein, p63, actins, calponin, and GFAP
 - Renal cell carcinoma (RCC) antibody, CD10, PAX2, PAX8, and CAIX negative
- Electron microscopy:
 - Features of duct cell differentiation including microvilli, tight junctions, desmosomes, tonofilaments, and basal lamina
 - Absence of myoepithelial differentiation
- Cytogenetics and molecular genetics:
 - No specific findings
- Hyalinizing clear cell carcinoma (HCCC)
 - Unencapsulated infiltrative submucosal neoplasm characterized by presence of markedly thickened bands of sclerotic or hyalinized collagen:
 - Hyalinized stroma may be intimately admixed with lesional cells, creating a somewhat

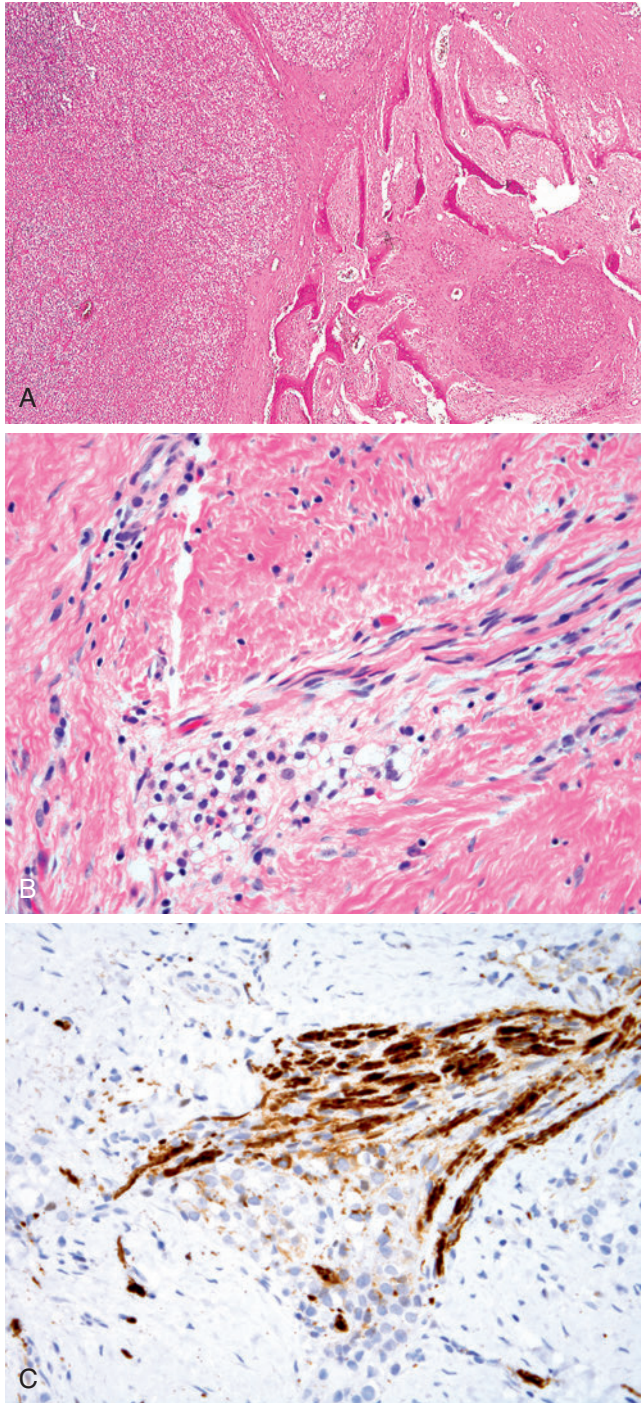


Fig. 20-108. Clear cell carcinoma of minor (oral cavity) salivary glands.

The tumor is infiltrative, including (A) invading into and through palatal bone and (B) perineural invasion, the latter confirmed by (C) S100 protein staining.

- cribriform arrangement that may simulate other more common salivary gland tumors
- In addition, a fibrocellular stroma that may appear myxoid (similar to pleomorphic adenoma) may be seen.
- Juxtaposition of two stroma types within the tumor essentially pathognomonic seen in most but not all cases
- Predominance of clear cells seen in a minority of cases:
 - Often cells with pale eosinophilic cytoplasm rather than clear cytoplasm are seen or there is an admixture of both cell types.
 - Nuclei are oval to round with finely granular-appearing chromatin, centrally to eccentrically located and inconspicuous to small nucleoli.
 - Cell borders/membranes are distinct.
 - “Raisinoid” or “popcorn”-appearing nuclear membrane irregularities may be seen.
 - Occasional pseudonuclear inclusions may be present.
- Cytomorphologically, cells are rather uniform in appearance with mild nuclear pleomorphism scarce to absent mitotic figures; necrosis is not usually identified.
- Cells are arranged in small nests, short and long cords, interconnecting thin trabecular structures, and single cells.
 - Tendency for cells in center of mass to be surrounded by or admixed with a hyalinized basement membrane-like material
 - Cells often sharply demarcated from desmoplastic or fibrocellular stroma
 - Cells at periphery have greater tendency for nest formation and for infiltration without stromal deposition or desmoplastic response.
 - May appear in short thin cords
 - Owing to absence of desmoplasia such cells at periphery may be difficult to appreciate by light microscopy
- Tumors often connect to surface mucosal epithelium either abruptly or as pagetoid-like growth of single cells and may be accompanied by pseudoepitheliomatous hyperplasia.
- Other findings may include:
 - Occasional presence of focal squamous differentiation
 - Occasional duct formation, which may be true ductal differentiation in the neoplasm or more likely represents entrapped ducts:
 - Particularly common in parotid gland cases and absent in oral cavity cases
- Histochemistry:
 - Intracytoplasmic diastase-sensitive, PAS-positive material indicative of glycogen

- Mucicarmine staining may show dot-like or frank intracytoplasmic positive material in a high proportion of cases.
- Congo red staining for amyloid is negative.
- Immunohistochemistry
 - Majority diffusely positive for pancytkeratin
 - In addition, most cases positive for high molecular weight cytokeratins, p63 (suggestive of squamous differentiation), and CK14
 - Many cases focally or diffusely positive for EMA, CK7, CK19, and CAM5.2
 - Negative for myoepithelial-related markers including S100 protein, actins, calponin, and GFAP
 - Renal cell carcinoma antibody, CD10, PAX2, PAX8, and CAIX negative
- Electron microscopy:
 - Shown to have tonofilaments, well-formed desmosomes, and hemidesmosomes:
 - These features suggestive of squamous differentiation
 - Additional findings include basal lamina.
- Cytogenetics and molecular genetics:
 - Consistent *EWSR1-ATF1* gene fusion:
 - Represents another lesion type associated with *EWSR1-ATF1* gene fusion (see Table 20-2)
 - This molecular signature not present in other clear cell neoplasms that may share features with HCCC; notable exception is clear cell odontogenic carcinoma
- Infiltration often present for CCC and HCCC including invasion:
 - Into (minor) salivary gland parenchyma
 - Neurotropism (perineural and intraneural)
 - Lymph-vascular invasion
 - Invasion into muscle and bone

Differential Diagnosis (Table 20-10)

- Clear cell oncocytoma
- Clear cell myoepithelioma
- Mucoepidermoid carcinoma, clear cell variant
- Acinic cell adenocarcinoma, clear cell variant
- Epithelial-myoepithelial carcinoma
- Clear cell odontogenic carcinoma:
 - Shown to have *EWSR1-ATF1* translocation supporting link with HCCC
- Squamous cell carcinoma with prominent clear cells (clear cell variant)
- Metastatic tumors composed of clear cells, a rare phenomenon including:
 - Renal cell carcinoma:
 - Presence of RCC antibody, CD10, PAX2, PAX8, and CAIX immunoreactivity

- Thyroid carcinoma:
 - Presence of thyroglobulin and thyroid transcription factor 1 (TTF-1) immunoreactivity

Treatment and Prognosis

- Complete surgical resection is preferred treatment.
- Considered to be a low-grade malignancy associated with a good prognosis following complete surgical excision
- Overall prognosis considered to be excellent:
 - Local recurrence may occur in up to 17% of cases.
 - May occasionally metastasize to regional lymph nodes or metastasize distantly (e.g., lungs):
 - Although usually very low rates of metastatic disease, nodal metastasis at presentation reported in 25% of cases
 - Death due to disease rarely may occur.
- Rare example of high-grade transformation of HCCC reported, raising the possibility that HCCC may represent yet another tumor type that can transform to a histologically higher grade neoplasm with potential for more aggressive biologic behavior

SALIVARY DUCT CARCINOMA (SDC)

(Figs. 20-109 through 20-112)

Definition: High-grade malignant epithelial salivary gland neoplasm arising from the excretory ducts histologically resembling ductal carcinoma of breast.

Synonym: Cribriform salivary gland carcinoma of excretory ducts

Clinical

- Represents less than 10% of all salivary gland malignancies
- More common in men than in women; most frequently identified in the sixth through eighth decades of life and tends to be uncommon in patients under the age of 50
- Parotid gland (related to Stensen duct) is most common site of occurrence:
 - Other sites of involvement may include:
 - Submandibular gland
 - Minor salivary glands, most often related to palate
 - Rare sites of involvement include sublingual gland, paranasal sinuses, larynx.
- Symptoms include a (parotid) mass often with associated rapid enlargement with or without pain or facial nerve paralysis:
 - At presentation, cervical lymphadenopathy may be present.

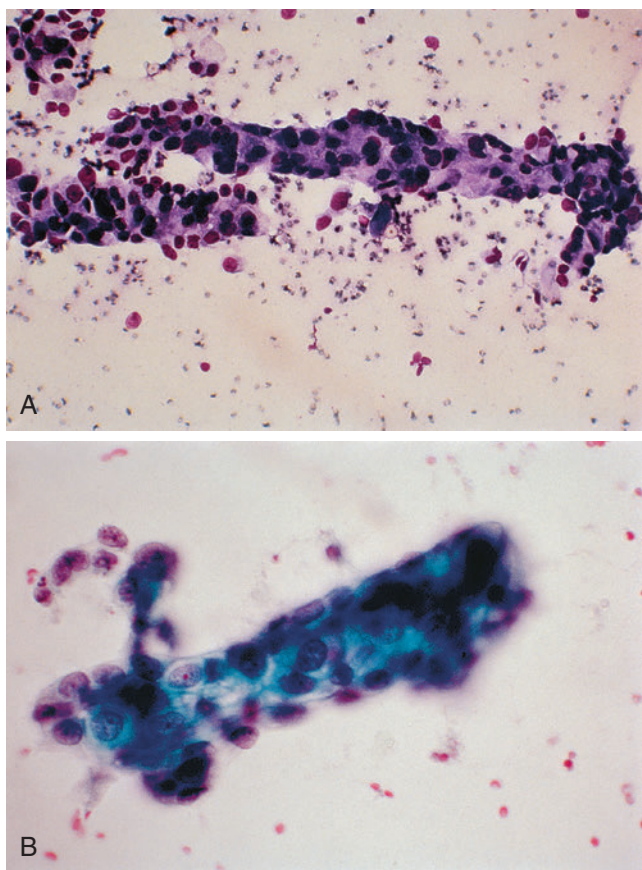


Fig. 20-109. Salivary duct carcinoma, fine-needle aspiration biopsy.

A, B, Aspirate of parotid gland lesion showing cohesive sheets of epithelial cells with hyperchromatic, pleomorphic round to oval nuclei, prominent nucleoli, and granular cytoplasm. Following resection the tumor proved to be a salivary duct carcinoma.

- Majority arise de novo but may also occur as malignant component in carcinoma ex pleomorphic adenoma:
 - Clinical scenario in the setting of a carcinoma ex pleomorphic adenoma is that of rapid enlargement of a long-standing salivary gland mass lesion.

Pathology

Gross

- Majority are poorly circumscribed and infiltrative but may occasionally appear circumscribed.
- Cut section reveals a tan-white to gray-yellow solid mass ranging in size from 1 to 10 cm in greatest dimension; on average these tumors measure 3.5 cm.
- Cystic spaces filled with necrotic material may be identified.

Fine-Needle Aspiration Biopsy

- Characteristic cytomorphologic features include presence of three-dimensional cohesive clusters and flat sheets of epithelial cells:
 - Cribriform and papillary pattern of growth
 - Tumor cells are large polygonal and spindle shaped.
 - Eccentrically located, hyperchromatic, pleomorphic round to oval nuclei with indistinct to prominent nucleoli
 - Abundant finely granular cytoplasm or vacuolated cytoplasm
 - Increased mitotic activity
 - Necrosis in the smear background

Histology

- Intraductal and infiltrating neoplasm with a variety of growth patterns including cell nests, nodules or lobules with central comedo-type necrosis, cribriform, solid, cystic, and papillary:
 - Multiple growth patterns can be seen in any given tumor.
 - Comedotype necrosis is a characteristic but not pathognomonic finding.
 - Larger nodules tend to be cystic and irregular in shape.
 - Appearance may suggest growth confined to within ducts (intraductal) but features of invasive growth include:
 - Absence of myoepithelial layer
 - Much larger size of cystic foci as compared with normal ducts (intralobular and interlobular)
 - Presence of stromal fibrosis
 - Absence of normal (non-neoplastic) salivary gland parenchyma within neoplastic foci
- Neoplastic cells are large, cuboidal to polygonal with round often centrally situated hyperchromatic nuclei, prominent eosinophilic nucleoli, and abundant eosinophilic cytoplasm; apocrine features including decapitation secretion are commonly present.
 - Moderate to marked nuclear pleomorphism present
 - Significant increase in mitotic activity that may include atypical mitoses
- Cribriform pattern reminiscent of intraductal mammary carcinoma and includes so-called Roman bridge pattern characterized by bands of neoplastic epithelium arched over luminal spaces:
 - This pattern contrasts with the cribriform pattern seen in adenoid cystic carcinoma, which lacks Roman bridge appearance.
 - In addition, adenoid cystic carcinoma demonstrates an admixture of abluminal cells lining

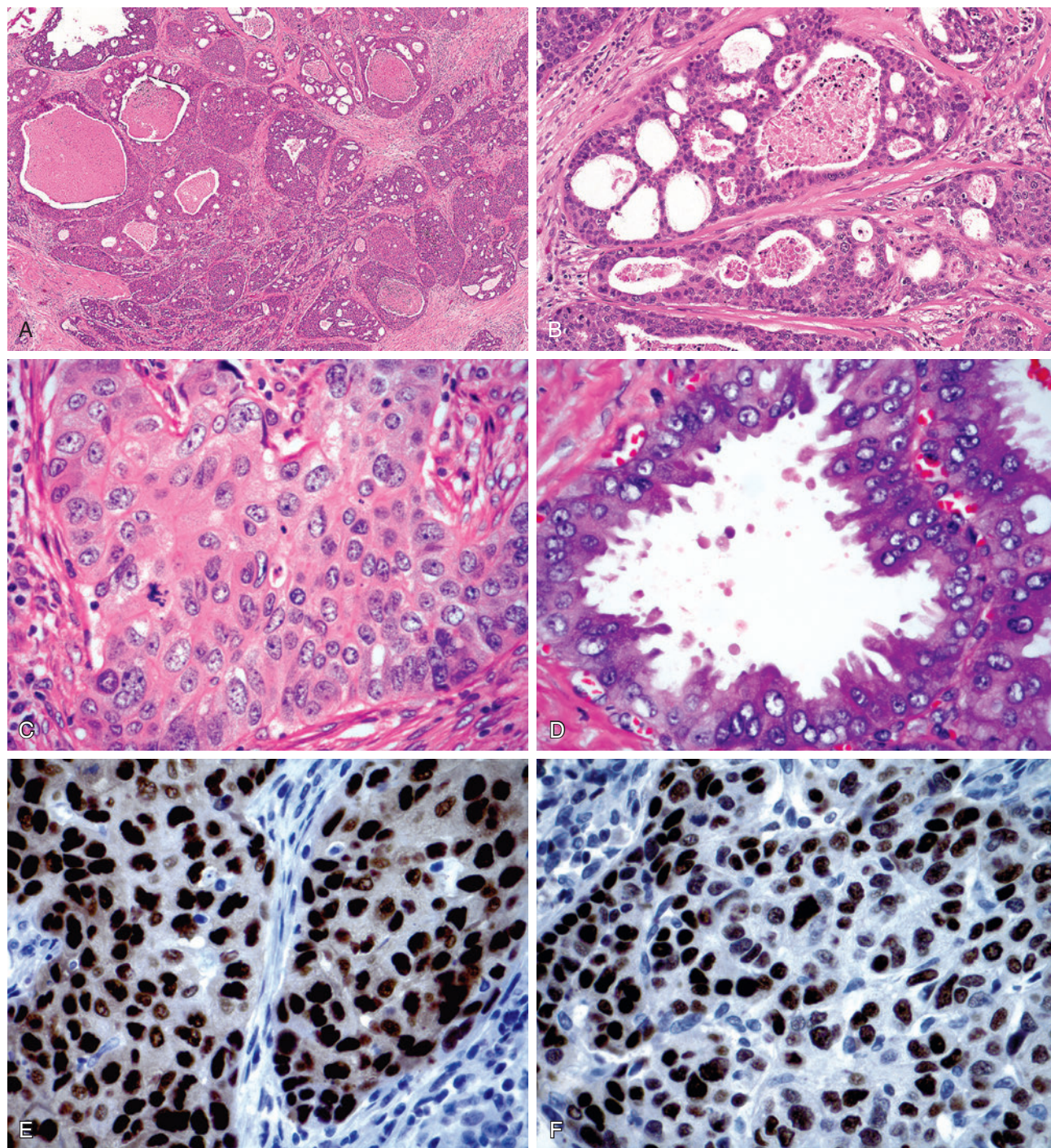


Fig. 20-110. Salivary duct carcinoma.

A and **B**, Infiltrative parotid gland tumor characterized by varied growth, including cystic, cribriform, and solid with foci of comedotype necrosis. **C** and **D**, The cytologic features include large cells with pleomorphic vesicular nuclei, eosinophilic nucleoli, and abundant eosinophilic cytoplasm; **C**, mitotic activity and **D**, apocrine features are commonly seen. **E**, Diffuse and strong nuclear staining for androgen receptor is a characteristic although not pathognomonic finding. **F**, Diffuse GATA-3 (nuclear) staining is another marker seen in salivary duct carcinoma.

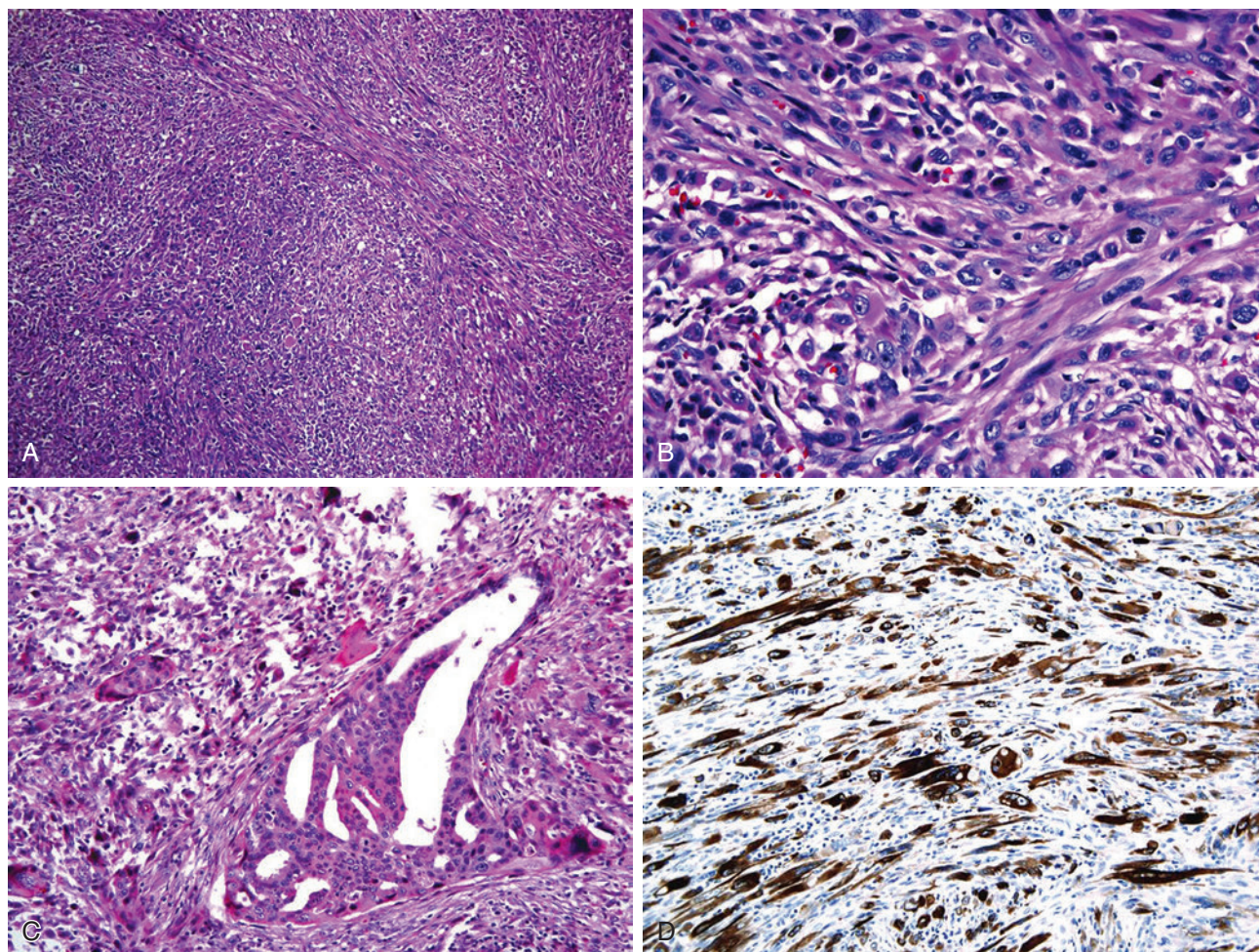


Fig. 20-111. Salivary duct carcinoma.

Sarcomatoid variant of salivary duct carcinoma characterized by **(A)** fascicular to storiform growth and **(B)** spindle-shaped cells with marked nuclear pleomorphism and increased mitotic activity. There is an absence of identifiable ductal component. **C**, Focally a ductal component is seen in association with the malignant spindle-shaped cells. **D**, Diffuse cyokeratin immunoreactivity confirms the epithelial nature of the malignant spindle cells.

pseudocysts and scattered epithelial cells lining small duct-like spaces, a pattern not seen in salivary duct carcinoma.

- Papillary pattern includes projections of neoplastic epithelium with fibrovascular cores.
- Additional findings may include:
 - Apocrine-like apical globules (apocrine SDC)
 - Oncocytic cytoplasmic changes may be present.
 - Squamous differentiation/metaplasia in form of keratinization and intercellular bridges
 - Psammoma-like bodies may be present.
- Stromal changes include the presence of fibrosis, often dense or sclerotic, as well as a mixed lymphoplasmacytic cell infiltrate.
- Invasive growth includes angioinvasion, neural invasion, and invasion of adjacent salivary gland parenchyma and surrounding soft tissue structures, including adipose tissue, skeletal muscle, and overlying skin:
 - Often there is extraglandular extension.
- Histologic variants include:
 - SDC, sarcomatoid variant:
 - Characterized by SDC with associated malignant spindle-shaped and pleomorphic cell infiltrate
 - Sarcomatoid proliferation may predominate with only limited evidence of ductular component.
 - Heterologous elements such as osteosarcomatous foci may be present; similar findings can be seen in spindle cell squamous carcinoma and is not indicative of a carcinosarcoma

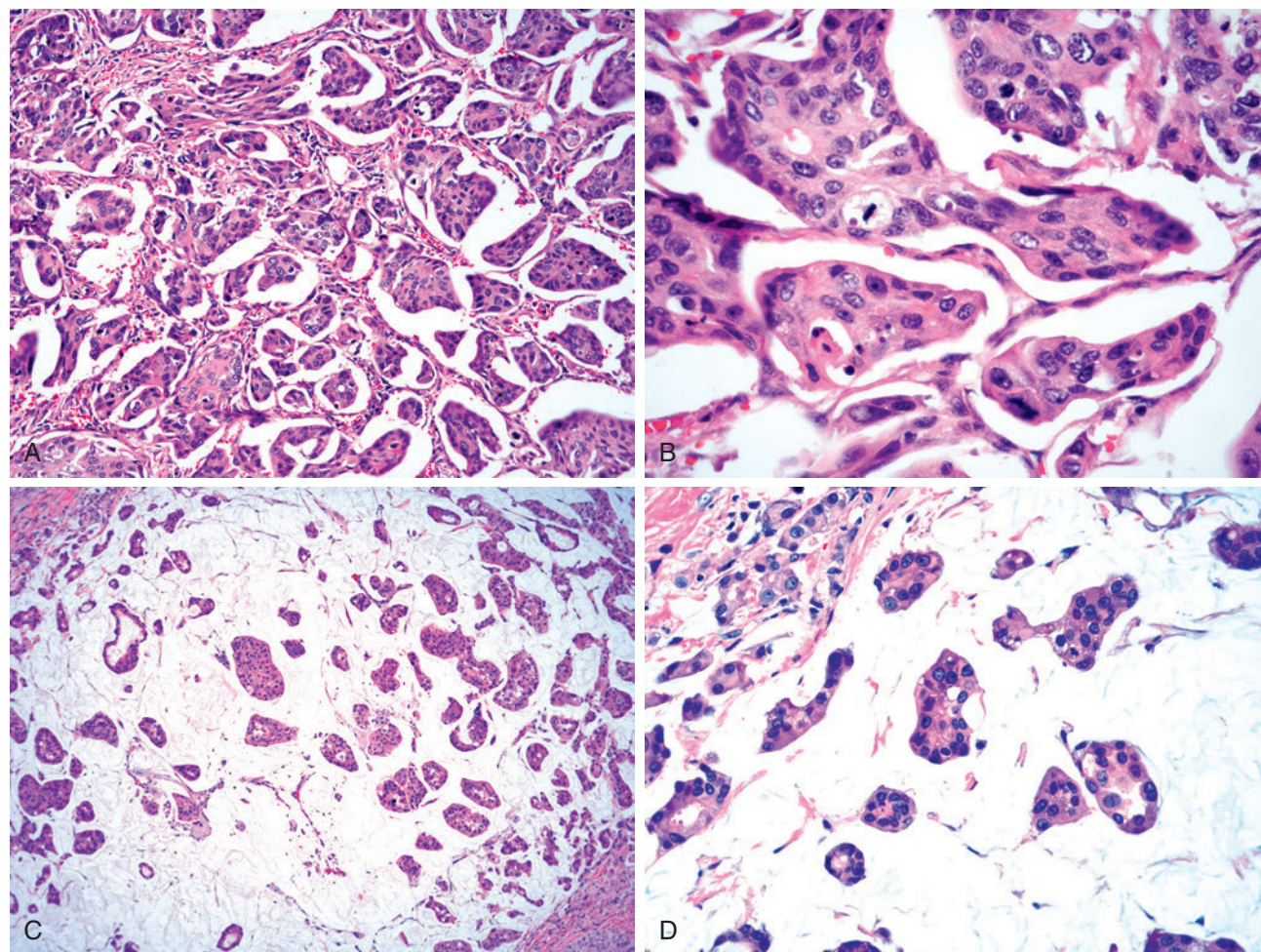


Fig. 20-112. Salivary duct carcinoma.

Other variants of salivary duct carcinoma include (**A** and **B**) micropapillary characterized by clusters of morula-like epithelial cells with fibrovascular cores; (**C** and **D**) mucin-rich characterized by presence of lakes of extracellular mucin within which are nests or islands of neoplastic epithelium.

- SDC, micropapillary variant:
 - Characterized by SDC with associated clusters of morula-like epithelial cells with fibrovascular cores
 - Reported to be more aggressive than “conventional” salivary duct carcinoma
- SDC, mucin-rich variant:
 - Characterized by conventional SDC with associated lakes of extracellular mucin within which are nests or islands of neoplastic epithelium
- SDC, oncocytic variant:
 - Characterized by conventional SDC with oncocytic cells, the latter showing abundant eosinophilic cytoplasm
 - At least 50% of the neoplasm should be composed of oncocytic cells to invoke a diagnosis of this variant.
- SDC, osteoclast-like giant cell variant:
 - Characterized by conventional SDC with associated osteoclast-like giant cells, latter resembling cells seen in giant cell tumor of bone
 - In contrast to cells in a giant cell tumor, osteoclast-like giant cells in SDC are immunoreactive for epithelial markers and androgen receptor.
- High-grade SDC in situ (SDCIS)
 - Rare variant that may occur in major and minor glands
 - Characterized by intraductal proliferation of high-grade malignant cells similar to ductal carcinoma in situ of the breast:
 - Variable degrees of nuclear pleomorphism, prominent central nucleoli, eosinophilic to vacuolated cytoplasm, some with apocrine snouts

- Absence of mucocytes
- High mitotic rate
- Comprised of ducts and cysts often containing comedo-like necrotic debris sometimes with calcification
- Lumina are lined throughout by atypical cells varying in thickness from one to several layers.
 - In smaller ducts proliferation can fill whole lumen.
 - In larger cysts a variety of architectural patterns can be seen, including Roman bridges, papillary, cribriform.
- Lining cells display variable degrees of nuclear pleomorphism, and central nucleoli may be prominent.
- Cancerization of acini can be identified.
- Strict criteria required for diagnosis including:
 - Absence of local invasion determined by adequate sampling of the whole lesion and presence of an intact myoepithelial layer around all tumor islands ideally confirmed by immunohistochemistry for basal-myoepithelial markers (e.g., CK5/6, CK14, p63, calponin, smooth muscle myosin heavy chain)
- Too few cases to determine with certainty natural history of pure SDCIS but limited cases with adequate follow-up have survived for years following complete excision with no recurrence or progression of disease
- Relationship of SDCIS to low-grade cribriform cystadenocarcinoma (LGCCC) remains unclear:
 - May represent separate entities
 - May represent extreme low-grade end of spectrum of SDCIS
- Rare examples reported in:
 - Setting of carcinoma ex pleomorphic adenoma described with rhabdoid features
 - In association with IgG4-related salivary gland disease
- Histochemistry:
 - Intracytoplasmic diastase-sensitive, PAS-positive material can be seen.
 - Intracytoplasmic mucicarmine staining is usually negative.
 - Intraluminal mucicarminophilic material may be present.
- Immunohistochemistry:
 - Cytokeratins (low and high molecular weight), CK7, EMA, and CEA
 - Androgen receptor (AR):
 - Most cases AR positive
 - Represents characteristic although not pathognomonic finding

- Diffuse GATA-3 (nuclear) staining
- Estrogen and progesterone receptor markers usually negative but 1q or both may be positive in minority of cases
- GCDFFP-15 (BRST-2) may be focally positive.
- *HER-2* (membranous staining) and *EGFR* positive in high proportion of cases
- CK5/6 and p63 focal to absent staining
- S100 protein and markers indicative of myoepithelial differentiation, including calponin, p63, smooth muscle actin, and vimentin are typically negative:
 - Similar to its use in ductal carcinomas of the breast, myoepithelial markers have been used to identify a peripheral non-neoplastic myoepithelial layer that, if identified, may indicate a tumor confined to within a duct (intraductal carcinoma) as opposed to absent staining that may indicate an infiltrative process.
 - However, similar cells can be seen in metastatic foci and reactivity with stromal myofibroblasts may suggest myoepithelial layering and therefore an intraductal process, when in fact the carcinoma is invasive.
- Rare documentation of neuroendocrine differentiation as evidenced by presence of chromogranin and synaptophysin reactivity
- Prostate-specific antigen and prostatic acid phosphatase may be positive.
- High proliferative index ranging from 25% to 80% by Ki-1 (MIB1) staining

NOTE: Molecular classification of SDC similar to breast cancer proposed but clinical relevance remains uncertain; such suggested classification includes (see below):

- Luminal AR-positive SDC
- *HER-2*-positive SDC
- Basal-like SDC
- Electron microscopy:
 - Desmosomes, tight junctions, rough endoplasmic reticulum, mitochondria, basal lamina, and luminal cells with microvilli
- Cytogenetics and molecular genetics:
 - Loss of heterozygosity in chromosome 9p21, 6q, 16q, 17p, 17q regions
 - *ERBB2* (*HER-2*) gene amplification in up to 36% of cases and protein expression from 26% to 100%
 - *EGFR* gene mutation may be present in minority (fewer than 10%) of cases.
 - Frequent *TP53* gene mutation and protein overexpression
 - Deletion of *PTEN* tumor suppressor in majority of cases
 - Apoptosis-related genes *CASP10* and *MMP11* overexpressed

- *CDKN2a/p16* gene inactivation
- *PIK3CA* and *HRAS* mutations recently reported in 33% and 34% of cases analyzed, respectively, and *BRAF* mutation identified in a minority of cases.
- Absence of *MECT1-MAML2* fusion
- Molecular classification of SDC
 - Proposal made to classify SDC into three molecular subtypes analogous to breast cancer
 - Luminal androgen receptor-positive subtype (most common):
 - Androgen receptor positive, *HER-2* negative, CK5/6 negative
 - *HER-2* subtype:
 - *HER-2* immunohistochemical expression 3+, *HER-2/neu* gene amplified
- Basal phenotype (least common):
 - Androgen receptor negative, *HER-2* negative, CK5/6 positive
- Unclassifiable group also identified

Hybrid Tumors

- Hybrid tumors represent the occurrence of a neoplasm composed of two or more histologic distinct types, each of which conforms with an exactly defined tumor category having an identical origin within same topographic area
- Most common tumor types include:
 - Adenoid cystic carcinoma
 - Salivary duct carcinoma
 - Epithelial-myoepithelial carcinoma
- Prognosis predicated on highest histologic grade malignancy (e.g., salivary duct carcinoma)

Differential Diagnosis

- Mucoepidermoid carcinoma, high grade:
 - Consistent CK5/6 and p63 staining that contrasts to SDC showing limited to absent reactivity for these markers
- Adenoid cystic carcinoma
- Acinic cell adenocarcinoma
- Cribriform cystadenocarcinoma (low-grade salivary duct carcinoma); see below
- Oncocytic carcinoma
- Papillary cystadenocarcinoma
- Metastatic mammary carcinoma:
 - Overlapping histologic and immunohistochemical features but rarity of breast cancer metastasizing to salivary glands essentially excludes the diagnosis
- Metastatic prostatic adenocarcinoma:
 - Although SDC may be reactive with prostatic-specific immunomarkers, rarity of prostate cancer metastasizing to salivary glands essentially excludes the diagnosis.

Treatment and Prognosis

- Aggressive management requiring combination complete (radical) surgical extirpation with radical neck dissection and postoperative radiotherapy represent preferred treatment.
- Recurrent disease occurs from approximately one third to two thirds of patients.
- Lymphatic and hematogenous spread occurs:
 - Regional nodal metastases occur in approximately 66% of patients:
 - Nodal metastases may occur at the initial presentation or subsequent
 - Distant metastasis occurs in from 50% to 70% of patients:
 - Most common sites for distant spread include the lungs, bone, and brain.
 - May metastasize to skin
- Mortality rates attributed to this neoplasm are high: from 60% to 80% of patients die from disease within 5 years from the diagnosis.
- Adverse prognostic features include:
 - Tumors greater than 3 cm in diameter
 - Distant metastasis
 - *HER-2* overexpression
 - Micropapillary pattern
 - *CDKN2a/p16* gene inactivation
- Frequent expression of *HER-2*, *EGFR*, and AR in SDC suggest that these receptors can be suitable molecular targets of systemic therapy for patients with SDC:
 - Treatment may include trastuzumab, lapatinib, and bevacizumab individually or in combination.
 - Efficacy of anti-*HER-2* and anti-androgen therapy for receptor-positive SDC yet to be fully proven but preliminarily has shown favorable response

LOW-GRADE INTRADUCTAL CARCINOMA (Figs. 20-113 and 20-114)

Definition: Cystic epithelial salivary gland neoplasm characterized by intraductal epithelial proliferation surrounded by myoepithelial cells composed of histologically low-grade nuclei, absence of infiltrative growth, and overall indolent biologic behavior.

- Likely represents preinvasive phase of an invasive carcinoma (e.g., salivary duct carcinoma, cystadenocarcinoma)
- Strict criteria required for diagnosis, including:
 - Absence of local invasion determined by adequate sampling of the whole lesion and presence of an intact myoepithelial layer around all

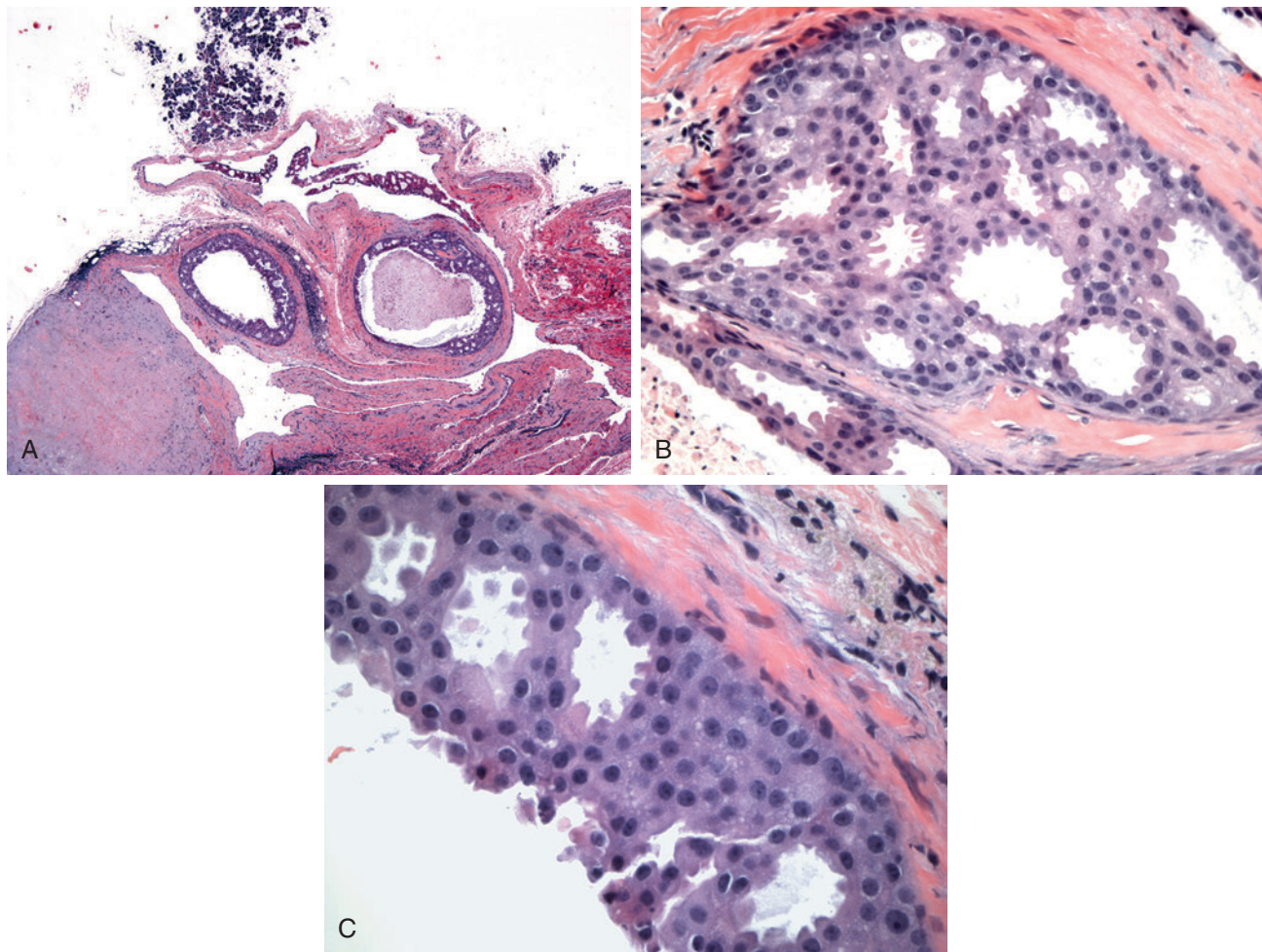


Fig. 20-113. Low-grade intraductal carcinoma of the parotid gland.

A, Unencapsulated multicystic proliferation with cribriform growth. **B** and **C**, Cribriform growth composed of cells with apocrine-like features. The cellular proliferation is rather bland composed of relatively uniform-appearing epithelial cells with round nuclei, fine-stippled chromatin and small nucleoli; nuclear pleomorphism is limited and there is no appreciable increase in mitotic activity; necrosis is absent.

tumor islands confirmed by immunohistochemical staining

Synonyms: Low-grade salivary duct carcinoma; low-grade cribriform cystadenocarcinoma (LGCCC); in situ carcinoma

NOTE:

- Classification of this tumor type is controversial and evolving:
 - Initially, considered to represent low-grade variant of salivary duct carcinoma

Clinical

- Rare tumor
- Slightly more common in women than in men; tumor of elderly adults
- Almost exclusively a tumor of parotid gland:

- May exceptionally occur in oral cavity (e.g., palate, tongue)
- Rarely reported as arising within a periparotid lymph node
- Presentation that of slow-growing, asymptomatic mass or swelling

Pathology

Gross

- May show nodular and cystic appearance

Fine-Needle Aspiration Biopsy

- Smears reveal tumor cells arranged in irregular overlapping and show inconspicuous nuclear atypia with variable-sized and irregularly shaped cytoplasmic vacuoles

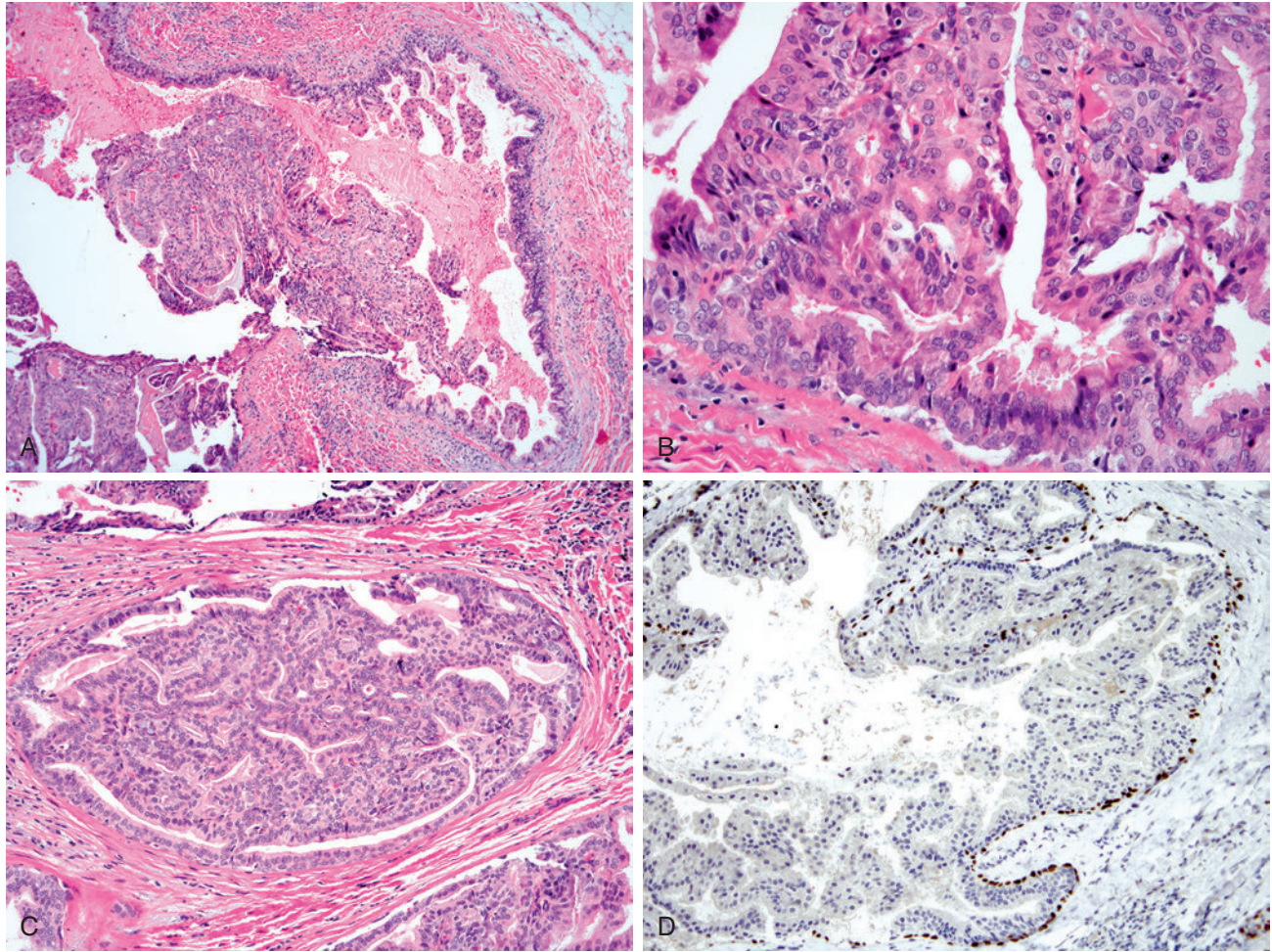


Fig. 20-114. Low-grade intraductal carcinoma of the oral cavity.

A, Dilated duct with cystic, micropapillary, cribriform, and solid growth. **B**, Cells show moderate nuclear pleomorphism. **C**, Areas showing similar features to atypical ductal hyperplasia of the breast may be identified. **D**, p63 immunoreactivity highlights the myoepithelial cells confirming the proliferation is intraductal.

Histology

- Unencapsulated tumor composed of dominant cyst or multiple variably sized cysts
- Cystic epithelial proliferation shows cribriform and papillary growth patterns with fibrovascular cores:
 - “Roman arches” similar to those seen in relation to mammary lesions
- Cellular proliferation includes:
 - Relatively uniform-appearing epithelial cells with round nuclei, fine stippled chromatin, and small nucleoli
 - Apocrine-appearing cells may represent dominant cell type or may focally be present.
 - Nuclear pleomorphism is limited.
 - No appreciable increase in mitotic activity
 - Comedotype necrosis may or may not be present.
- Myoepithelial cells present and may appear monolayered and attenuated but may not be identifiable by light microscopy requiring immunohistochemical staining for identification (see below).
- In addition to cystic foci, separate ductal epithelial proliferation identified composed of small ducts with cribriform, micropapillary, and solid growth consisting of cells cytologically similar to those seen in cystic foci.
- Transition from low nuclear grade to higher nuclear grade (i.e., intermediate and high grade)
- Invasive carcinoma or micro-invasion reported in up to 23% of cases
- Invasive carcinoma may rarely occur and may be identified in recurrent lesions:
 - Invasion may be in the form of microinvasive carcinoma.
 - Less often, includes presence of solid nests of tumor within adjacent salivary gland parenchyma or connective tissue

- Stromal fibrosis/sclerosis and mixed chronic inflammatory infiltrate may be present, especially in areas of invasive carcinoma.
- Neurotropism and angioinvasion not typically present
- Cells may contain:
 - Apical apocrine-like microvacuoles/globules which are diastase resistant, PAS positive
 - Yellow- to brown-appearing intracytoplasmic pigment resembling lipofuscin
- Immunohistochemistry:
 - Lesional cells:
 - Cytokeratin, EMA, S100 protein positive
 - Calponin, smooth muscle actin, vimentin usually negative
 - Androgen receptor, *HER-2*, and GCDP15 (BRST-2) may be positive
 - Estrogen receptor, progesterone receptor usually negative
 - GATA-3 (nuclear) staining may be focally positive.
 - Low proliferative activity (<5%) seen by Ki-67
 - Myoepithelial cell layer:
 - Reactive for p63, CK14, actins (smooth muscle, muscle specific), calponin

Differential Diagnosis

- Sclerosing polycystic adenosis
- Cystadenoma
- Cystadenocarcinoma
- Acinic cell adenocarcinoma, papillary-cystic variant
- High-grade salivary duct carcinoma in situ

Treatment and Prognosis

- Surgical excision is preferred treatment.
- Excellent prognosis with no reported metastasis or mortality over 2- to 12-year follow up

CYSTADENOCARCINOMA

(Figs. 20-115 through 20-118)

Definition: Malignant epithelial salivary gland tumor characterized by predominant cystic and papillary growth and lacking defining histomorphologic features of another type of salivary gland malignancy.

Synonyms: Papillary cystadenocarcinoma; malignant papillary cystadenoma; low-grade papillary adenocarcinoma of the palate

Clinical

- Rare tumor
- No gender predilection; occurs over a wide age range but the majority of patients are older than the sixth decade of life



Fig. 20-115. Cystadenocarcinoma.

Cystadenocarcinoma of the parotid gland appearing as a predominantly cystic and focally solid lesion.

- Tend to be tumors of major salivary glands, in particular the parotid gland
 - Less often occurs in the sublingual gland and minor salivary glands, including buccal mucosa, palate, lips, floor of mouth, and tongue
- Presentation that of slow-growing, asymptomatic mass or swelling; erosion of bone particularly related to palate tumors may occur:
 - Rarely associated with pain and facial paralysis

Pathology

Gross

- Delineated or partially circumscribed cystic or multicystic mass ranging in size from 0.4 to 6 cm in greatest dimension

Histology

- Circumscribed but unencapsulated cystic or multicystic proliferation separated by fibroconnective tissue or approximating one another
- Cysts haphazardly arranged varying in size and shape
- Lumens may contain mucinous material as well as calcifications; latter may also be present outside the cysts in stroma.

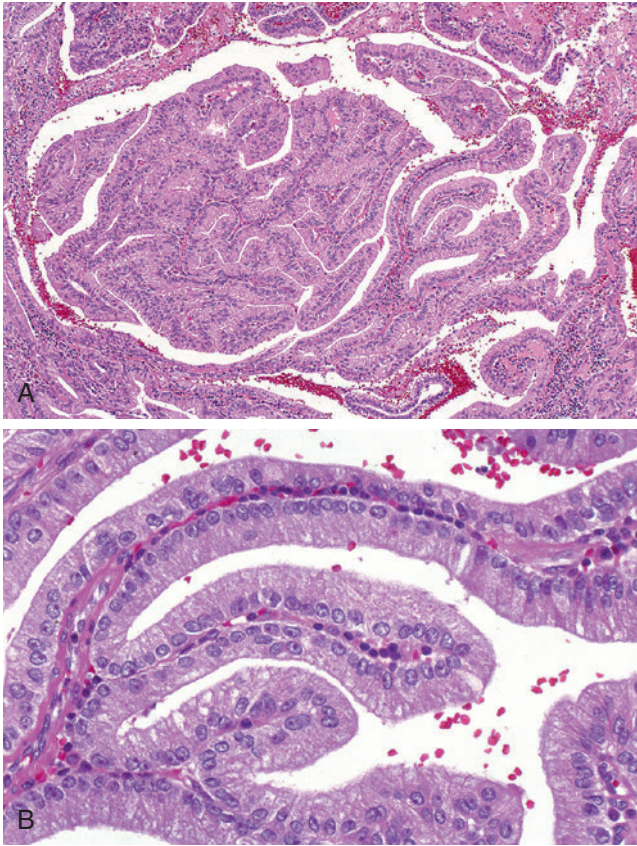


Fig. 20-116. Cystadenocarcinoma, low grade.

A, Cystic and predominantly papillary architecture with fibrovascular cores. **B,** At high magnification the cells are rather uniform with bland-appearing nuclei. The findings could be those of a papillary cystadenoma but invasion was present (not shown), allowing for a diagnosis of a low-grade (papillary) cystadenocarcinoma.

- Small duct-like structures and solid epithelial islands with or without lumens may be identified between cysts:
 - Duct-like structures and solid islands may be infiltrative into non-neoplastic salivary gland parenchyma and/or surrounding fibroconnective tissues.
- Epithelial cell proliferation varies in growth and cell type:
 - Papillary architecture is present in the majority of cases, varying from simple/single papillary projection to multiple papillae and creating a complex papillary to solid appearance that may fill involved lumen.
 - Cribriform growth may be seen especially in cases in which epithelial lining cells become thickened.
 - Cystic epithelial lining cells may form a single layer or multiple layers in thickness.

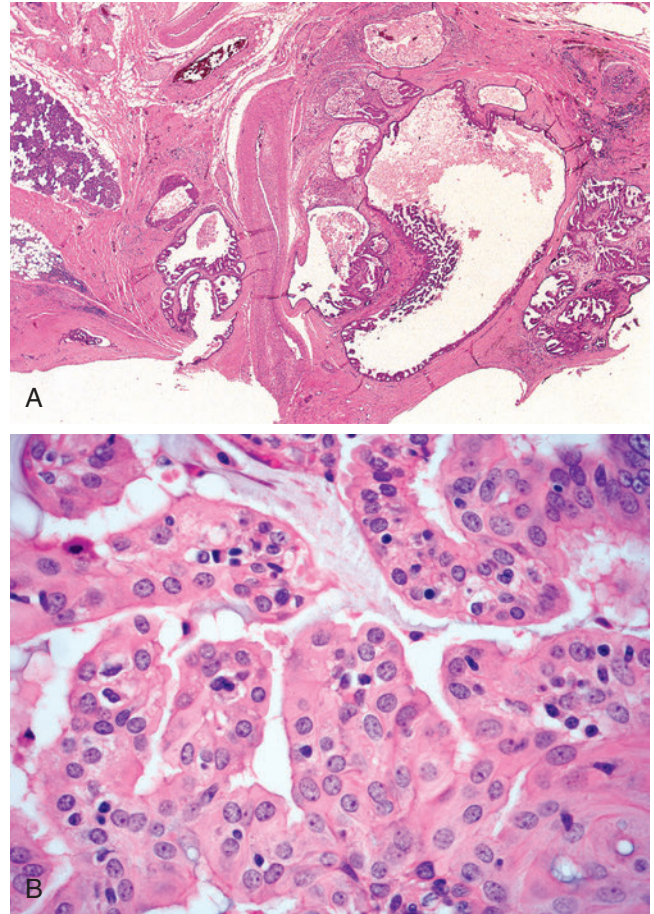


Fig. 20-117. Cystadenocarcinoma, intermediate grade.

A, Unencapsulated, multicystic and infiltrative parotid gland tumor in which the cysts are haphazardly arranged, vary in size and shape, and show a variable epithelial pattern of growth, including macrocystic, cribriform, and papillary.

B, At high magnification the cells show greater disorganization and nuclear pleomorphism as compared with low-grade neoplasms but not as significant as seen in higher grade neoplasms.

- Most often cell type is small cuboidal, less often larger cuboidal or tall columnar cells
- Other cell type that may be identified include mucous, oncocytic, clear, and epidermoid cells.
- Majority histologically low grade, characterized by:
 - Cytomorphologic uniformity with minimal pleomorphism, although moderate pleomorphism may be present.
 - Prominent nucleoli may be identified.
 - Low to absent mitotic activity
 - Necrosis usually absent
 - Cytomorphologically high-grade nuclear features may be present.
- Histologically higher-grade lesions may occur, including intermediate and high grade:

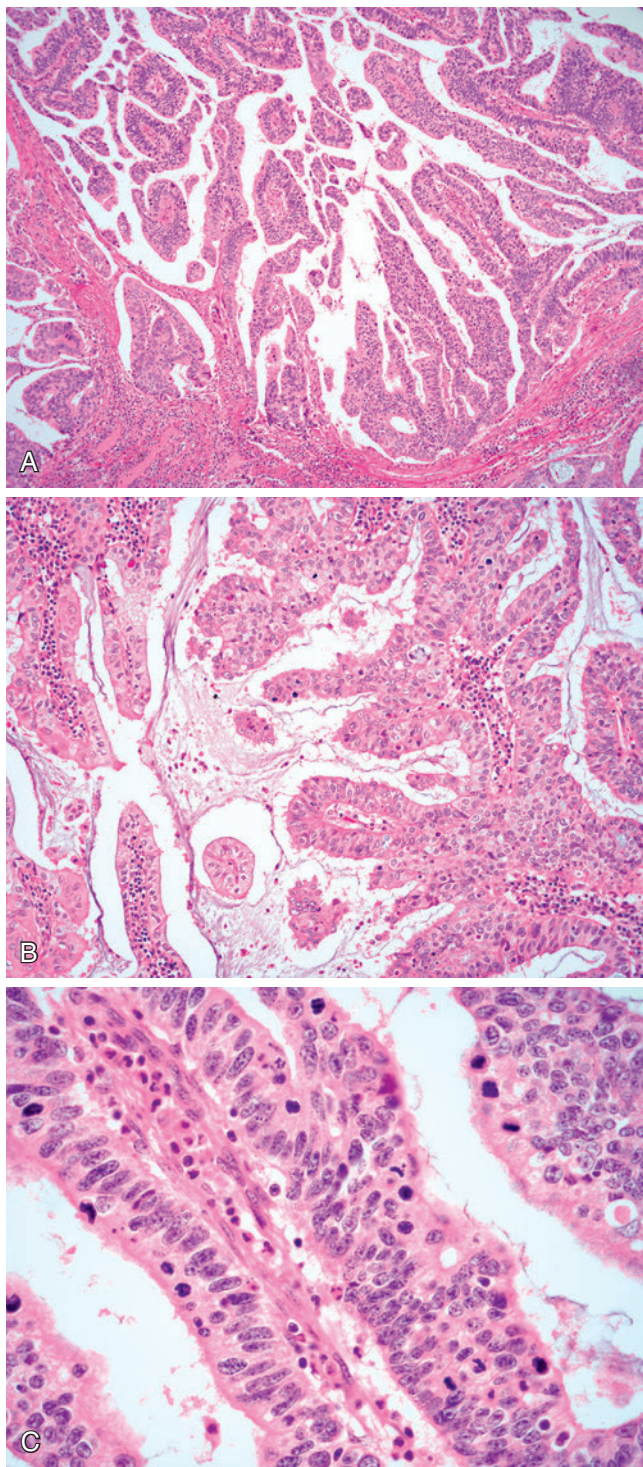


Fig. 20-118. Cystadenocarcinoma, high grade.

A, Cystic and papillary neoplasm. **B**, Focally intracystic mucinous material may be present. **C**, At high magnification there is marked nuclear pleomorphism and increased mitotic activity.

- Intermediate grade:
 - As compared with low grade, greater degree of nuclear pleomorphism and increased mitotic activity but not reaching levels associated with histologically high-grade neoplasms
- High grade:
 - Marked nuclear pleomorphism, increased mitotic activity, atypical mitoses, and necrosis
- Invasive growth is prerequisite for diagnosis:
 - Invasion may be limited in extent requiring liberal sampling of the resection specimen.
 - Neurotropism may be present in minority of cases (<10%).
- Stromal findings may include:
 - Lymphoplasmacytic cell infiltrate that occasionally may be dense.
 - Ruptured cysts may result in stromal hemorrhage, hemosiderin-laden macrophages, and granulation tissue.
- Histochemistry:
 - Mucin stains are usually negative.

Differential Diagnosis

- Cystadenoma
- Warthin tumor
- Acinic cell adenocarcinoma, papillary-cystic variant
- Mucoepidermoid carcinoma, low grade
- Low-grade intraductal carcinoma
- Salivary duct carcinoma
- Polymorphous low-grade adenocarcinoma

Treatment and Prognosis

- Complete surgical resection is preferred treatment:
 - Parotid gland: superficial parotidectomy with sparing of facial nerve unless involved by tumor
 - Submandibular and sublingual glands: glandectomy
 - Minor salivary glands: wide excision to include tumor-free margins:
 - In presence of osseous invasion that can be seen in palatal lesion, more radical excision is required.
- In absence of clinical evidence of neck disease, neck dissection would not appear to be warranted.
- Recurrence and metastasis (regional and distant) are uncommon, occurring in less than 8% and 10% of patients, respectively.
- To date, no reported tumor-related death

MYOEPITHELIAL CARCINOMA

(Figs. 20-119 through 20-123)

Definition: Malignant salivary gland tumor composed exclusively of cells with myoepithelial differentiation as determined by light microscopic, immunohistochemical,

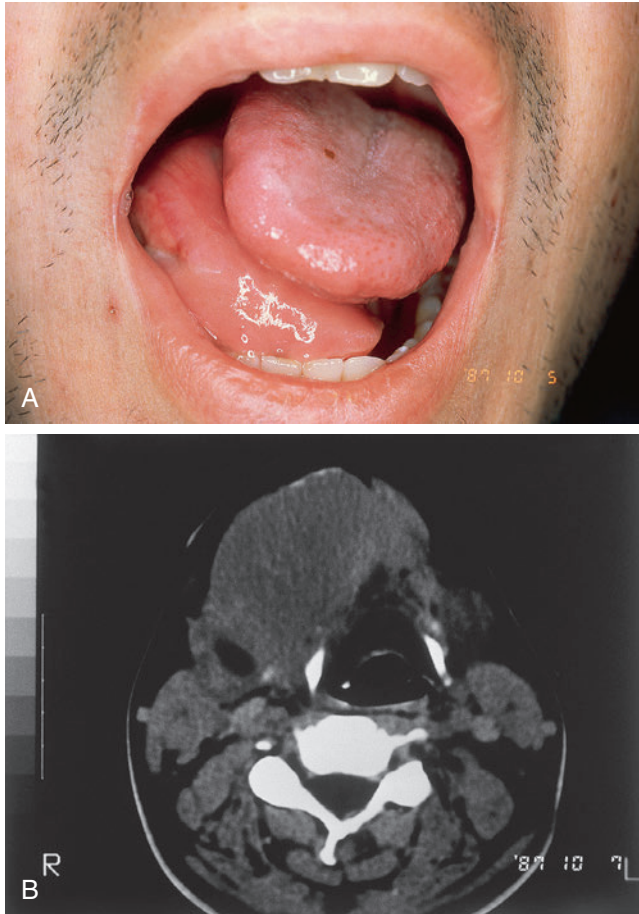


Fig. 20-119. Myoepithelial carcinoma.

A, Large floor of mouth solid mass with deviation of the tongue. **B**, On imaging the mass is large and infiltrative.

and/or ultrastructural findings, and with invasive growth and metastatic potential:

- Represents malignant counterpart of myoepithelioma.

Synonym: Malignant myoepithelioma

Clinical

- Uncommon tumor
- No gender predilection; tumor of adults with occurrence over wide age range from second to ninth decades of life; mean age at presentation in mid-sixth decade
- Most common site of occurrence is parotid gland
 - Less common sites of occurrence include:
 - Submandibular gland
 - Minor salivary glands:
 - Palate most common
- Presentation usually that of asymptomatic mass or swelling:
 - Duration of symptoms usually from months to years

- Pain, dysphagia, and hoarseness uncommonly may occur.
- Invasion of bone with bone destruction may occur in association palatal tumors.
- May arise:
 - As de novo neoplasm
 - From preexisting pleomorphic adenoma (myoepithelial carcinoma ex pleomorphic adenoma) or myoepithelioma
 - Clinical presentation may be that of a long-standing mass with recent rapid increase in size
 - Alternatively, develops following multiple recurrences
- No known etiologic factors

Pathology

Fine-Needle Aspiration Biopsy

- Aspirates show similar findings to those seen in myoepithelioma (see previous) but with cytologic features indicative of a malignancy, including:
 - Marked nuclear pleomorphism, increased mitotic activity, atypical mitoses, and necrosis

Gross

- Unencapsulated, nodular tumor that on cut section is gray-white and firm, measuring from 2 to approximately 6 cm, although examples can be larger
- Cystic areas and necrosis may be identified.

Histology

- Unencapsulated tumor that may be circumscribed characteristically with nodular or multinodular appearance:
 - Growth patterns include sheets, nests, trabeculae, fascicular, storiform, or cord-like (also referred to as reticular)
- Cellular components similar to those seen in myoepithelial predominant pleomorphic adenomas or in myoepithelioma, including:
 - Spindle-shaped, plasmacytoid (hyaline), epithelioid, and clear cells:
 - Combination of cell types is usually present, although a given tumor may be predominantly or exclusively composed of a single cell type.
 - Epithelioid cell type reported to be most common
- Nuclear pleomorphism varies from case to case and may be mild, moderate, or severe; mitotic activity varies from scarce or few in number to examples with high mitotic rate; necrosis may be present.
- Metaplastic changes, including squamous and sebaceous cells, may be identified.
- Stroma varies from copious amount of mucoid or myxoid-appearing stroma to sparse stromal tissue in markedly cellular tumors:

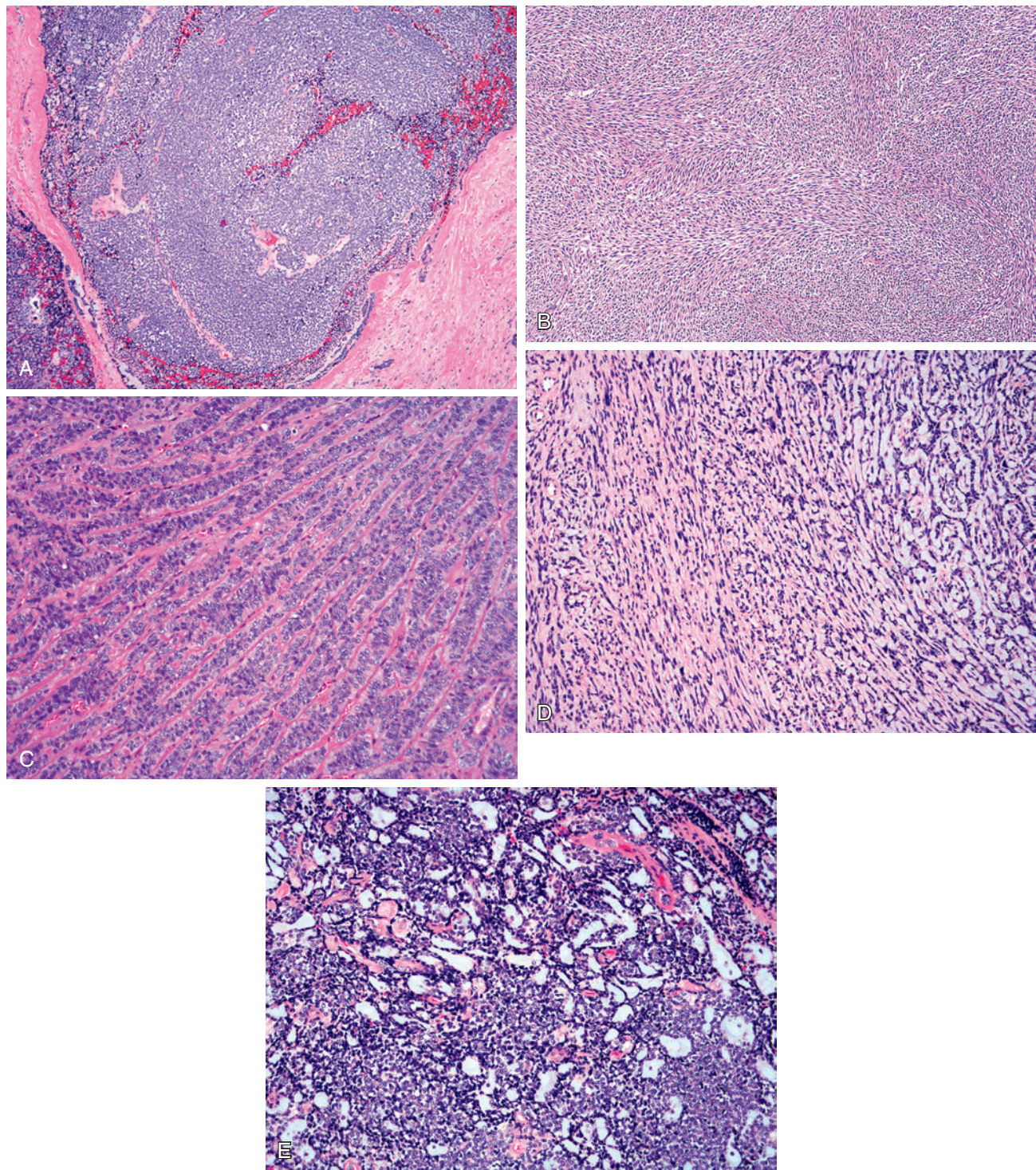


Fig. 20-120. Myoepithelial carcinoma.

Multiple growth patterns can be seen in myoepithelial carcinomas including (A) large solid nest; (B) fascicular and storiform; (C) trabecular; (D) cordlike/reticular; and (E) microcystic. A variable stroma is present from sparse to fibrous to mucinous appearing.

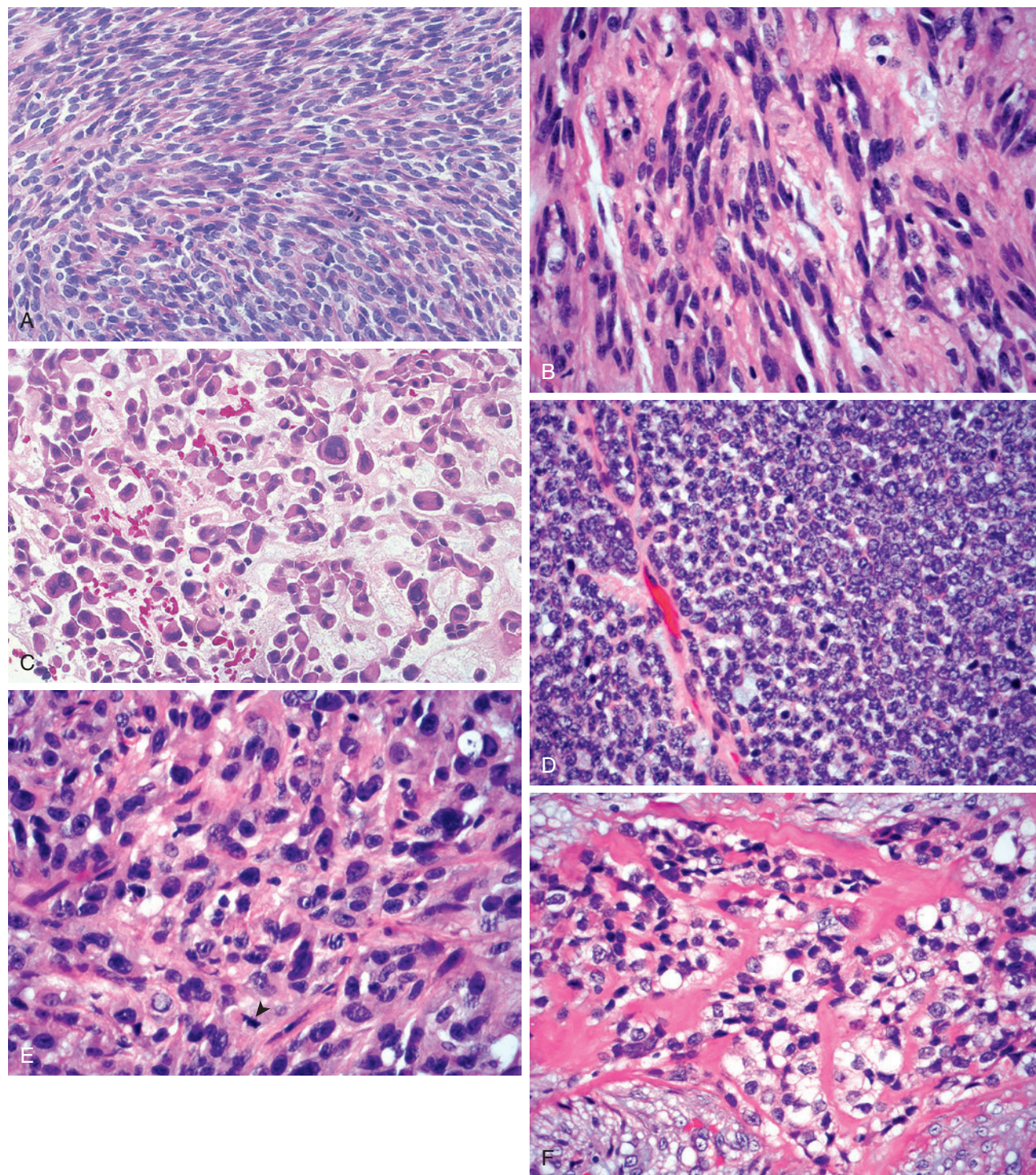


Fig. 20-121. Myoepithelial carcinoma.

The cell types in myoepithelial carcinoma include (**A** and **B**) spindle-shaped; (**C**) plasmacytoid; (**D**, **E**) epithelioid; and (**F**) clear. The degree of nuclear pleomorphism varies from case to case. In panels **A** and **D** there is limited nuclear pleomorphism, whereas in panels **C** and **E** nuclear pleomorphism is present; note the mitotic figure in panel **E** (arrowhead).

Continued

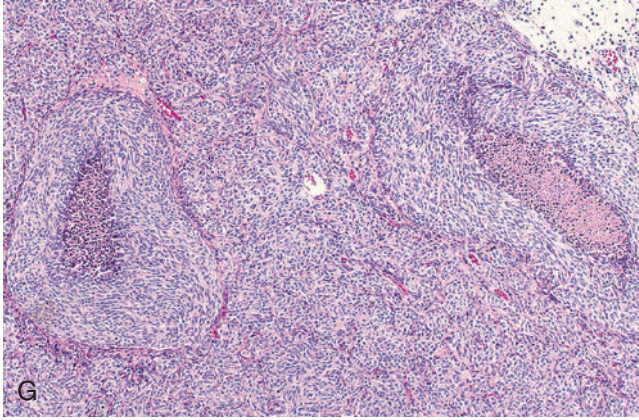


Fig. 20-121, cont'd

G, Areas of necrosis in a comedotyped pattern may be present.

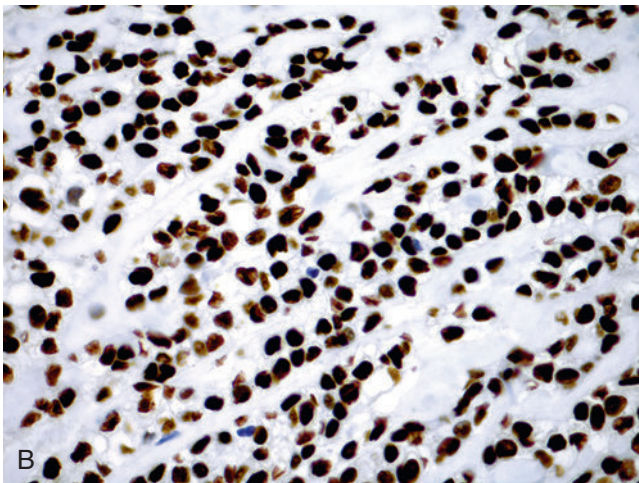
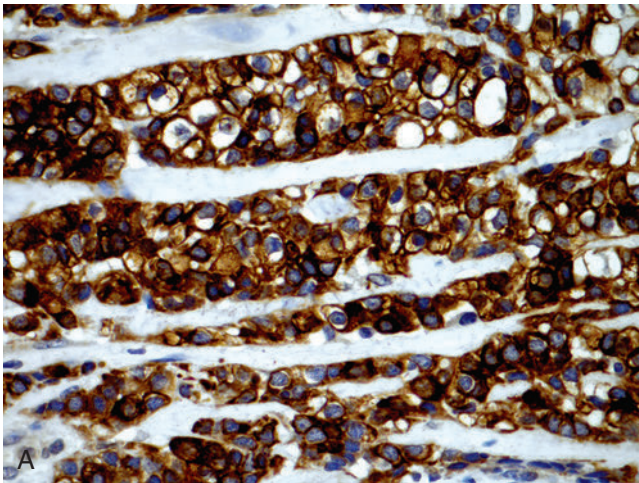


Fig. 20-122. Myoepithelial carcinoma.

Immunoreactivity in myoepithelial carcinomas includes **(A)** cytokeratin (AE1/AE3); **(B)** p63 (nuclear staining).

- Limited to abundant reduplicated basement membrane-like material appearing as eosinophilic hyaline material may be present.
- Cystic degeneration may be present.
- Although cytomorphologic evidence of malignancy may be readily identified, these findings may not be present and an unequivocal diagnosis is predicated on infiltrative growth, including:
 - Invasion into nonneoplastic salivary gland parenchyma
 - Adjacent fibroconnective tissues
 - Neurotropism
 - Angioinvasion
- By definition, ductal differentiation is not a component except in cases arising in association with a pleomorphic adenoma:
 - Presence of duct differentiation would confer a different designation (e.g., epithelial-myoepithelial carcinoma, others)
 - Presence of duct differentiation in this tumor type is the subject of debate with some authorities allowing for limited ductal differentiation.
- Immunohistochemistry:
 - Pancytokeratin (e.g., AE1/AE3) is consistently reactive.
 - Other cytokeratins including CAM5.2, CK903 (34BE12), CK5/6, CK7, and CK14 are variably expressed.
 - Vimentin positive
 - Immunoreactivity for a marker associated with myoepithelial differentiation should be identified for diagnosis, including:
 - p63, calponin, S100 protein, smooth muscle actin, smooth muscle myosin heavy chain:
 - Smooth muscle actin is seen in spindle-shaped myoepithelial cells but not in plasma-cytoid myoepithelial cells.
 - Desmin and c-kit (CD117) reactivity are uncommonly seen.
 - Myogenin, melanocytic markers negative.
- Electron microscopy:
 - Variable identification of cytoplasmic microfilaments with focal dense bodies, pinocytotic vesicles, desmosomes, basal lamina, and intermediate filaments
- Cytogenetics and molecular genetics:
 - Not known to have *EWSR1* rearrangement(s) with one exception
 - Clear cell variant of myoepithelial carcinoma of major and minor salivary glands (de novo and ex pleomorphic adenoma) shown to harbor *EWSR1* rearrangement:
 - Prognosis of clear cell type of myoepithelial carcinoma with *EWSR1* rearrangement appears to be aggressive with poor clinical outcomes, including:

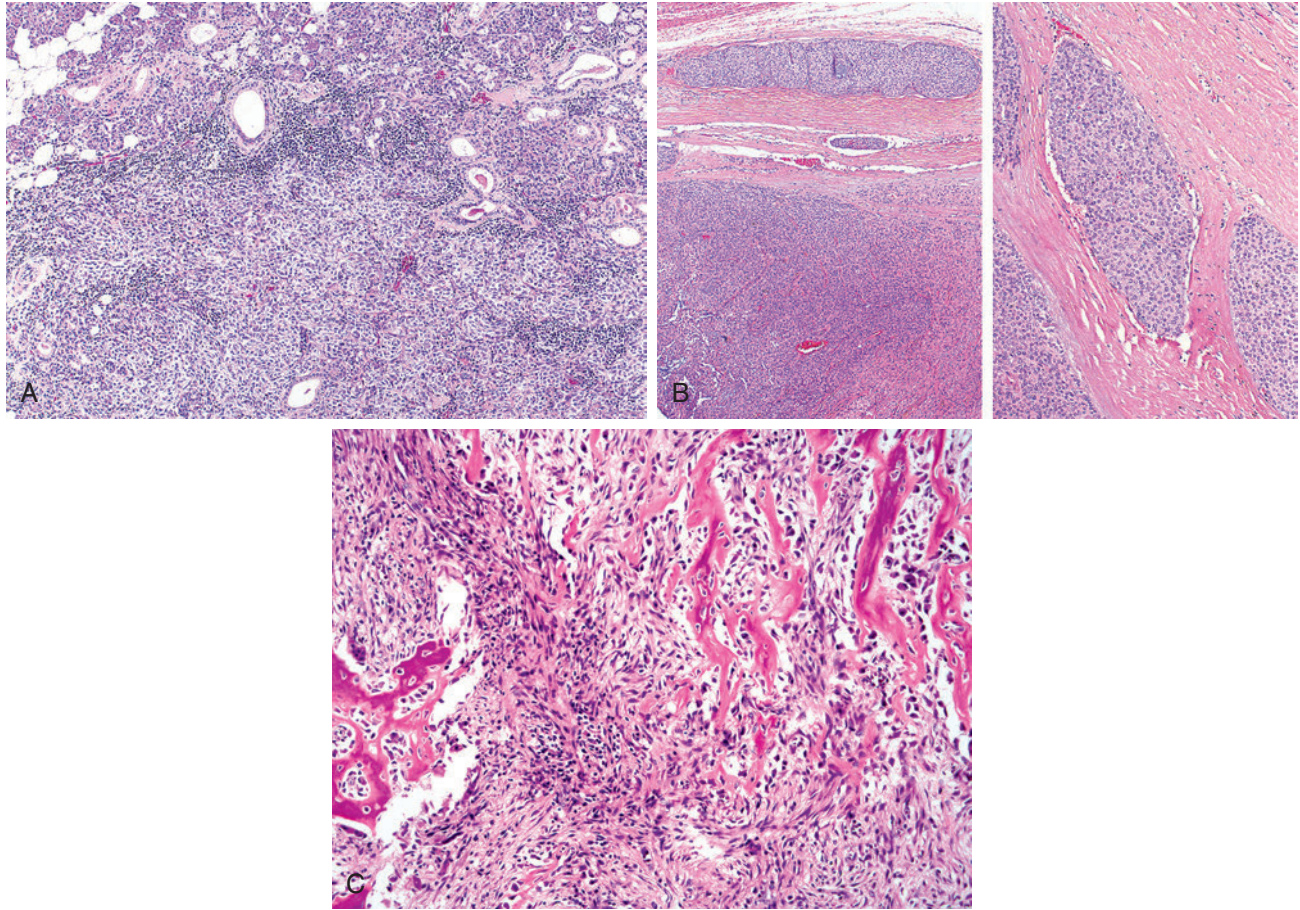


Fig. 20-123. Myoepithelial carcinoma.

An unequivocal diagnosis of a malignant tumor is predicated on infiltrative growth that may include (A) invasion into parotid gland parenchyma; (B) (left and right) angioinvasion; (C) osseous invasion.

- Increased incidence of nodal metastasis and distant metastasis
- Increased incidence of disease-associated mortality due to disseminated disease

Hybrid Tumors

- Uncommonly may be a tumor type occurring as a hybrid tumor representing occurrence of neoplasm composed of two or more histologic distinct types, each of which conforms with an exactly defined tumor category having an identical origin within same topographic area
- Prognosis predicated on highest histologic grade malignancy (e.g., salivary duct carcinoma)
- High-grade transformation (“dedifferentiation”) of myoepithelial carcinoma
 - Rare examples of transition to histologically higher-grade neoplasm reported
- Secretory myoepithelial carcinoma:
 - Recently described
 - Dual secretory and myoepithelial phenotype

- Mucicarmine-positive vacuolated/signet ring cells embedded in myxoid stroma
- At least focal p63 staining and/or calponin reactivity
- Membranous E-cadherin positive
- FISH negative for ETV6, EWSR1, and ALK1 rearrangements
- Fairly indolent fashion

Differential Diagnosis

- Myoepithelioma:
 - Differentiation may be possible on basis of cytomorphic features in cases of myoepithelial carcinoma with:
 - Marked cellular pleomorphism
 - Increased mitotic activity
 - High proliferation indices (>10%) by Ki67 staining
 - However, as previously noted, in any given example of myoepithelial carcinoma there may not be significant cytomorphic findings to

allow differentiation on such features alone and in such scenarios presence of infiltrative growth differentiates myoepithelial carcinoma from myoepithelioma.

- Epithelial-myoepithelial carcinoma
- Clear cell carcinoma
- Sarcoma (in those cases dominated by a spindle-shaped cellular component):
 - Synovial sarcoma
 - Malignant peripheral nerve sheath tumor
 - Leiomyosarcoma
 - Sclerosing rhabdomyosarcoma:
 - May occur in parotid gland simulating myoepithelial carcinoma
 - Presence of desmin and myogenin and absence of cytokeratin, p63, and S100 protein
- Spindle cell squamous carcinoma (sarcomatoid carcinoma):
 - Cytokeratins and p63 immunoreactivity may be present in spindle cell squamous carcinoma, but typically such tumors lack evidence of other myoepithelial markers, including calponin.
- Metastatic malignant melanoma
- Plasmacytoma
- Soft tissue myoepithelial carcinoma:
 - Primary myoepithelial tumors of soft tissues are uncommon.
 - Classification includes:
 - Benign neoplasm (myoepithelioma) (see under [myoepithelioma](#))
 - Malignant neoplasms (myoepithelial carcinoma)
 - As compared with their salivary gland counterpart:
 - A higher proportion of myoepithelial tumors of soft tissues are malignant.
 - Unlike salivary gland myoepithelial carcinoma, in which a majority arise in association with a pleomorphic adenoma (i.e., myoepithelial carcinoma ex pleomorphic adenoma), this occurrence is rare relative to soft tissue myoepithelial carcinoma, the majority of which occur as a de novo malignancy.
 - Clinical:
 - Sites of involvement:
 - Majority occur in soft tissues outside head and neck most commonly arising in limbs (upper and lower) and girdle with involvement of the subcutis and deep soft tissues
 - Among more common sites of occurrence in head and neck is neck (See Section 4) and craniofacial region
 - Demographics:
 - Occur over a wide age range with many cases affecting pediatric ages but develop in adult populations as well
- Clinical symptoms usually include a mass with or without associated pain.
- Pathology:
 - Most tumors are circumscribed; however, they may have infiltrative margins.
 - Histologically, at low magnification a multinodular or lobular architecture is evident; at periphery of lobules lesion is hypercellular arranged in reticular, trabecular, nests, or solid patterns.
 - Lesional cells may be epithelioid, clear, spindle, or plasmacytoid:
 - Characterized by cytomorphologic heterogeneity; although epithelioid type predominates, majority of cases are composed of more than one myoepithelial cell type
 - Cytologic atypia of at least moderate degree is present, including nuclear enlargement, vesicular to coarse-appearing nuclei, and variably prominent nucleoli.
 - Increased mitotic activity, tumor necrosis, and lymph-vascular invasion may be present.
 - Rare examples with rhabdoid morphology described
 - Stromal component includes myxoid change and/or hyalinization.
 - Cartilaginous differentiation and metaplastic ossification may be present.
 - Immunohistochemical staining:
 - Lesional cells reactive for cytokeratins (AE1/AE3, CAM5.2, PAN-K), EMA, S100 protein, calponin, p63, SMA, MSA, GFAP, CD10, and vimentin
 - CD99 immunoreactivity may be present.
 - Desmin, CD34, and brachyury typically negative
 - Nuclear expression of INI-1 may be lost in a minority of cases; loss of INI1 may be seen in cases with rhabdoid morphology, making distinction from other INI1-negative rhabdoid tumors difficult
 - Well established that myoepithelial carcinomas demonstrate *EWSR1* gene rearrangement, making them genetically distinct from salivary gland counterpart:
 - Identification of *EWSR1-POU5F1* or *EWSR1-PBX1* gene fusion
 - Differential diagnosis rather broad and may include:
 - Extraskelatal myxoid chondrosarcoma, epithelioid malignant peripheral nerve sheath tumor, synovial sarcoma (poorly differentiated), undifferentiated carcinoma, and Ewing sarcoma/PNET

- Treatment and prognosis:
 - Protocols include wide surgical resection for localized tumors and adjuvant radiotherapy with or without nodal dissection.
 - Potential for local recurrence and/or metastases (nodal and viscera).
 - More aggressive behavior occurs in pediatric ages than in adult population, including death from disease.
 - Use of chemotherapy is unproven and appears in limited studies to offer no added benefit.

Treatment and Prognosis

- Complete surgical resection is preferred treatment, which includes:
 - Parotid gland: superficial parotidectomy
 - Submandibular gland: glandectomy
 - Minor salivary glands: wide excision to include tumor-free margins
 - In presence of osseous invasion a more radical excision is required.
- In absence of clinical evidence of neck disease, a neck dissection would not appear to be warranted.
- Radiotherapy used in select situations with mixed outcomes
- Efficacy of chemotherapy not proven
- Behavior of these tumors is variable:
 - Some behave in indolent/low-grade manner.
 - Others behaving more aggressively (intermediate to high grade)
- From 50% to 67% develop recurrent tumor; often multiple recurrences
- Approximately 50% of patients develop metastatic disease:
 - Lung most common site of metastasis
 - Distant metastasis more frequent than regional (nodal) metastasis
- Approximately 30% of patients die of disease.

PRIMARY SQUAMOUS CELL CARCINOMA (SCC)

(Figs. 20-124 and 20-125)

Definition: Malignant epithelial neoplasm of major salivary glands composed of squamous cells characterized by presence of keratinization and/or intercellular bridges:

- Diagnosis predicated on absence of clinical or historical evidence of a squamous cell carcinoma in another (head and neck) site that has metastasized to the salivary gland or invaded directly into the salivary gland from a mucosal or cutaneous primary squamous cell carcinoma
- Diagnosis of primary SCC relative to minor salivary glands not considered appropriate due to the



Fig. 20-124. Parotid squamous cell carcinoma.

Primary squamous cell carcinoma of the parotid presenting as an ulcerated and necrotic, firm mass extending behind the ear, with separate tumor nodules just anterior to the gland, and associated with facial nerve invasion and paralysis. From this appearance and obvious cutaneous involvement, a primary cutaneous carcinoma cannot be ruled out and is clinically the most likely origin rather than originating in the parotid gland. The majority of squamous cell carcinomas of the parotid gland represents secondary involvement from a separate primary cancer rather than being a primary parotid squamous cell carcinoma.

inability to exclude a mucosal squamous cell carcinoma secondarily involving minor salivary glands

Clinical

- Rare tumor
- More common in men than in women; occurs over a wide age range but most frequently identified in the seventh to eighth decades of life; rarely may occur in pediatric ages
- Primarily identified in parotid gland but may also be seen in submandibular gland:
 - In parotid gland nearly all cases identified in superficial lobe
- Most common symptom is mass lesion with or without pain and/or cranial nerve paralysis:
 - Rapid enlargement of the mass may be a presenting complaint.
 - Fixation to adjacent structures and associated ulceration may be present.
 - Duration of symptoms is usually relatively short (within 1 year).
 - Due to high frequency of regional (nodal) metastases at the initial presentation, patients

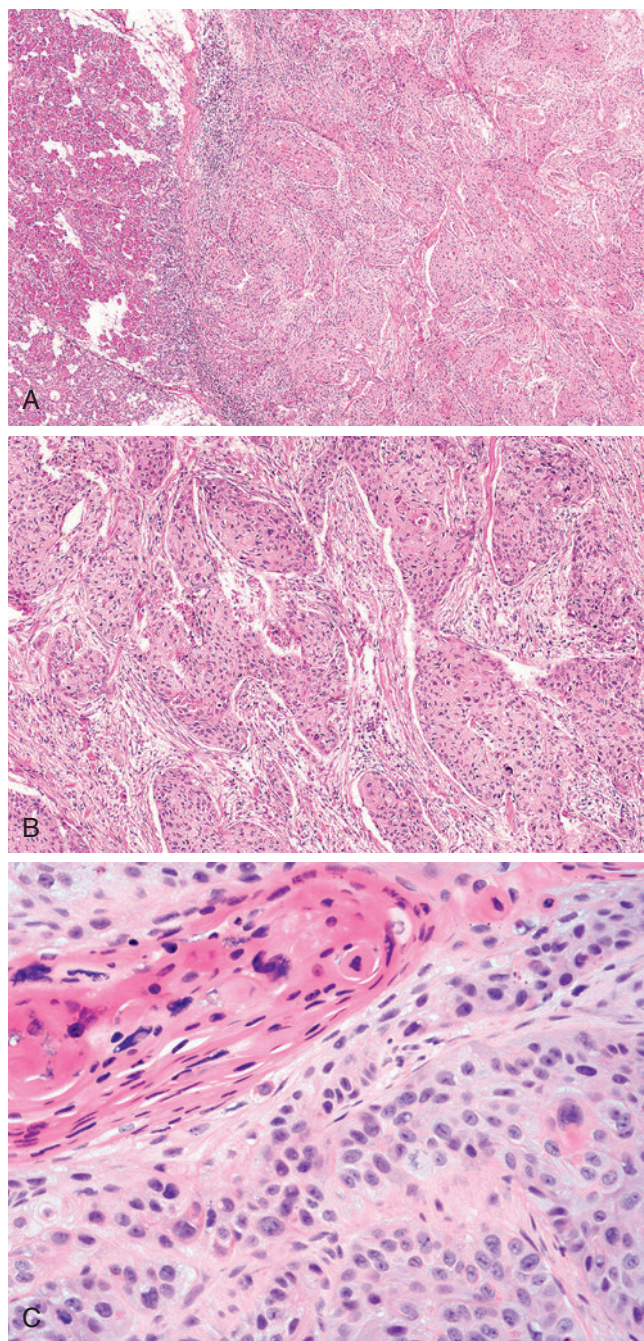


Fig. 20-125. Parotid squamous cell carcinoma.

A, Although the tumor appears circumscribed and separate from the parotid gland parenchyma (*left*), it was infiltrative with an associated desmoplastic stroma; **B**, trabecular and anastomosing cordlike growth; **C**, keratinizing squamous cell carcinoma histologically similar to squamous carcinomas occurring in more usual sites. Prior to rendering a diagnosis of a primary parotid squamous cell carcinoma, a primary carcinoma of another site (e.g., skin) either with direct invasion of the parotid gland or metastasis to the parotid gland must be excluded.

may also present with cervical lymphadenopathy.

- Cause may be related to prior radiotherapy to head and neck, included for treatment of:
 - Neoplasms
 - Acne
 - Glandular (tonsillar, thyroid, thymic) enlargement
 - Median time frame of 15½ years from radiation exposure to development of carcinoma, with range of 7 to 32 years
 - Not all reported cases of salivary gland squamous cell carcinoma associated with prior radiation exposure

Pathology

Gross

- Unencapsulated, firm to hard, gray to white mass usually measuring more than 3 cm in greatest dimension
- Ulcerated and fixation to adjacent tissues is commonly present.

Histology

- Infiltrating well to moderately differentiated squamous cell carcinoma similar to those occurring in other head and neck sites:
 - Invasive tumor has variable growth patterns including trabecular, nested, or anastomosing cords
 - Intracellular keratin, keratin pearl formation, and intercellular bridges are seen.
 - Presence of keratinization and intercellular bridges confers the designation of squamous rather than epidermoid although these terms have been used interchangeably.
 - Less often, carcinoma is poorly differentiated and/or spindle cell squamous carcinoma but still retains histologic evidence of squamous cell differentiation allowing for classification in this category of tumor rather than another tumor category (e.g., salivary duct carcinoma, undifferentiated carcinoma).
 - Increased mitotic activity and necrosis may be present.
- Invasive tumor includes:
 - Infiltration of adjacent salivary gland parenchyma
 - Invasion into surrounding fibroconnective tissues
 - Neurotropism
 - Angioinvasion
 - Osseous invasion (e.g., mandible, temporomandibular point)
- Tissue invasion often (but not always) produces a desmoplastic response in and around the neoplastic infiltrate.

- A marked chronic inflammatory cell infiltrate occasionally may be associated with the invasive tumor nests.
- Salivary duct changes, including squamous metaplasia and/or dysplasia, may be identified:
 - Transition from normal to dysplastic duct epithelium to squamous cell carcinoma may occasionally (and fortuitously) be identified.
- In patients exposed to radiation, the non-neoplastic salivary gland may show radiation-induced changes, including atrophy and fibrosis.
- May be the malignant component or one of the malignant components of:
 - Carcinoma ex pleomorphic adenoma
 - Malignant transformation of Warthin tumor
- Histochemistry:
 - Special stains for epithelial mucin are negative but should be performed to rule out the presence of high-grade mucoepidermoid carcinoma.
- Immunohistochemistry:
 - Diffuse and strong reactivity for cytokeratins (AE1/AE3, CAM5.2, CK5/6, others) and p63
 - Absence of reactivity for androgen receptor, GATA3, *HER-2*
- Cytogenetics and molecular genetics:
 - No reported *MECT1-MAML2* translocation
- Salivary duct carcinoma:
 - Generally not problematic in differentiating from squamous cell carcinoma but occasional cases may show squamous differentiation or predominance of spindle-shaped cells (i.e., sarcomatoid variant) that in conjunction with high-grade cytomorphology and perhaps absence of ductal differentiation may create problems in differentiating from squamous cell carcinoma:
 - Presence of reactivity for androgen receptor, GATA3 and to a lesser extent *HER-2* should allow for differentiating salivary duct carcinoma or a variant thereof from SCC
- Ductal squamous metaplasia
- Necrotizing sialometaplasia
- Keratocystoma:
 - Histologically characterized by presence of multicystic spaces lined by stratified squamous cells lacking cytomorphologic evidence of malignancy or invasive growth
 - Transformation from parotid ductal epithelium to tumor may be identified.
 - Foreign body giant cell reaction to keratin can be seen.
 - Immunoreactivity for cytokeratin but not for S100 protein or smooth muscle actin; low proliferative rate as determined by Ki-67 (MIB1) staining

Hybrid Tumors

- Uncommonly may be a tumor type occurring as a hybrid tumor, representing occurrence of neoplasm composed of two or more histologic distinct types, each of which conforms with an exactly defined tumor category having an identical origin within same topographic area

Differential Diagnosis

- Nonprimary salivary gland squamous cell carcinoma:
 - More often than not, presence of squamous cell carcinoma in salivary glands represents a nonprimary salivary gland malignancy, either metastatic from a separate primary site or direct invasion from a cutaneous or mucosal-based squamous cell carcinoma
 - Detailed clinical history indicated to determine if the patient has history (current or remote) of a squamous cell carcinoma of another site either within or outside head and neck area
- Mucoepidermoid carcinoma, high grade
- Adenosquamous carcinoma (see Section 5, Larynx, for full description):
 - Represents a mucosal-based carcinoma arising from surface epithelium composed of an admixture of squamous cell carcinoma and adenocarcinoma
 - Rarely if ever develops in major salivary glands
- Treatment and Prognosis
 - Complete surgical excision (e.g., parotidectomy, submandibular glandectomy) is preferred treatment:
 - Direct involvement of facial nerve is not uncommon, often necessitating facial nerve resection.
 - Neck dissection:
 - Owing to high rate of nodal metastases routine neck dissection advocated
 - High rate of microscopic nodal metastases in patients with no palpable cervical lymphadenopathy (clinical N0 neck)
 - Adjunctive radiotherapy may be beneficial in controlling local disease and/or may improve survival.
 - Treatment failure as manifested by local recurrence and/or metastatic disease common
 - Survival rates include:
 - 5-year of 24%
 - 10-year of 18%
 - 15-year of 17%
 - 20-year of 17%
 - Adverse prognostic findings include:
 - Presence of ulceration or fixation
 - Older-aged patients (greater than 60 years)
 - Larger tumors (T3 or greater)
 - Higher-stage tumor

- Most patients with salivary gland squamous cell carcinoma present with higher clinical stage tumors
- Facial paralysis
- Deep tissue fixation
- Prognosis does not correlate to the histology.

LYMPHOEPITHELIAL-LIKE CARCINOMA (LEC)

(Figs. 20-126 and 20-127)

Definition: Undifferentiated carcinoma with associated prominent non-neoplastic lymphoplasmacytic cell infiltrate:

- Histologic features similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type

Synonyms: Undifferentiated carcinoma; lymphoepithelioma-like carcinoma; lymphoepithelial-like carcinoma; undifferentiated carcinoma with lymphoid stroma; malignant lymphoepithelial lesion; carcinoma ex lymphoepithelial lesion

Clinical

- Rare salivary gland tumor
- Unique ethnic and demographic features:
 - Predilection for Arctic region natives (Eskimos/Inuits from Alaska, Canada, Greenland), South-eastern Chinese and Japanese
 - Highest incidence worldwide of salivary gland lymphoepithelial carcinoma is in Eskimo/Inuit population
 - Familial predisposition reported:
 - Inherited trichoepitheliomas also reported in this setting, suggesting hereditary predisposition
 - In Eskimos/Inuits:
 - More common in women
 - Predilects to the parotid gland
 - More aggressive clinical course presents with higher clinical stage disease.
- In general, occurs over a wide age range with most patients in the fifth decade of life
- Most common site of occurrence is in the parotid gland (80%) followed by the submandibular gland with rare occurrence in minor salivary glands throughout the upper aerodigestive tract.
- Presentation is usually that of a mass swelling with or without associated pain and/or facial nerve paralysis:
 - Fixation to skin and/or underlying structures seen in advanced tumors
 - High frequency (10% to 40%) of concurrent cervical lymphadenopathy
- Most develop de novo but may arise in association with lymphoepithelial sialadenitis (LESA):

- Possibility that presence of LESA represent reactive process and not precursor lesion
- No known association with other autoimmune disorders (e.g., Sjögren disease)
- Etiology:
 - Linked to Epstein-Barr virus:
 - Near 100% association in patients from endemic areas
 - In non-endemic areas EBV is usually absent, but may rarely be identified
 - Presence of EBV in clonal episomal form suggests role in tumor development
 - Elevated serologic titers of anti-EBV viral capsid antigen IgA, anti-EBV nuclear antigen IgG seen in the majority of patients from endemic regions.

Pathology

Gross

- Circumscribed but unencapsulated, lobulated, firm, tan-white mass measuring from 1 to 10 cm in greatest dimension

Fine-Needle Aspiration Biopsy

- Carcinoma cells variably seen in smears in cohesive aggregates or individual cells and include medium to large size cells with large vesicular-appearing nuclei, one or more prominent nucleoli, high nuclear-to-cytoplasmic ratio
- Associated mature lymphocytes and plasma cells are typically numerous.

Histology

- Infiltrative tumor characterized by presence of lobules, sheets, nests, islands, trabeculae, or cords of neoplastic cells separated by or overrun by lymphoid stroma
- Neoplastic cells are polygonal to spindle-shaped with large round to oval, basophilic to vesicular-appearing nuclei, one or more prominent nucleoli, and abundant amphophilic to lightly eosinophilic cytoplasm
- Cells have indistinct cell borders and syncytial growth is usually evident.
- Moderate to marked nuclear pleomorphism present
- Increased mitotic activity and necrosis seen
- Squamous differentiation may be present.
- Prominent basaloid morphology may be seen (basaloid LEC):
 - Identified in Inuit population
 - Associated with EBV
- A dense non-neoplastic lymphoplasmacytic cell infiltrate with or without germinal centers is present:
 - Identified between and around tumor nests or may overrun and obscure presence of epithelial component

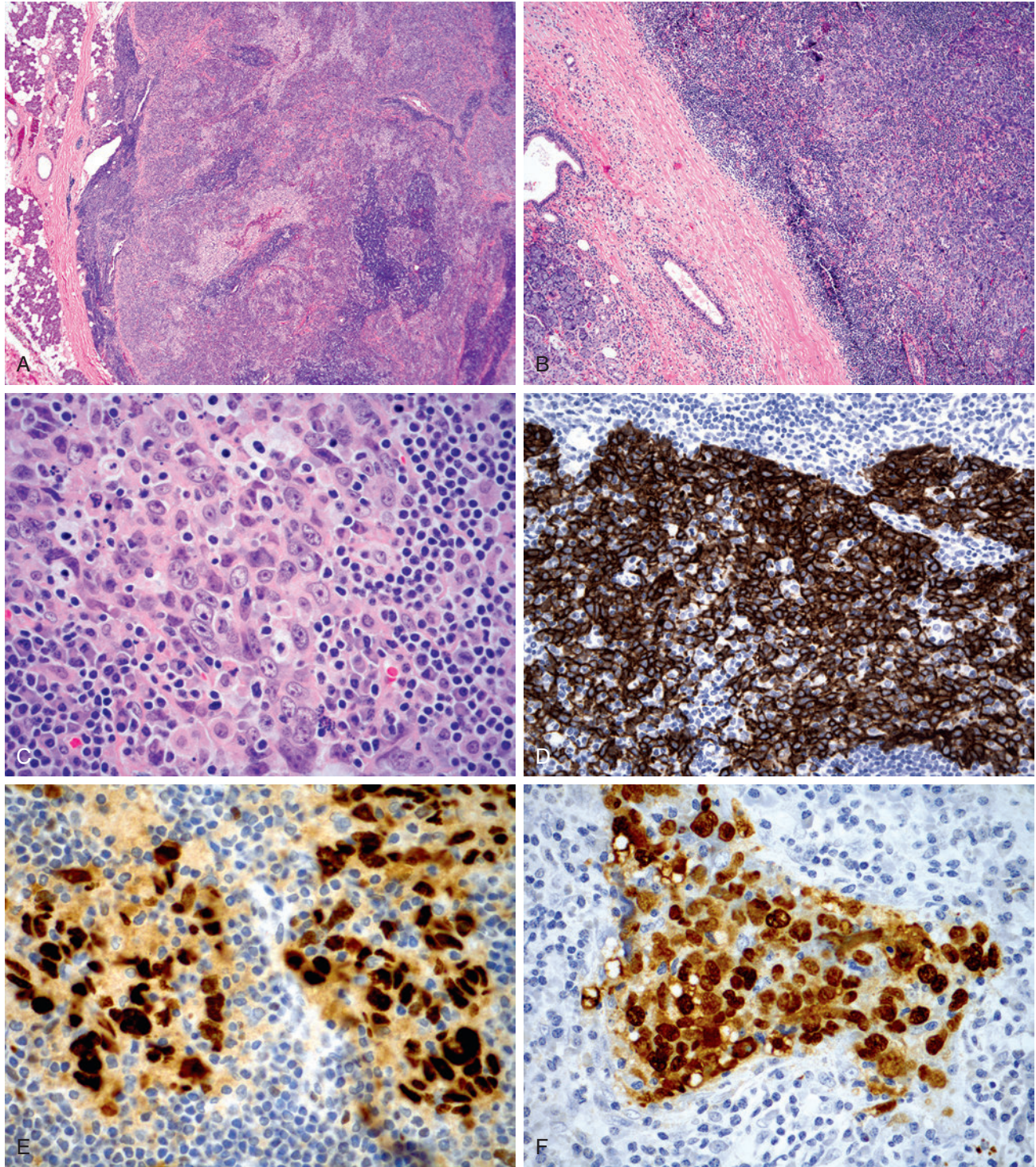


Fig. 20-126. Lymphoepithelial-like carcinoma of the parotid gland.

A and **B**, Infiltrative but circumscribed cellular proliferation separated from the adjacent parotid gland parenchyma (left) that includes clusters of lighter staining neoplastic foci in a background of dense lymphocytic cell infiltrate including germinal centers. Note the absence of an associated desmoplastic reaction to the infiltrative neoplasm. **C**, Cohesive cluster of neoplastic cells characterized by cells with enlarged vesicular nuclei, prominent eosinophilic nucleoli, and indistinct borders creating a syncytial growth. These histologic features are similar to nasopharyngeal carcinoma, nonkeratinizing undifferentiated type. The lesional cells are (**D**) cytokeratin positive; (**E**) p63 positive (nuclear staining); and (**F**) positive by in situ hybridization for Epstein-Barr encoded RNA (EBER).

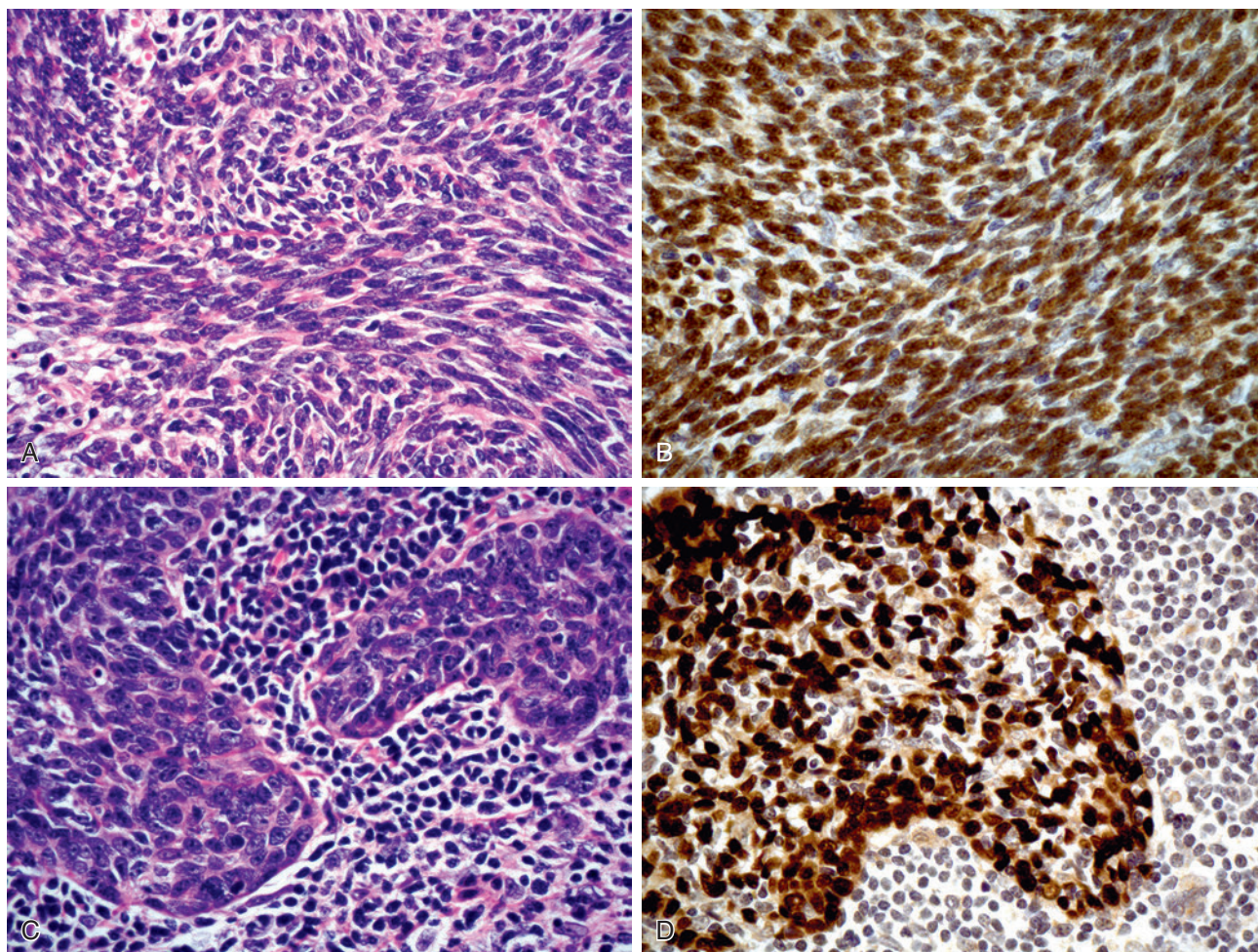


Fig. 20-127. Lymphoepithelial-like carcinoma of the parotid gland.

Variant histologic features may include (A) fascicular growth with spindle-shaped neoplastic cells that were cytokeratin and p63 reactive (not shown) and also (B) EBER positive; (C) basaloid cell features that were cytokeratin and p63 reactive (not shown); and also (D) EBER positive.

- Abundant histiocytes may be seen creating a “starry sky” appearance
- Noncaseating granulomatous inflammation may be identified.
- An amyloid stroma may also be present.
- Invasion is present, including into non-neoplastic salivary gland parenchyma, surrounding connective tissues, neurotropism, and angioinvasion.
- Immunohistochemistry:
 - Epithelial cells:
 - Cytokeratins and EMA positive
 - p63 positive but variable reactivity may be present from case to case and even within the same case
 - c-kit (CD117) reactivity may be present
 - p16 negative
 - Lymphoid cells:
 - Reactive for B-cell (CD20) and T-cell (CD3) markers
- Epstein-Barr virus:
 - In-situ hybridization for Epstein-Barr encoded RNA (EBER) consistently positive in cases from endemic regions
 - Usually negative but can occasionally be positive in cases from nonendemic regions
- Electron microscopy:
 - Epidermoid cell features, including desmosomes, tonofilaments, and cytoplasmic microfilaments

Differential Diagnosis

- Metastatic EBV-associated carcinoma
 - Overlapping histologic, immunohistochemical, and molecular features
 - Differentiation predicated on detailed clinical evaluation to exclude primary nasopharyngeal or less commonly oropharyngeal carcinoma
- Metastatic HPV-associated oropharyngeal carcinoma:

- Presence of p16 and/or identification of high-risk HPV by molecular testing (PCR, ISH) and absence of EBV would allow for differentiation.
- Malignant lymphoma
- Lymphoepithelial sialadenitis
- Malignant melanoma
- Nonsebaceous lymphadenoma

Treatment and Prognosis

- Combined (multimodality) therapy, including surgical resection, neck dissection, and radiation therapy preferred treatment:
 - Up to 40% of patients may present with regional lymph node metastasis.
- Local recurrence and distant metastasis may occur.
- 5-year survival rate reported to be 75% to 86%
- Prognosis linked to clinical stage

NEUROENDOCRINE CARCINOMAS

- Represent group of malignant neoplasms with epithelial and neuroendocrine differentiation
- Classification includes:
 - Typical carcinoid (well-differentiated neuroendocrine carcinoma)
 - Atypical carcinoid (moderately differentiated neuroendocrine carcinoma)
 - Small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)
 - Large cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)
- Rare tumor type in salivary glands:
 - In salivary glands, primarily involve parotid and much less often submandibular gland
 - Most common type is small cell neuroendocrine carcinoma.
 - Rarely, atypical carcinoid and large cell neuroendocrine carcinoma may arise in salivary glands

Small Cell Undifferentiated (Neuroendocrine) Carcinoma (Figs. 20-128 and 20-129)

Definition: Malignant salivary gland tumor composed of undifferentiated small cells showing epithelial and neuroendocrine differentiation:

- Histologically similar to pulmonary counterpart
- May in fact be better considered as neuroendocrine carcinoma, Merkel cell type (see below)

Synonyms: Small cell carcinoma; extrapulmonary oat cell carcinoma; neuroendocrine carcinoma; poorly differentiated neuroendocrine carcinoma

Clinical

- Rare primary salivary gland tumor
- Slightly more common in men than women; occur over a wide age range but most common in the fifth to seventh decades of life
- Most common site of occurrence is the parotid gland (80% of cases); less common sites include the submandibular gland, sublingual gland, and minor salivary glands:
 - Minor salivary gland involvement includes intra-oral sites, as well as throughout the upper aerodigestive tract.
- Presentation usually that of rapidly enlarging and painless mass
 - Facial nerve paralysis commonly present (60%)
 - Duration of symptoms is typically short, occurring over several months
 - Cervical lymphadenopathy fairly common finding at presentation
- Neuroendocrine cells originating from the neural crest migrate to a variety of sites including to salivary glands (major and minor salivary glands):
 - Neuroendocrine cells identified in intercalated ducts and seromucous acini
- Rarely, patients present or have an associated paraneoplastic syndrome.

Pathology

Gross

- Poorly circumscribed, multilobulated, firm, gray-white mass; infiltration into adjacent structures may be evident.
- Hemorrhage and necrosis may be identified.

Histology

- Infiltrative tumor growing in diffuse sheets, cord, trabeculae, ribbons, or irregular nests:
 - Associated fibrous and/or fibrovascular stroma with or without hyalinization may be present.
- Histologically may be classified into:
 - Pulmonary subtype:
 - Absence of CK20 reactivity
 - Merkel cell subtype:
 - Presence of CK20 reactivity
 - May or may not show expression of Merkel cell polyoma virus (MCPyV)

Pulmonary Subtype

- Infiltrative neoplasm with diffuse, cord-like, trabecular growth and variable fibrovascular stroma
- Lesional cells are rather uniform composed of round to oval nuclei with dispersed (stippled) appearing nuclear chromatin, inconspicuous to small nucleoli, minimal cytoplasm, and indistinct cell borders:

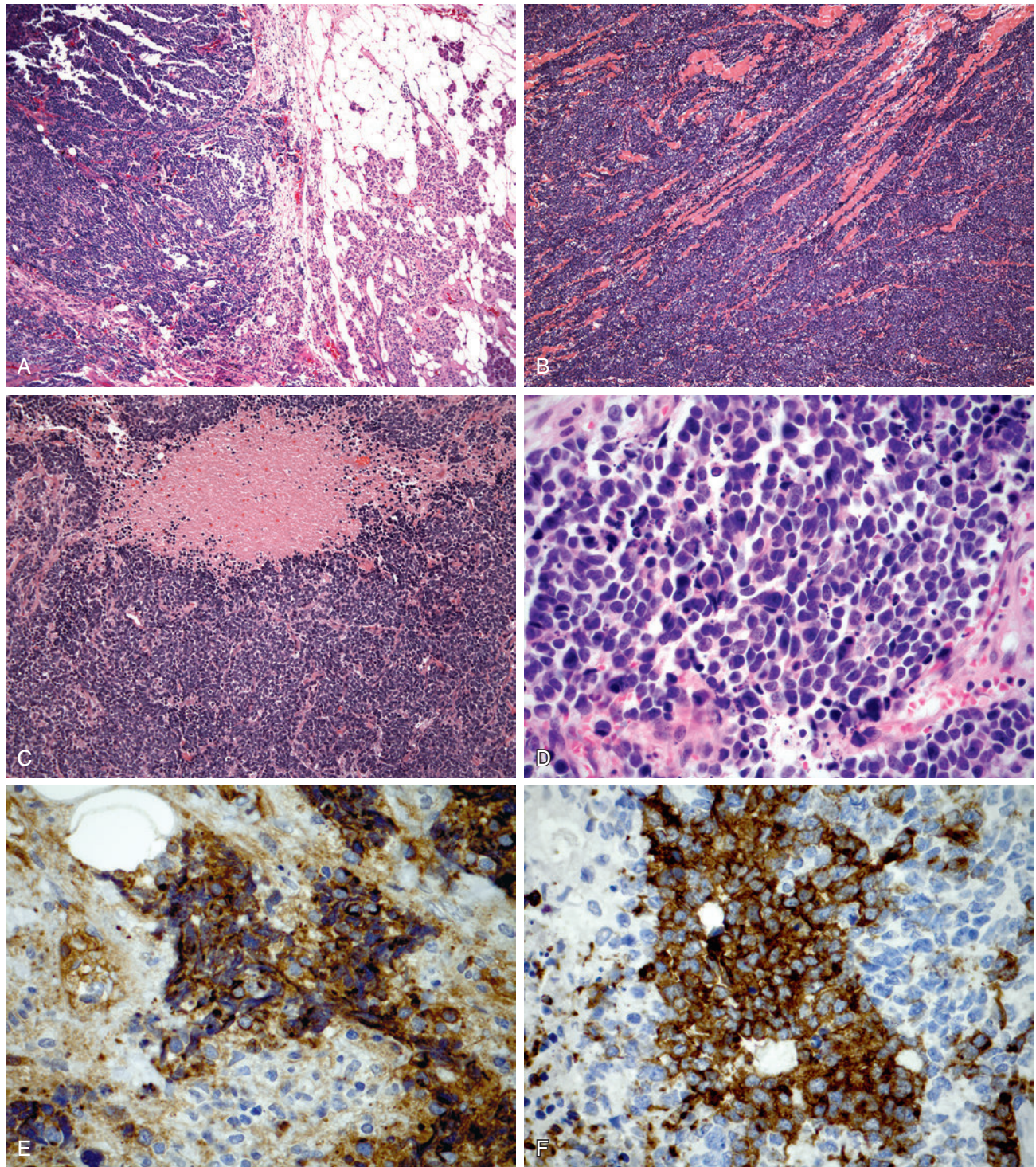


Fig. 20-128. Small cell (neuroendocrine) carcinoma, pulmonary type, of the parotid gland.

A, Hypercellular tumor (*left*) infiltrative in the parotid gland (*right*). **B**, Growth patterns include diffuse or sheet-like and trabecular. **C**, Confluent focus of necrosis. **D**, Small cells with hyperchromatic nuclei, dispersed (stippled) appearing nuclear chromatin, inconspicuous nucleoli, minimal cytoplasm, and indistinct cell borders; nuclear molding, mitotic figures and individual cell necrosis are present. Lesional cells are immunoreactive for **(E)** cytokeratin (CAM5.2) with dot-like paranuclear staining and **(F)** synaptophysin. Staining for CK20 was negative (not shown).

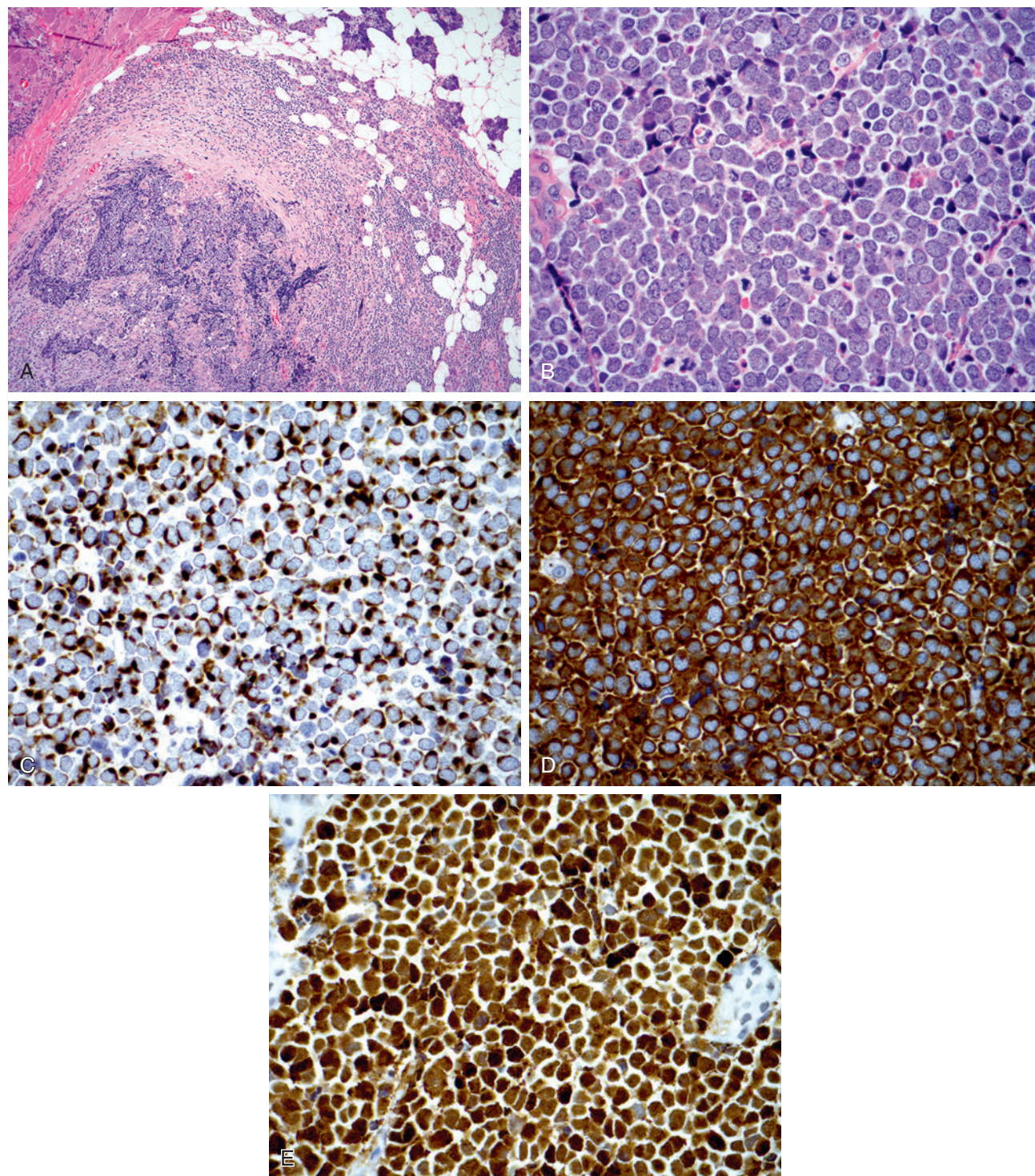


Fig. 20-129. Small cell (neuroendocrine) carcinoma, Merkel cell type, of the parotid gland.

A, Intraparotid infiltrative neoplasm appearing as cohesive clusters and trabeculae; an associated inflammatory cell infiltrate is present. **B**, Lesional cells are uniform, composed of round to oval nuclei with pale or washed out chromatin. The lesional cells are immunoreactive for **(C)** CK20 with a paranuclear dot-like staining pattern; **(D)** synaptophysin and **(E)** Merkel cell polyoma virus (nuclear staining). In addition to CK20, other cytokeratins including AE1/AE3 and CAM5.2 were positive with paranuclear dot-like staining pattern (not shown).

- Cell are approximately two times larger than mature lymphocytes, but occasionally larger tumor cells may be present.
- Fusiform to polygonal shaped cells may occasionally be present.
- Crush artifact resulting in nuclear clumping and diffusion of chromatin material may be identified
- Nuclear molding and peripheral nuclear palisading may be present.
- Tumor necrosis readily apparent either as confluent foci of necrosis or individual cell necrosis
- A high mitotic rate, including atypical mitoses, is present.
- Neural-type rosettes including pseudorosettes (Homer Wright-type) or true rosettes (Flexner-Wintersteiner-type) may be identified.
- Immunohistochemistry:
 - Cytokeratins positive, including pancytokeratin (AE1/AE3), CAM 5.2:
 - Typically shows a punctate or globular paranuclear pattern of staining
 - EMA positive
 - p63 may be positive and if present tends to be focal or scattered positive cells
 - CK7 and CK20 negative
 - Neuroendocrine marker(s) positive, including at least one of the following:
 - Synaptophysin, chromogranin, CD56
 - Neuron-specific enolase positive
 - S100 protein is usually negative.
 - No immunoreactivity for Merkel cell polyoma virus (MCPyV), thyroid transcription factor 1 (TTF-1), melanocytic cell markers (HMB45, melan A, tyrosinase, MITF1), hematolymphoid markers (leukocyte common antigen), myogenic markers (desmin, actins, myogenin, myoglobin), or vimentin
- Electron microscopy:
 - Membrane-bound neurosecretory granules
 - Sparse cytoplasmic organelles; well to poorly formed desmosomes

Merkel Cell Type

- Sheet-like growth
- Lesional cells rather uniform composed of round to oval nuclei with pale or washed out chromatin described as “blown up balloons”:
 - Minimal nuclear molding
- Immunohistochemistry:
 - Similar to pulmonary subtype except for the presence of CK20 reactivity
 - Merkel cell polyoma virus (MCPyV):
 - Discrepant findings in the literature with some reports documenting presence of MCPyV while other reports document absence of MCPyV

- Rarely, foci of ductal differentiation and squamous differentiation may be seen:
 - Tumors with ductal differentiation have been termed ductal-type of small cell carcinoma.
- Small cell carcinoma may rarely be the malignant component in carcinoma ex pleomorphic adenoma.

Hybrid Tumors

- Uncommonly may be a tumor type occurring as a hybrid tumor, representing occurrence of neoplasm composed of two or more histologic distinct types, each of which conforms with an exactly defined tumor category having an identical origin within same topographic area

Other Histologic Types of Salivary Gland Neuroendocrine Carcinomas

- In addition to small cell neuroendocrine carcinoma, other types of salivary gland neuroendocrine carcinomas are rare but may include:
 - Typical carcinoid (well-differentiated neuroendocrine carcinoma):
 - Extraordinarily rare parotid tumor with scattered reports that appear to indicate parotid involvement occurred secondary to a primary carcinoid of a separate site
 - Atypical carcinoid (moderately differentiated neuroendocrine carcinoma):
 - Invasive malignant neoplasm characterized by trabecular, solid, and focally organoid growth patterns
 - Lesional cells characterized by round to oval nuclei with dispersed (“salt and pepper” or neuroendocrine type) chromatin and granular eosinophilic-appearing cytoplasm
 - Mild to moderate nuclear pleomorphism
 - Increased mitotic activity
 - Necrosis (individual cell and confluent “comedotype”)
 - Neural-type rosettes may be identified.
 - Infiltrative growth may include invasion of salivary gland parenchyma, perineural invasion, lymph-vascular invasion
 - Immunohistochemical staining:
 - Lesional cells reactive for:
 - Cytokeratins (AE1/AE3, CAM5.2) with punctate paranuclear staining,
 - Neuroendocrine markers including chromogranin, synaptophysin, CD56
 - p63 may be positive.
 - Negative for CK20, melanocytic cell markers, S100 protein, CD45, calcitonin, TTF1, and MCPyV
 - Large cell neuroendocrine carcinoma:
 - Requisite pathologic criteria include all four of the following:

- Tumor cells with moderate to abundant cytoplasm
- Features of neuroendocrine differentiation (organoid nesting, trabecular growth, rosettes, and peripheral palisading)
- Mitotic activity > 10/10 hpf (2 mm²)
- Confirmation of neuroendocrine differentiation using immunohistochemical staining for chromogranin-A, synaptophysin, neuron-specific enolase, and/or neural cell adhesion molecule (CD56)
- Other typical but not requisite findings include:
 - Nuclei with prominent nucleoli
 - Cellular pleomorphism
 - Large areas of necrosis

Differential Diagnosis

- Metastatic small cell (neuroendocrine) carcinoma of lung (or other) origin
- Metastatic Merkel cell carcinoma
- Adenoid cystic carcinoma, solid variant:
 - Cribriform growth and rather diffuse reactivity for p63, calponin, and absence of neuroendocrine markers assist in diagnosis.
- Malignant lymphoma
- Malignant melanoma
- Rhabdomyosarcoma

Treatment and Prognosis

- Combined multimodality therapy, including surgical resection, regional lymph node dissection, and adjunctive radiotherapy, represents preferred treatment.
- Local recurrence and metastasis occur in approximately 50% of patients:
 - Hematogenous spread is more common than lymphatic spread.
 - Distant metastatic sites include liver and brain.
- Chemotherapy has been used with questionable efficacy in patients with recurrence and distant metastases.
- Survival rates include:
 - 2-year of 70%
 - 5-year of 46%
- Adverse prognostic findings include:
 - Tumor size:
 - Tumors greater than 4 cm more apt to demonstrate neurotropism, invasion of surrounding soft tissues, and increased incidence of local failure.
- Better prognosis associated with:
 - Merkel cell subtype
 - Smaller tumor size (<4 cm)

LARGE CELL UNDIFFERENTIATED CARCINOMA (Fig. 20-130)

Definition: High-grade malignant epithelial salivary gland tumor lacking evidence of glandular, squamous or neuroendocrine differentiation and an inability to classify in another (more specific) salivary gland carcinoma.

Clinical

- Extraordinarily rare salivary gland tumor type
- No gender predilection; tumor of adults with patients usually in seventh to eighth decades
- No ethnic or racial predilection or association with EBV (unlike lymphoepithelial carcinoma)
- Majority of parotid gland origin:
 - Submandibular gland, lacrimal gland, and minor salivary glands may rarely be primary sites of occurrence
- Presentation usually that of rapidly enlarging mass often with associated facial nerve paralysis and cervical lymphadenopathy; fixation to adjacent tissues is commonly present.

Pathology

Fine-Needle Aspiration Biopsy

- Isolated and loosely cohesive large cells with abundant cytoplasm, and variably pleomorphic nuclei with prominent nucleoli
- Multinucleated tumor giant cells and macrophage polykaryons may be present.
- No evidence of squamous, myoepithelial, or widespread mucinous differentiation
- Focal rare mucin production may be identified on special stains.

Gross

- Poorly circumscribed, obviously invasive, firm, solid, gray-white mass measuring from 2 to 10 cm in greatest dimension
- Hemorrhage and necrosis are often identified.

Histology

- Widely invasive tumor composed of sheets, nests, and trabeculae lacking evidence of specific cellular differentiation and separate by a fibrous stroma.
- Lesional cells:
 - Large usually measuring greater than three times the size of cells in small cell neuroendocrine carcinoma
 - Usually polygonal with enlarged round to oval, vesicular nuclei, one or more prominent nucleoli, abundant amphophilic to eosinophilic cytoplasm and rather distinct cell borders

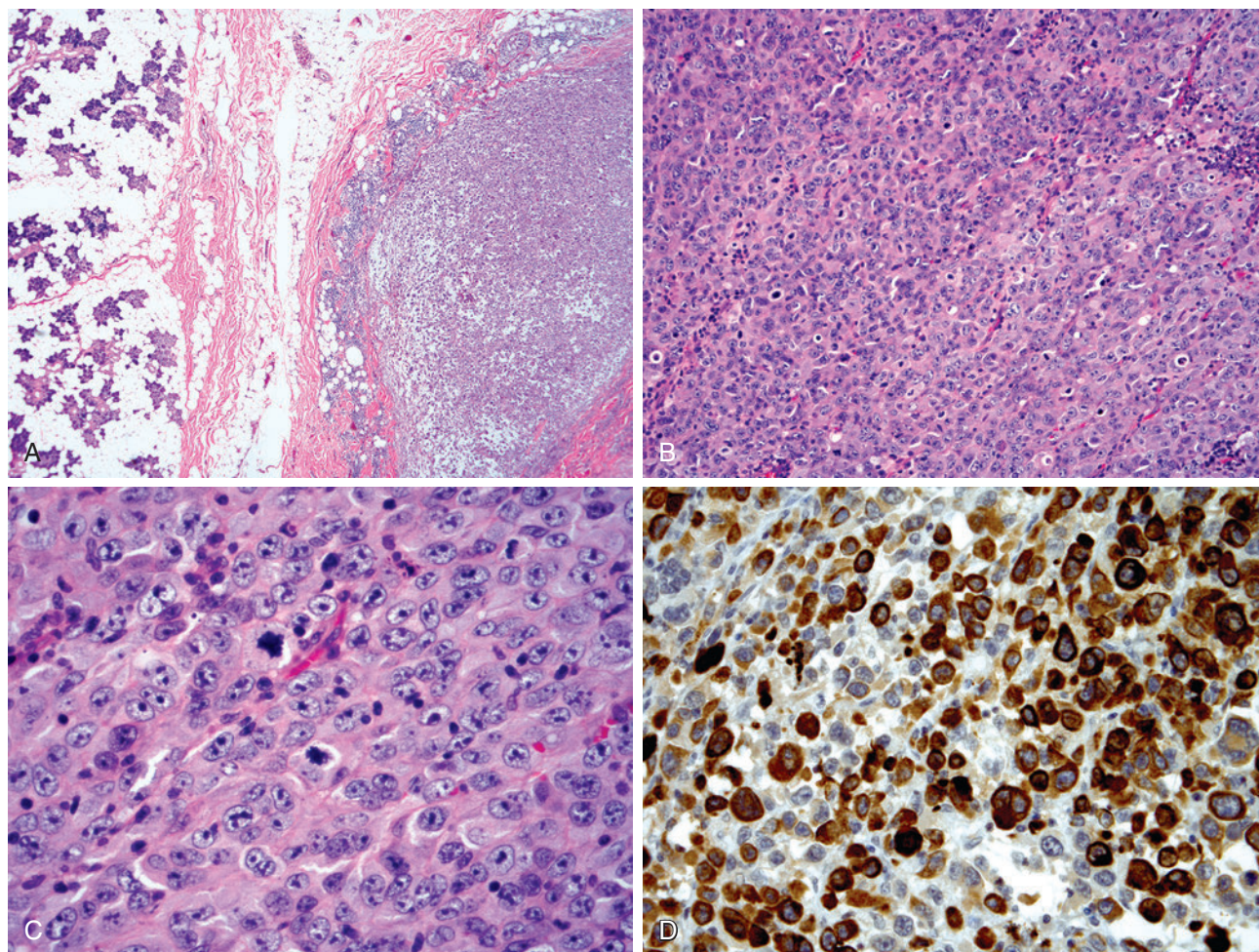


Fig. 20-130. Large cell undifferentiated carcinoma of the parotid gland.

A, Intraparotid infiltrative neoplasm appearing as a nodular focus with diffuse growth; **(B)** diffuse (sheet-like) growth; **(C)** at high magnification the lesional cells are characterized by markedly enlarged and pleomorphic round to oval nuclei with vesicular nuclear chromatin, prominent eosinophilic nucleoli, and indistinct eosinophilic cytoplasm. Increased mitotic activity is present. There is an absence of any type of cellular differentiation (e.g., squamous, glandular, other). The lesional cells were only reactive for several different cytokeratins including **(D)** OSCAR.

- Alternative cytoplasmic findings include vacuolated to partially clear appearance.
- Nuclear pleomorphism commonly seen but occasional cases may display nuclear uniformity
- Increased mitotic activity including atypical mitoses and tumor necrosis commonly identified
- Multinucleated (osteoclast-like) giant cell may be identified.
- Invasion readily apparent including into non-neoplastic salivary gland parenchyma, surrounding connective tissues, perineural invasion, and lymphovascular invasion.
- Desmoplastic stroma that may include benign lymphoplasmacytic cell infiltrate but does not approach the density and/or extent seen in lymphoepithelial carcinoma.
- May represent the dedifferentiated cellular component of a number of differentiated salivary gland tumors (e.g., acinic cell adenocarcinoma, others) and may be the malignant component or one of the malignant components seen in carcinoma ex pleomorphic adenoma.
- Histochemistry:
 - Stains for epithelial mucin are negative.
 - Intracytoplasmic glycogen (diastase-sensitive, PAS-positive) may be present.
- Immunohistochemistry:
 - Cytokeratins positive (pancytokeratin, others)
 - CK20 negative
 - Should be negative for neuroendocrine markers:
 - Presence of neuroendocrine markers may result in classification large cell type of

neuroendocrine carcinoma if requisite histologic features are present (see above)

- Melanocytic, hemolymphoid and mesenchymal markers negative
- EBV negative (by immunohistochemistry and/or in situ hybridization)
- p16 negative
- Cytogenetics and molecular genetics:
 - TP53 mutations
 - Loss of heterozygosity at chromosome 17p

Differential Diagnosis

- Squamous cell carcinoma, poorly differentiated
- Adenocarcinoma, NOS, poorly differentiated
- Mucoepidermoid carcinoma, high grade
- Cystadenocarcinoma, poorly differentiated
- Large cell neuroendocrine carcinoma
- Malignant lymphoma
- Malignant melanoma
- Sarcomas
- Metastatic carcinoma to salivary glands from separate primary carcinoma

Treatment and Prognosis

- Radical surgical extirpation with postoperative radiotherapy represents preferred treatment.
- Chemotherapy has been used in treatment with varying success.
- Aggressively behaving tumor with high rate recurrence and metastases (regional and distant).
- Prognosis is poor:
 - 36% 2-year survival
- Factors adversely affecting prognosis include:
 - Large tumor size (4 cm or greater)
 - Age >50 years
- Metastatic disease

ONCOCYTIC CARCINOMA

(Fig. 20-131)

Definition: Malignant salivary gland epithelial tumor predominantly or exclusively composed of oncocytic cells with cytomorphologic features of malignancy (adenocarcinomatous features) and invasive growth but lacking findings that might allow classification into another tumor type.

Synonyms: Malignant oncocytoma; oncocytic adenocarcinoma; malignant oxyphilic adenoma

Clinical

- Exceedingly rare tumor type
- More common in men than in women; most frequently occurs in the fifth through eighth decades of life

- Occur predominantly but not exclusively in the parotid gland (80%)
 - Other sites of occurrence may include:
 - Submandibular gland and much less often in association with minor salivary glands
- Presents as mass or swelling with or without associated pain and/or facial nerve paralysis
 - Cervical lymphadenopathy at presentation is fairly common.
- May arise as a de novo neoplasm or in association with a long-standing benign oncocytoma
 - Cases occurring in association with oncocytoma may present with rapid enlargement of a preexisting mass lesion.
 - Rarely occur following radiation treatment

Pathology

Fine-Needle Aspiration Biopsy

- Aspirates show similar findings to those seen in oncocytoma (see [Oncocytoma](#)).
- Cytologic features indicative of a malignancy, including marked nuclear pleomorphism, increased mitotic activity with atypical mitoses, and necrosis may not be present.

Gross

- Unencapsulated single or multinodular, firm mass lesion with tan-gray appearance; foci of necrosis may be present.

Histology

- Partially encapsulated or unencapsulated lesion showing varied growth patterns, including sheets and nests of neoplastic cells infiltrating surrounding tissues with loss of normal lobular architecture
- Lesional cells characterized by:
 - Presence of large, round to oval cells with abundant granular eosinophilic cytoplasm due to the absolute increase in the number of cytoplasmic mitochondria
 - Nuclei tend to be enlarged, centrally located, round to oval, with vesicular chromatin and often with prominent nucleoli.
 - Ductal differentiation may be present.
 - Oncocytic cells may form pseudoluminal spaces.
- Nuclear pleomorphism varies from case to case and even within the same case:
 - Any given tumor may demonstrate foci with absent nuclear pleomorphism adjacent to or admixed with cells showing moderate to marked nuclear pleomorphism.
 - These features raise possible occurrence of an oncocytic carcinoma arising in association with oncocytoma.

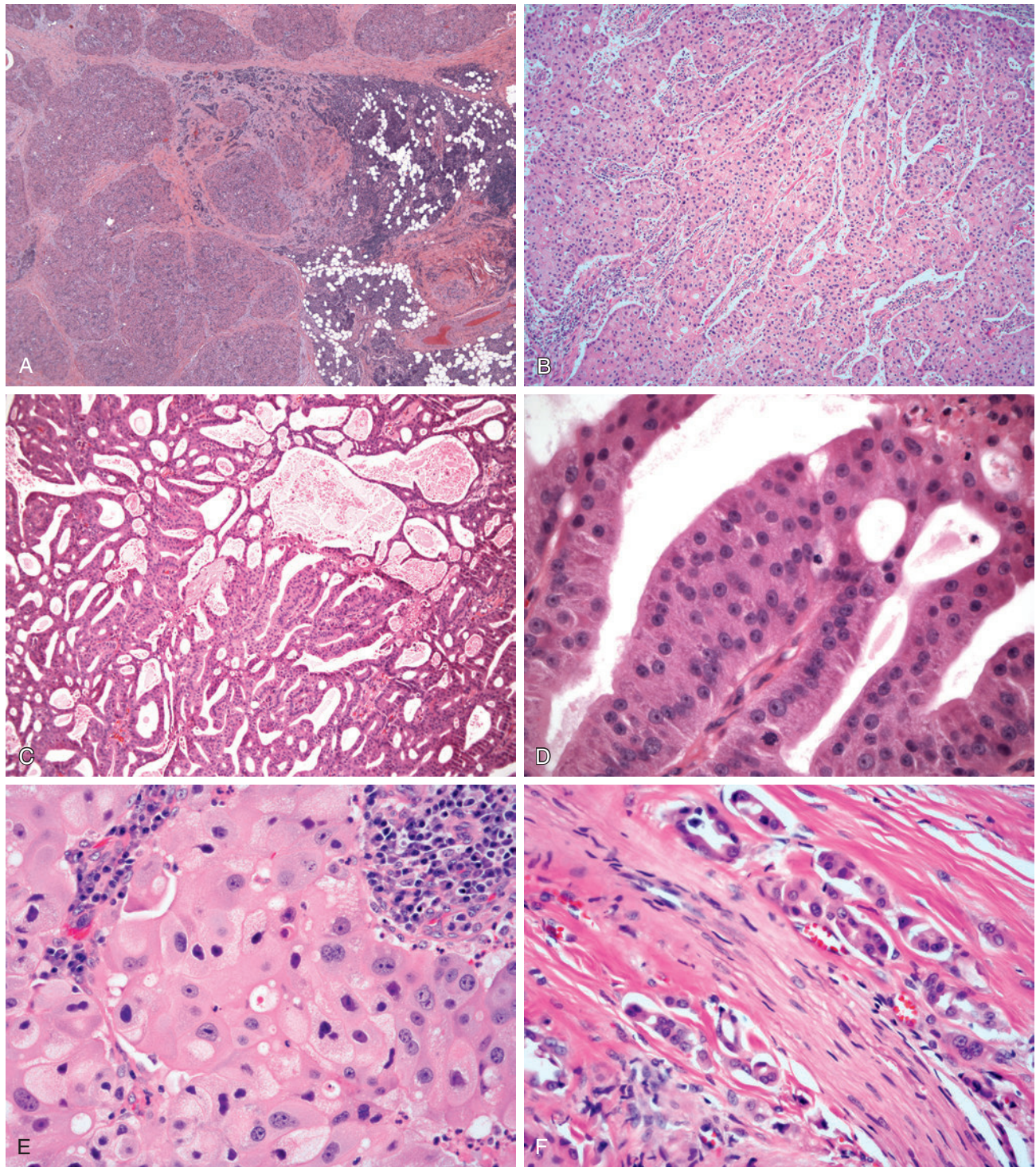
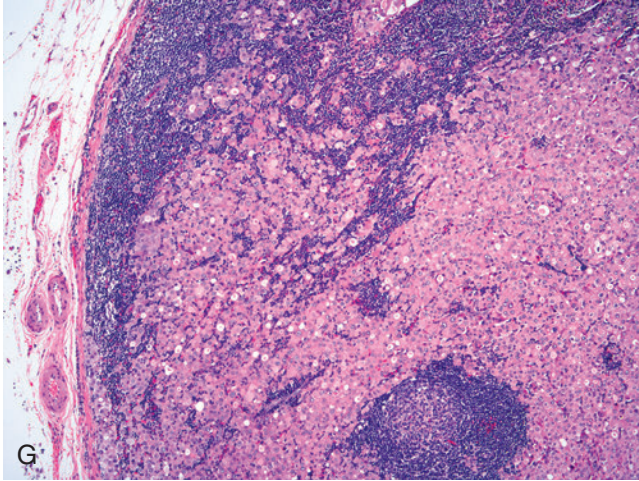


Fig. 20-131. Oncocytic carcinoma of the parotid gland.

A, The tumor is unencapsulated and infiltrative into parotid parenchyma, appearing as multiple discrete nodules. A variety of growth patterns can be seen, including **(B)** trabecular, cord-like, and solid; **(C)** complex back-to-back glandular-appearing (pseudoluminal) spaces and cysts. **D** and **E,** The lesional cells are characterized by the presence of cells with prominent granular eosinophilic-appearing cytoplasm but vary in their degree of pleomorphism from case to case and even within a given case including **(D)** limited nuclear pleomorphism and **(E)** moderate to marked nuclear pleomorphism. Irrespective of the presence or absence of nuclear pleomorphism these are malignant neoplasms that may include **(F)** perineural invasion and/or

**Fig. 20-131, cont'd****(G)** nodal metastasis.

- Increased mitotic activity, including atypical mitoses and necrosis (coagulative type), may be present.
- Invasion is present and includes:
 - Infiltration of non-neoplastic salivary gland parenchyma
 - Surrounding connective tissues
 - Neurotropism and/or lymph-vascular invasion
- Histochemistry:
 - Stains for mitochondria including Novelli and phosphotungstic acid hematoxylin (PTAH) show purplish and blue cytoplasmic granules, respectively.
 - Stains for epithelial mucin are negative.
- Immunohistochemistry:
 - Cytokeratin positive, including pancytokeratin (AE1/AE3), CK7, CK8, and CK19
 - CEA and EMA positive
 - S100 protein, p63, calponin, smooth muscle actin negative
 - Antimitochondrial antibodies, used infrequently, may be of assistance in the diagnosis.
 - Increased proliferative activity as determined by Ki-67 (MIB1) staining may be present.
- Electron microscopy:
 - Numerous mitochondria that vary in size and shape
 - Desmosomes, nearly continuous basal lamina and lumina with microvilli, are present.

Differential Diagnosis

- Oncocytoma:
 - Generally devoid of nuclear pleomorphism, increased mitotic activity, and coagulative necrosis
 - Necrosis and/or infarction may be present, especially following traumatic events such as

fine-needle aspiration biopsy, and such findings should not be construed as evidence of malignancy.

- Rare examples of (encapsulated) oncocytoma with metastatic tumor reported (so-called metastasizing oncocytoma):
 - Primary tumor showed minimal cytologic atypia.
 - Nodal metastasis at presentation
 - Distant metastases months after diagnosis
 - Patient died 18 months after diagnosis.
- Oncocytosis
- Salivary gland tumors with oncocytic cells as either an admixed cellular component or the predominant component, including:
 - Mucoepidermoid carcinoma
 - Acinic cell adenocarcinoma
- Salivary duct carcinoma
- Metastatic carcinoma with oncocytic features, including origin from the kidney, pancreas

Treatment and Prognosis

- Treatment is complete surgical excision that often necessitates total parotidectomy; nodal dissection is advocated given the increased incidence of regional (nodal) metastasis.
- Efficacy of radiotherapy in treatment of these tumors has not been definitively proven.
- Behavior is that of a high-grade malignancy:
 - Tendency to recur (56%)
 - Tendency to metastasis (80%), including regional lymph nodes and distant metastases
 - Distant metastases occur to lungs, kidney, mediastinum, liver, bone, and thyroid gland.
 - Distant metastasis is associated with poor prognosis, resulting in tumor-related death within 4 years.

MALIGNANT SEBACEOUS TUMORS

Sebaceous Carcinoma

(Figs. 20-132 and 20-133)

Definition: Malignant epithelial salivary gland neoplasm with infiltrative growth composed of islands and sheets of atypical cells, including sebaceous cells of varying maturity.

Synonym: Sebaceous adenocarcinoma

NOTE: Cells with sebaceous differentiation may be seen in other salivary gland neoplasms including (but not limited to) pleomorphic adenoma, oncocytomas, Warthin tumors, basal cell adenoma, mucoepidermoid carcinoma, acinic cell adenocarcinoma, adenoid cystic carcinoma.

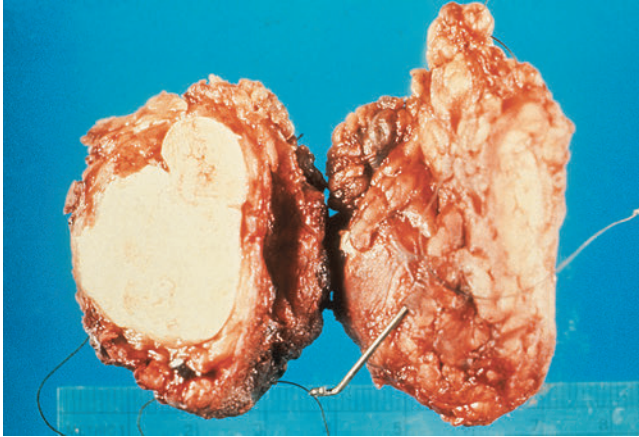


Fig. 20-132. Parotid gland sebaceous carcinoma.

Sebaceous carcinoma of the parotid gland appearing as a circumscribed, tan-white to yellowish mass.

Clinical

- Rare neoplasm
- No gender predilection; bimodal age distribution with peak incidences in third decade and seventh and eighth decades
- Majority occur in parotid gland:
 - Rare cases identified in oral cavity, vallecula, submandibular gland, sublingual gland, and epiglottis.
- Most common symptom is that of a slow-growing mass or swelling with or without associated pain and/or facial nerve paralysis:
 - Cutaneous fixation may be present.

Pathology

Gross

- Circumscribed or partially encapsulated, yellow to tan-white mass measuring from 0.6 to 8.5 cm in diameter with pushing or infiltrative margins

Histology

- Encapsulation may be present but these lesions demonstrate at least focally infiltrative margins:
 - Infiltration includes into surrounding fibroconnective tissue and/or salivary gland parenchyma
- Growth patterns include solid, sheet-like, irregular islands or nested:
 - Coalescence into large solid sheets may occur.
 - Numerous and occasionally cystic well-formed ductal structures seen:
 - Cells lining ducts are cuboidal to low columnar with abundant eosinophilic cytoplasm
- Neoplastic cells are mostly characterized by squamous or basaloid cell types both outnumbering sebaceous cells:

- Variable degree of sebaceous differentiation:
 - In some cases very few easily overlooked, appearing in small clusters of individual cells
 - In some cases large islands of sebaceous cells are seen in association with squamous and basaloid cells
 - Sebaceous cells are large with hyperchromatic nuclei and abundant clear to eosinophilic cytoplasm.
- Squamous and basaloid cells show cytologic atypia, including:
 - Enlarged, moderate to marked pleomorphic and hyperchromatic nuclei
 - Increased mitotic activity including atypical forms and necrosis may be present.
- Invasive growth including:
 - Perineural invasion (20%)
 - Angioinvasion is uncommon.
- Oncocytes, mucocytes, and foreign body giant cells may rarely be identified.
- Histochemistry
- Immunohistochemistry
 - Sebaceous cells:
 - EMA positive

Differential Diagnosis

- Sebaceous adenoma
- Metastatic sebaceous carcinoma from orbital or cutaneous sites

Treatment and Prognosis

- Surgical excision (subtotal or total parotidectomy) is preferred treatment.
- Adjunctive radiotherapy and chemotherapy have been used, but of questionable efficacy in controlling disease
- Appear to behave as low-grade to intermediate-grade neoplasms:
 - Local recurrence may occur.
 - Metastatic disease (regional lymph node or to distant sites) may develop late in the disease course.
 - 5-year survival rates are reported to be approximately 62%.
 - Appears to be a more aggressive neoplasm than its counterpart in orbit

Sebaceous Lymphadenocarcinoma

Definition: Malignant counterpart of sebaceous lymphadenoma from which it arises.

Clinical

- Rare tumor with only five reported cases in world literature to date

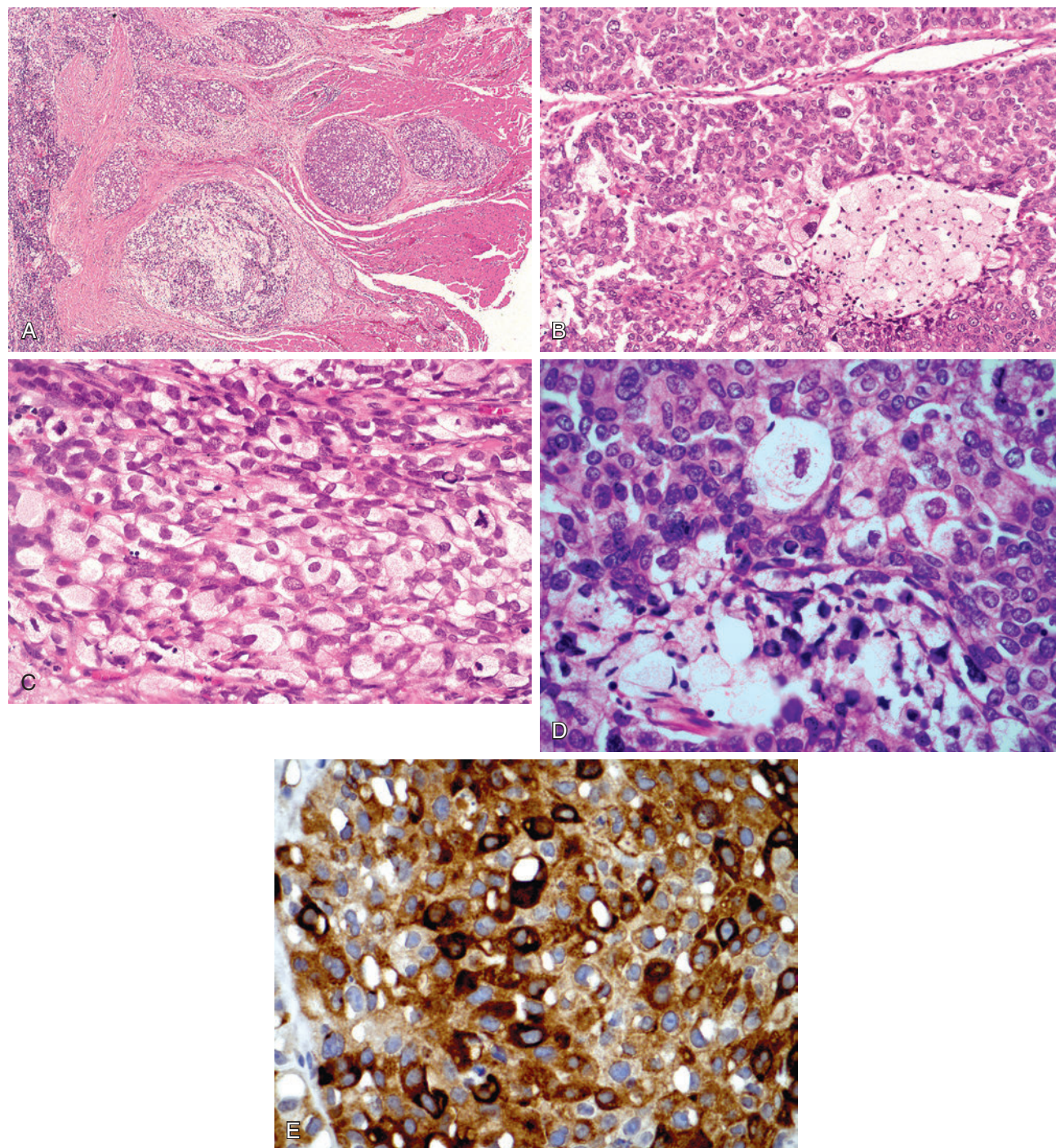


Fig. 20-133. Salivary gland sebaceous carcinoma.

Sebaceous carcinoma of the parotid gland. **A**, At the extreme left is parotid parenchyma from which the tumor originates and invades as solid cellular nodules with sheet-like growth into skeletal muscle. **B** through **D**, Cytologic features include a predominant basaloid cell proliferation with admixed larger sebaceous cells with abundant clear to eosinophilic-appearing cytoplasm. **E**, Lesional cells are EMA positive.

- More common in men than woman; majority were in seventh decade of life with one in sixth decade and one in fourth decade
- All of parotid origin except one purported to arise in periparotid lymph node
- Most common presentation was that of a painless mass or swelling; one had associated pain on palpation
 - Duration of symptoms includes 1 month, 2.5 years, 3 years, 10 years, and 20 years.

Pathology

Gross

- Partially encapsulated, yellow-tan-appearing lesion

Histology

- Histologic features are those of sebaceous lymphadenoma characterized by presence of sebaceous cell nests admixed with salivary ducts in a lymphoid background (with or without germinal centers) sharply demarcated from foci of carcinoma characterized by marked nuclear pleomorphism, increased mitotic activity, atypical mitoses and invasive growth including into adjacent parotid parenchyma and perineural invasion:
 - Carcinoma may include malignant sebaceous cells with ductal differentiation, poorly differentiated carcinoma, adenoid cystic carcinoma, undifferentiated carcinoma, and epithelial-myoepithelial carcinoma
 - Carcinomatous foci tend to lack lymphoid cell stroma.
- A foreign body giant reaction may be seen.
- Immunohistochemistry:
 - Variably staining in carcinomatous component, including:
 - For EMA, cytokeratins
 - Increased proliferation rate by Ki67 staining
 - p53 overexpression may be present.

Differential Diagnosis

- Sebaceous lymphadenoma

Treatment and Prognosis

- Surgical resection is preferred treatment.
- Postoperative radiotherapy may be beneficial.
- Given the rarity of this tumor with limited available follow-up information prognosis remains uncertain; of the reported cases with ample follow-up:
 - Three are alive and free of disease at 2, 6, and 14 years, respectively.
 - One patient died of unrelated causes.
 - One patient had pulmonary metastasis.

MUCINOUS ADENOCARCINOMA (Fig. 20-134)

Definition: Salivary gland epithelial malignancy characterized by presence of extracellular mucinous pools or lakes containing neoplastic epithelial cells.

Synonym: Signet ring adenocarcinoma

Clinical

- Rare salivary gland tumor
- Slightly more common in men than in women; occurs over a wide age range but most patients are in seventh decade of life or older:
 - Reported in patient in second decade of life
- Occur in minor salivary glands and major salivary glands:
 - In minor salivary glands, most common in oral cavity, particularly palate:
 - Other intraoral sites include buccal mucosa, lip, and tongue
 - Among major glands submandibular gland appears to be most commonly involved.
 - Presentation includes slow-growing, painless mass or swelling; occasionally may be associated with pain
 - Mucosal-based lesions may have associated ulceration.

Pathology

Fine-Needle Aspiration Biopsy

- Aspirates may include monomorphic, moderately atypical cells, single and clustered, associated with abundant mucoid material and focal necrosis.
- Tumor cells have eccentric nuclei, prominent nucleoli, and occasional cytoplasmic vacuolization.
- Binucleated and multinucleated tumor cells may be present.

Gross

- Tend to be soft in consistency due to prominent mucinous content with a glistening to gelatinous appearance; tumors range in size from 2.5 to 7 cm in greatest dimension.

Histology

- Characterized by presence of cystic cavities containing extracellular mucinous pools within which are epithelial cells appearing in clusters, nests, cords, or individual cells:
 - Epithelial cells appear to float in mucinous material.
 - Cavities separated by fibroconnective tissue
- Lesional (epithelial) cells:
 - Show varying architectural patterns, including branching cords, papillae, cribriform, solid

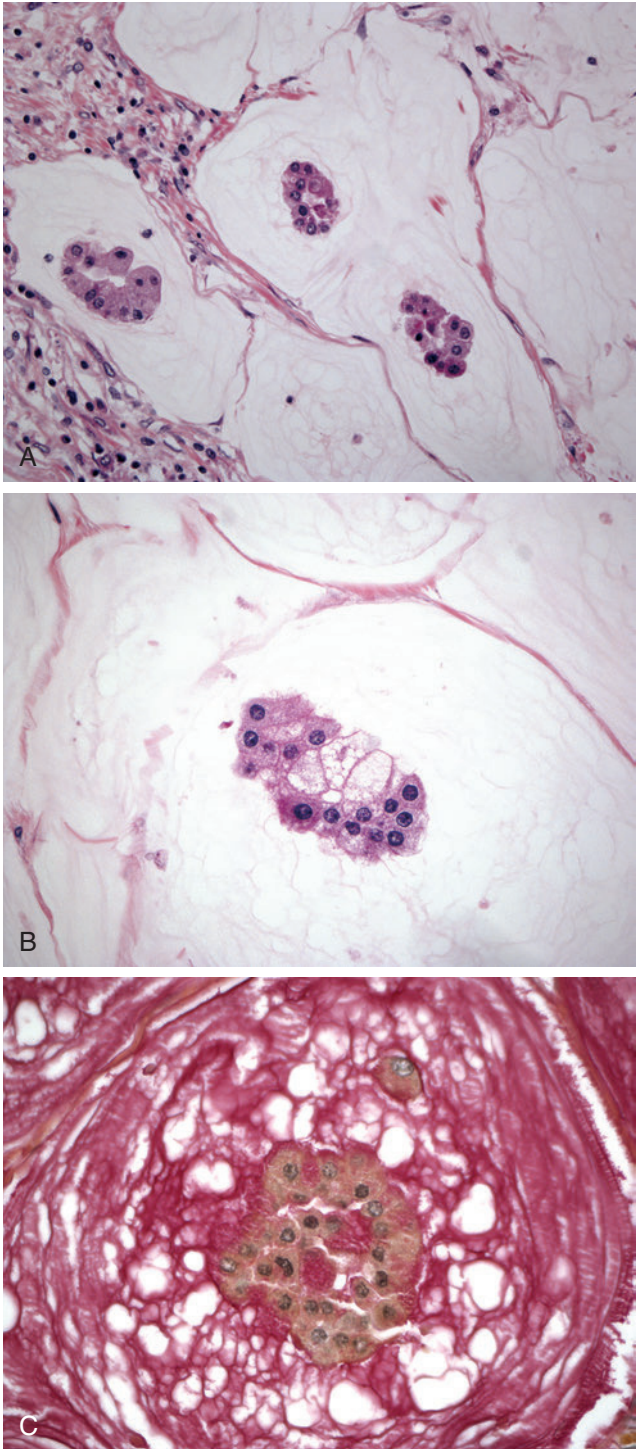


Fig. 20-134. Mucinous adenocarcinoma of the parotid gland.

A and B, This was an intraparotid neoplasm characterized by glands “floating” in mucous pools. **C,** Extracellular and intracytoplasmic mucin positive material is present.

clusters and lumens, or incomplete duct-like structures

- Are cuboidal to polygonal to columnar with hyperchromatic nuclei and abundant eosinophilic to clear to vacuolated-appearing cytoplasm:
 - Nuclear pleomorphism ranges from mild to moderate
 - Mitotic activity tends to be few to scarce.
- Histochemistry:
 - Extracellular mucinous material:
 - Mucicarmine positive
 - Diastase resistant, PAS positive
 - Intracytoplasmic mucin and diastase-resistant, PAS-positive material may be identified.
- Immunohistochemistry:
 - Cytokeratins including AE1/AE3, CK7, CK8, CK18, and CK19 positive
 - No immunoreactivity for CK20, CDX2, villin
 - Absence of myoepithelial, acinar, and neuroendocrine cell markers
 - Estrogen receptor and progesterone receptor negative

Differential Diagnosis

- Mucoepidermoid carcinoma
- Salivary duct carcinoma, mucin-rich variant:
 - De novo or arising in association with pleomorphic adenoma (i.e., mucin-rich salivary duct carcinoma ex pleomorphic adenoma)
- Colonic (or intestinal)-type adenocarcinoma of oral minor salivary glands:
 - Rare tumor reported to occur at base of tongue or anterior tongue occurring in absence of primary colonic adenocarcinoma:
 - To date, only four reported cases in the literature
 - One patient with 10-month history of occupational exposure to sawdust while working in hardware store prior to development of base of tongue tumor
 - Histologically similar to sinonasal intestinal-type adenocarcinoma (see Section 1, Sinonasal Tract) including presence of submucosal-based infiltrative neoplasm composed of admixture of well- to moderately differentiated colonic-type adenocarcinoma characterized by tubular/glandular structures with an associated mucinous component
 - Immunohistochemical staining includes:
 - Cytokeratins including AE1/AE3, CAM5.2, CK7
 - CK20, CDX-2 (nuclear staining), and villin positive
 - CEA, EMA positive
 - Nuclear staining for hMLH1, hMSH2, hMSH6, and hPMS-2 mismatch repair proteins reported

- No *KRAS* mutations of codons 12, 13, and 61 by DNA sequencing
- Metastases to cervical lymph nodes (unilateral or bilateral)
- Histogenesis uncertain but possibilities include:
 - Origin from transformed minor salivary duct epithelium at this location
 - Development from heterotopic gastrointestinal tissue
- Tendency to metastasize to regional cervical lymph nodes (unilateral or bilateral)
- One patient with long-term follow-up remained disease free for 14 months before developing multiple bilateral pulmonary metastatic disease and died from his disease 5 years after diagnosis.
- Cystadenocarcinoma, mucinous
- Cutaneous mucinous (eccrine) carcinoma
- Metastatic mucinous (colloid) carcinoma, including gastrointestinal, pancreatic, breast, sinonasal origin

Treatment and Prognosis

- Surgical resection is preferred treatment.
- Local recurrence in approximately 33%
- Aggressive tumors:
 - Most present with advanced clinical stage disease
 - Cervical node metastasis in 63%
 - Distant metastases in 29%
 - Death from disease in 47%

SIALOBLASTOMA (Fig. 20-135)

Definition: Rare congenital/perinatal low-grade malignant salivary gland tumor composed of basaloid cells and occasional ductal structures recapitulating primitive salivary gland anlage with unpredictable biologic behavior.

Synonyms: Embryoma; congenital basal cell adenoma; congenital carcinoma; low-grade basaloid adenocarcinoma; hybrid basal cell adenoma-adenoid cystic carcinoma

Clinical

- Very rare salivary gland tumor that to date number less than 50 cases reported in the world literature
- More common in males than in females; majority occurs in newborns or shortly after birth; less often, can occur in children over 2 years of age:
 - Rare purported cases reported in adults (see below under Differential Diagnosis with [adenoid cystic carcinoma](#))
- Essentially limited to parotid gland and submandibular gland:
 - Parotid gland >> submandibular gland
 - One case of eyelid in infant presumptively arising from lacrimal gland (palpebral lobe) reported

- One case reported in anterior cheek of infant presumptively arising in ectopic salivary gland tissue
- Presenting symptom(s) usually that of asymptomatic parotid or submandibular gland mass:
 - May include rapid growth
 - Rarely, may be associated with facial paralysis
 - May be fixed either to underlying structures or to skin with or without ulceration
- Radiology:
 - MRI may show a large facial mass, which is mostly hypointense to the brain and isointense with muscle on T1-weighted images, and mildly hyperintense on T2-weighted images and high-intermediate signal intensity similar to that of fat on T2-weighted images
 - Foci of hemorrhage and necrosis may be present.
 - Invasion into adjacent structures such as the maxilla and adjacent muscles may be present.
- Elevated levels of alpha-fetoprotein may be present.
- Association with hepatoblastoma and congenital nevi reported

Pathology

Fine-Needle Aspiration Biopsy

- Cytologic features include presence of variably arranged, tight, solid clusters of atypical-appearing, basaloid-like cells in a background of dispersed epithelial and myoepithelial cells.
- Clusters contain an admixture of benign ductal cells and dense, metachromatic, magenta hyaline globular material with smooth, rounded outlines.
- Cytologic findings show complete concordance with the histology of sialoblastoma.

Gross

- Circumscribed to partially encapsulated, nodular or lobulated, solid lesion with a tan-gray to yellow appearance, usually firm, measuring from 1.5 to 15 cm.
- Hemorrhage and necrosis may be present.

Histology

- May vary from being well circumscribed/semienapsulated and noninfiltrative to infiltrative, which may include:
 - Infiltration into adjacent structures such as salivary gland parenchyma
 - Facial nerve invasion
- Cellular neoplasm composed of a combination of solid islands of basaloid cells as well as ductal structures, which recapitulate appearance of the developing fetal salivary gland.
 - Hypercellular islands separated by fibrous or fibromyxomatous stroma

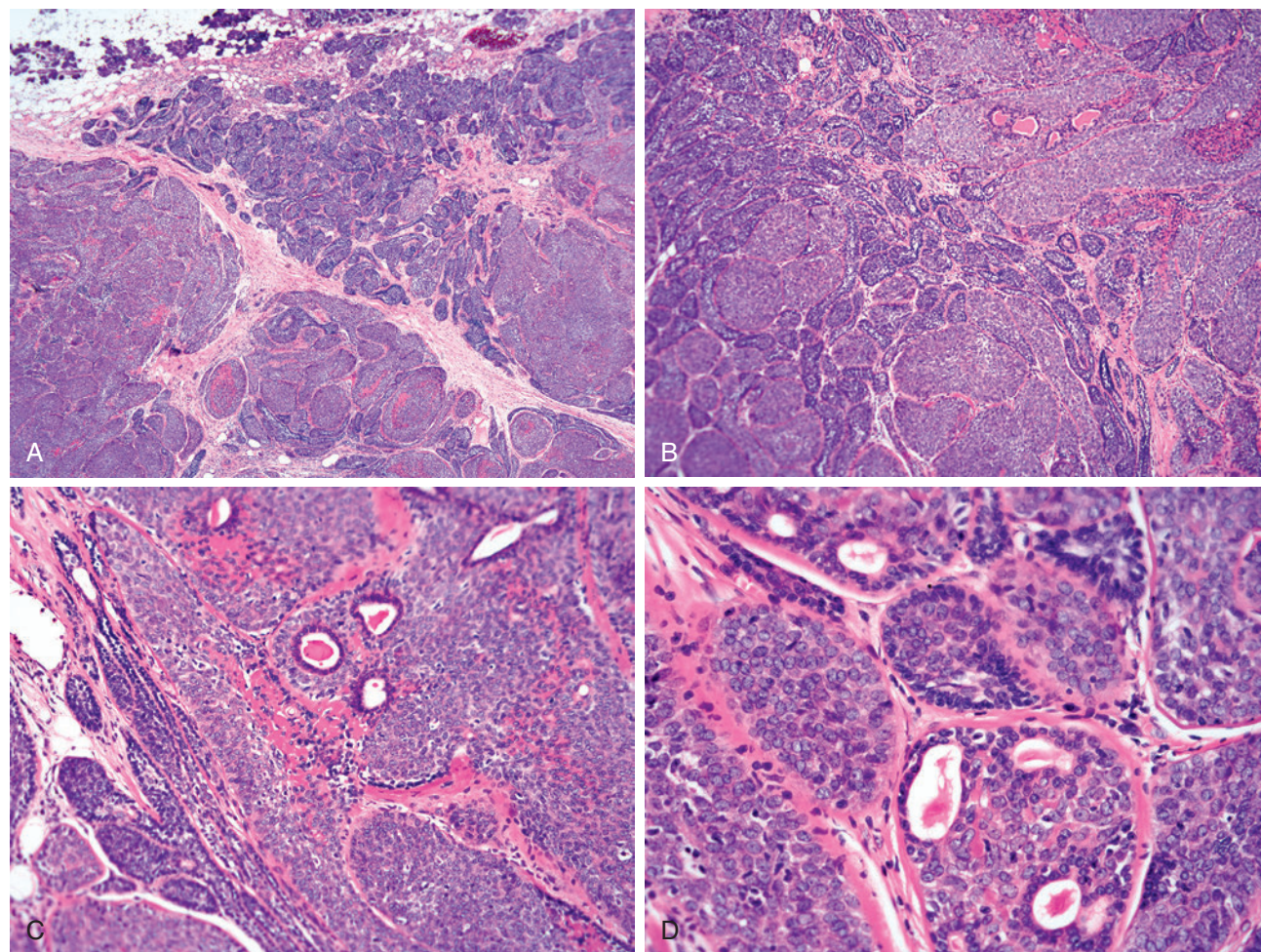


Fig. 20-135. Sialoblastoma.

A, Intraparotid infiltrative tumor characterized by lobular and nodular growth separated by varying degrees of fibroconnective tissue. **B** and **C**, The combination of solid islands of basaloid cells with admixed ductal structures recapitulate the appearance of the developing fetal salivary gland and is characteristic for sialoblastoma. **D**, At higher magnification the basaloid cells are primitive appearing with large round to ovoid vesicular to hyperchromatic nuclei; the ductal component includes small ducts with identifiable lumina lined by cuboidal to low columnar-appearing cells with eosinophilic cytoplasm; intraluminal secretory material is present.

- Islands may be tightly packed (i.e., solid growth) with little intervening (fibrovascular) stroma or may be loosely arranged with abundant intervening stroma.
- Basaloid cells:
 - Primitive-appearing with large round to ovoid vesicular nuclei, ample eosinophilic cytoplasm, one or more nucleoli, and indistinct cell borders
 - Vague peripheral nuclear palisading may be seen.
- Ductal component:
 - Small ducts have distinct lumina.
 - Lined by cuboidal to low columnar cells with eosinophilic cytoplasm can be present
 - Ductal lumina may contain basophilic secretory material.
- Favorable and unfavorable histologic patterns identified, including:
 - Favorable:
 - Semiencapsulation with cytologically bland basaloid tumor cells showing mild nuclear pleomorphism, identifiable mitoses but absent atypical mitoses, absent necrosis, and presence of intervening stroma:
 - Unfavorable:
 - Presence of anaplastic tumor cells, increased mitotic activity including atypical mitoses, necrosis, minimal stroma, and presence of broad pushing infiltrative periphery
- Cribriform growth similar in pattern to that seen in adenoid cystic carcinoma may be present.

- Other cell types that may occasionally be present include sebaceous, squamous, and acinar cells; calcification may also be seen.
- Malignant spindle cell (sarcomatoid) component rarely identified:
 - Spindle cells cytokeratin and S100 protein positive
 - Considered sarcomatoid transformation of basaloid (myoepithelial) cell component
- Immunohistochemistry:
 - Basaloid cells:
 - Diffuse reactivity for CK903 (34BE12); variable to absent expression of other keratins and EMA
 - Diffuse p63 reactivity
 - Positive staining often focal for S100 protein, calponin, smooth muscle actin
 - GFAP negative
 - Alpha-fetoprotein expression may be present (reported in cases with unfavorable histology)
 - Ductal cells:
 - Reactivity for cytokeratins including diffuse or focal luminal staining for pancytokeratin, CAM5.2, CK5/6, CK7, and CK903 (34BE12), as well as EMA
 - Focal S100 protein may be present.
 - Negative for CK20, p63, smooth muscle actin, calponin, and GFAP
- Proliferative indices may vary from low levels (<5% cases with favorable histology) to markedly increased levels (50% to >90% with unfavorable histology)
- p53 (nuclear) staining may be focal or diffuse in both cellular components
- Electron microscopy:
 - Cell junctions present between ductal and surrounding tumor cells
 - Basaloid cells have well-developed endoplasmic reticulum, free ribosomes, and surrounding basal lamina
 - Intracytoplasmic thin filaments and subplasmalemmal densities can be seen in peripheral cells:
 - Based on presence of actin immunoreactivity and intracytoplasmic thin filaments, cells surrounding ductal cells are believed to be of myoepithelial origin.

Differential Diagnosis

- Basal cell adenoma:
 - Basal cell adenomas in contrast to sialoblastoma occur in adults (rare prior to age 20) and are noninvasive and composed of less primitive cells, greater peripheral nuclear palisading, less cytomorphologic atypia, and less mitotic activity.
- Basal cell adenocarcinoma
- Adenoid cystic carcinoma:
 - Diagnosis of adenoid cystic carcinoma rare in neonates and infants:
 - Tumor with hallmark features of sialoblastoma but with cribriform growth in neonates or infants should be diagnosed as sialoblastoma.
 - Sialoblastoma in adults rarely if ever occurs, and in adults any degree of cribriform growth would result in classification of a tumor with features of sialoblastoma as an adenoid cystic carcinoma; however:
 - Three adult tumors with primitive histopathologic findings characteristic for sialoblastoma including cribriform growth reported:
 - Included 46-year-old female, 55-year-old male, and 83-year-old male
 - Two cases of palate and one of parotid
 - Differences in clinical behavior in these cases from adenoid cystic carcinoma cited as evidence to support diagnosis as sialoblastoma rather than adenoid cystic carcinoma including prolonged disease-free interval over long-term follow-up
 - Nevertheless, if confronted with such a lesion in adults, diagnosis of sialoblastoma in lieu of adenoid cystic carcinoma cannot be rendered with complete confidence, and treatment should follow that for adenoid cystic carcinoma.

Treatment and Prognosis

- Surgical resection with negative resection margins is preferred treatment:
 - In majority of cases results in cure
- Local recurrence reported in approximately 25% of patients:
 - Occur from months to a few years after resection
 - Local recurrences have been associated with increased nuclear pleomorphism, increased mitotic activity, necrosis, and increased proliferation indices.
- Regional nodal metastasis infrequently occurs.
- Chemotherapy (vincristine, actinomycin D, and cyclophosphamide) considered effective adjuvant or neoadjuvant treatment option for unresectable, recurrent or metastatic tumor
- Biologic behavior (presence or absence of recurrence and/or metastatic disease) may correlate to:
 - Histologic features:
 - Tumors with unfavorable histology (see above) associated with more aggressive biologic behavior
 - Proliferation indices and p53:
 - Increase proliferation rate and diffuse p53 staining associated with more aggressive biologic behavior

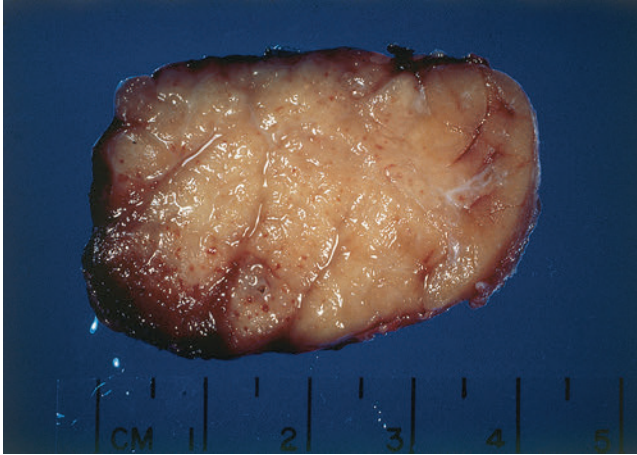


Fig. 20-136. Parotid malignant lymphoma.

MALT lymphoma of the parotid gland diffusely involving the gland with nodular and tan (fish-flesh) appearance.

NONEPITHELIAL MALIGNANT SALIVARY GLAND TUMORS

Primary Malignant Lymphoma (PML) of Salivary Glands

(Figs. 20-136 through 20-141)

Definition: Malignant neoplastic proliferation of lymphoid cells arising in salivary glands with involvement of glandular epithelium.

- Diagnosis predicated on absence of malignant lymphoma (ML) of noncontiguous site
- If ML of noncontiguous site identified by clinical staging and bulk of tumor is not in the salivary gland, then the salivary gland involvement is considered secondary.
- Complicating issue is presence of intraparotid lymph nodes, which may give rise to ML and therefore are nodal based.
- The distinction between a nodal-based ML secondarily involving parotid glandular epithelium from an ML originating in the parotid gland with secondary nodal involvement cannot always be determined.
- Most ML of salivary glands are non-Hodgkin lymphomas (NHL).
- Salivary gland NHL may develop essentially in two settings:
 - In setting of immune sialadenitis (Sjögren syndrome) with lymphoepithelial sialadenitis (LESA ML):
 - Most often extranodal marginal zone B-cell lymphoma (EMZBCL), which is a low-grade B-cell lymphoma arising in mucosal-associated lymphoid tissue (MALT) referred to as

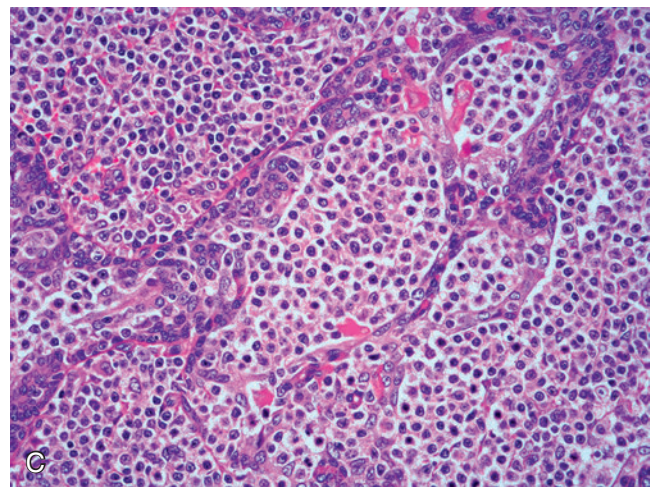
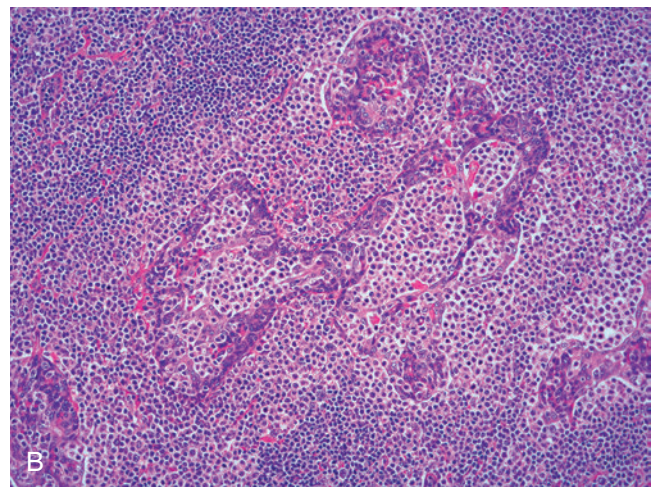
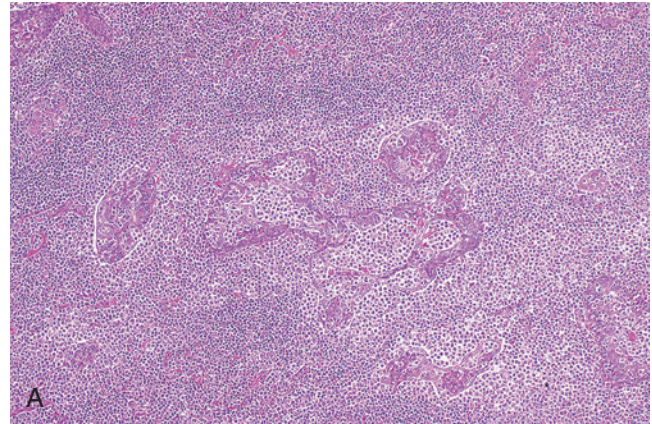


Fig. 20-137. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type.

A and B, Lymphomatous cells coalesce around and infiltrate into the characteristic lymphoepithelial lesions. **C,** At higher magnification the neoplastic (monocytoid B) cells are monomorphic with abundant, pale to clear cytoplasm and uniform-appearing nuclei.

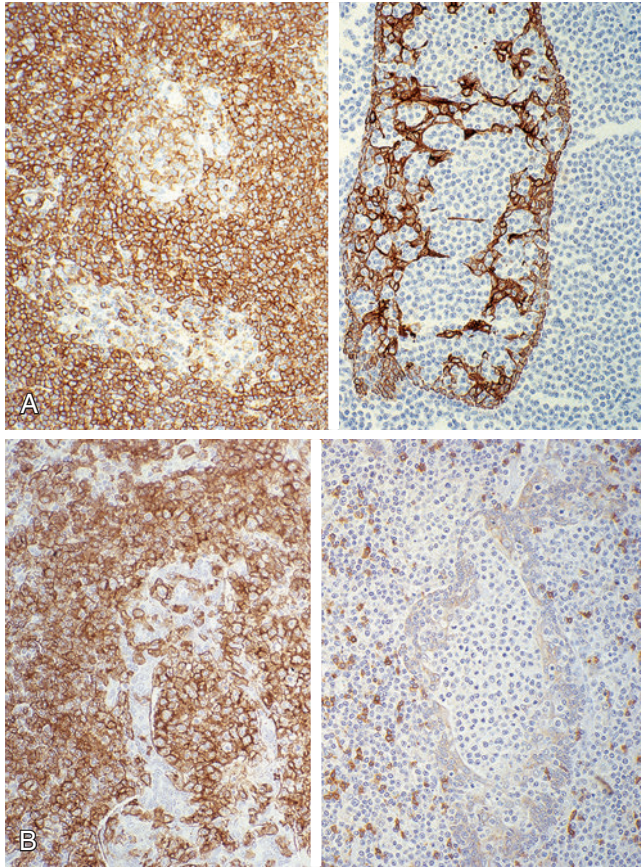


Fig. 20-138. MALT lymphoma.

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type. Immunohistochemical staining includes (A) *left panel*, leukocyte common antigen in the lymphomatous cells but not epithelial cells; *right panel*, cytokeratin reactivity in the lymphoepithelial lesions but not lymphomatous cells. B, Lesional cells are CD20 reactive (*left panel*) but nonreactive for CD3 (*right panel*); scattered CD3 positive T-cells are present.

extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

- As a *de novo* process unrelated to other diseases such as lymphoepithelial sialadenitis (non-LESA ML)
- Most often a diffuse large B-cell lymphoma (DLBCL)
- Rare salivary gland tumor:
 - Represents less than 5% (range 2.4% to 4.5%) of all primary extranodal NHL and approximately 2% of all salivary gland tumors:
 - Extranodal lymphoma includes those patients with stage IE or IIE disease.
 - Lymphomas of extranodal sites in patients with stage IIIIE and IV disease are considered to represent disseminated (systemic) disease rather than primary extranodal lymphoma.



Fig. 20-139. Diffuse large B-cell lymphoma of the parotid gland.

The gland is replaced by a homogeneous tan ("fish-flesh")-appearing proliferation.

- Excluded from category of primary extranodal lymphoma is relapse of nodal-based lymphoma in an extranodal site.
- Given the above, prior to rendering a diagnosis of a primary extranodal lymphoma, detailed clinical staging evaluation is indicated.
- In addition to immune sialadenitis (Sjögren syndrome) ML salivary glands are also closely linked to patients with hepatitis C virus (HCV) infection, suggesting a possible role in the pathogenesis of these lymphomas.
- Risk of developing a ML in patients with immune sialadenitis is markedly increased:
 - Risk of developing salivary gland NHL 44 times greater than control groups
 - Slightly less than 10% of patients with immune sialadenitis develop ML of extranodal sites including:
 - Salivary glands, lacrimal gland, lungs
 - Many of these patients develop benign atypical lymphoproliferative disorders.

MALT Lymphoma

Clinical

- Most common salivary gland lymphoma type
- Decided female predilection; occurs with wide age distribution but, in general, tends to occur in elderly people with mean age in mid-seventh decade of life:
 - 5% or less of patients with salivary gland NHL are younger than fifth decade of life.
 - Rarely, salivary gland NHL may occur in pediatric ages.

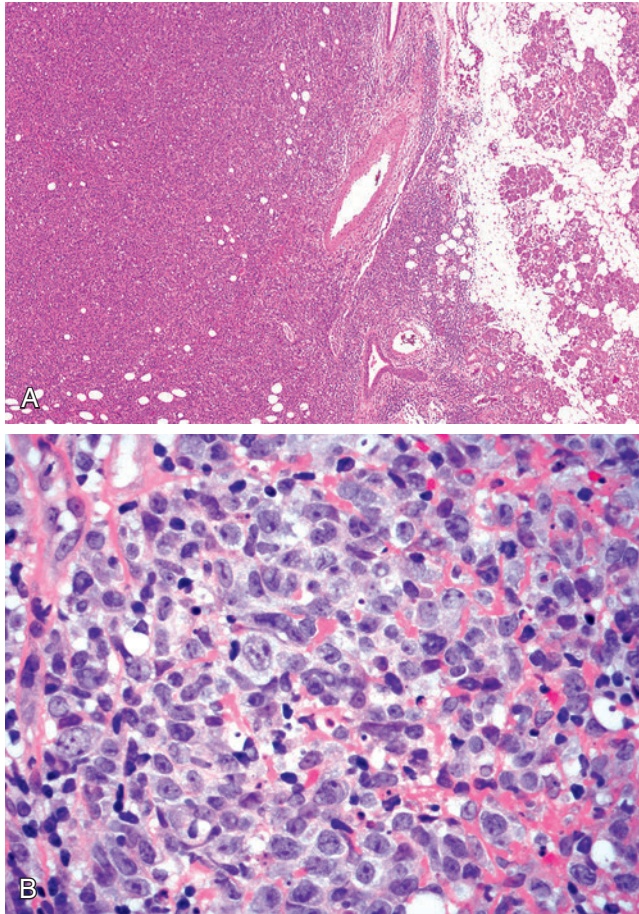


Fig. 20-140. Diffuse large B-cell lymphoma of the parotid gland.

A, Diffuse cellular proliferation effacing the parotid parenchyma with infiltration into the adjacent parotid parenchyma (*lower right of center*). **B**, Diffuse dyscohesive cellular proliferation composed of large cells with pleomorphic, vesicular nuclei, and eosinophilic nucleoli.

- Most often occurs in parotid gland, including approximately 75% of all cases
 - Less often, submandibular gland involvement occurs (from 17% to 20% of cases).
- Usual presentation includes slow growing salivary gland mass:
 - Cervical lymphadenopathy may be present at presentation in approximately 30% of patients.
- Presentation may also include ocular, oral, and extraglandular signs, including keratoconjunctivitis sicca and xerostomia:
 - Approximately one third have bilateral enlargement of affected salivary glands.
 - Salivary gland enlargement may be episodic or chronic.
 - Early diagnosis of MALT lymphomas in patients with immune sialadenitis (Sjögren

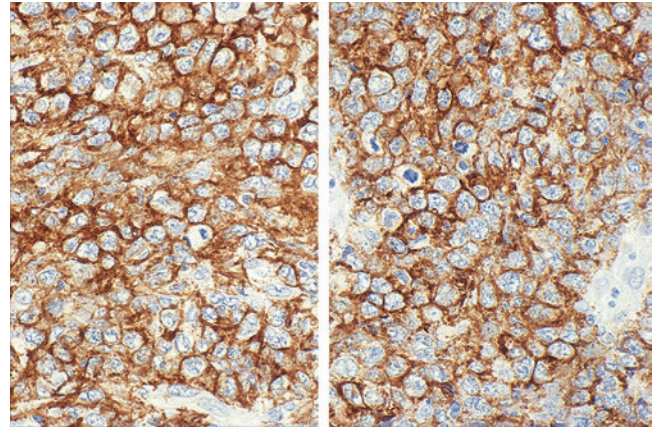


Fig. 20-141. Diffuse large B-cell lymphoma of the parotid gland.

Immunohistochemical staining shows the neoplastic cells to be *left panel*, CD45 (leukocyte common antigen) positive and *right panel* CD20 positive. The neoplastic cells were nonreactive for cytokeratins and T-cell markers (not shown).

syndrome) but without signs of pre-existing lymphoma may be possible by labial salivary gland biopsies as a routine part of screening for Sjögren syndrome

- In approximately 25% serum monoclonal component (IgG or IgM) may be identified.
- Occurs in association with immune sialadenitis (Sjögren syndrome):
 - Less often may occur with other associated diseases, including:
 - Rheumatoid arthritis, systemic lupus erythematosus, hypothyroiditis
 - In addition to immune sialadenitis also closely linked to patients with hepatitis C virus (HCV) infection, suggesting a possible role in the pathogenesis of these lymphomas:
 - HCV characterized by sialotropism and ability to replicate in salivary glands as well as by lymphotropism
 - Patients with HVC but without Sjögren syndrome not known to have increased risk of lymphoma in salivary glands
 - Overall importance of HCV in pathogenesis of ML arising in Sjögren syndrome remains uncertain
- Risk of developing an ML in patients with immune sialadenitis markedly increased:
 - Risk of developing salivary gland NHL 44 times greater than control groups
 - Slightly less than 10% of patients with immune sialadenitis develop ML of extranodal sites including:
 - Salivary glands, lacrimal gland, lungs

- Many of these patients develop benign atypical lymphoproliferative disorders.
- *Chlamydomydia psittaci* (Cp) implicated in ocular adnexa MALT lymphoma:
 - Cp infection identified in small percentage of patients with Sjögren syndrome developing lymphoma, suggesting its possible role in development of salivary gland lymphoma in patients with Sjögren syndrome

Pathology

- Characteristics include:
 - Occurs in setting of LESA with residual histologic evidence of LESA, including lymphoepithelial lesions
 - Nodular or diffuse (confluent) cellular infiltrate with partial or total effacement of normal lobular architecture:
 - Separate tumor foci may be seen.
 - Presence of “halo” formation surrounding lymphoepithelial lesions distorting or effacing salivary gland parenchyma:
 - Monocytoid and centrocyte-like cells coalesce and surround lymphoepithelial lesions
 - Represents early change
 - May link several or multiple lymphoepithelial lesions
 - Normal lobular architecture altered with replacement of acini and ducts and invasion of the neoplastic cells into surrounding structures
 - Heterogeneous B-cell infiltrate present including:
 - Sheets of lymphoid cells, monomorphic, medium-sized cells with abundant, pale cytoplasm and bland, uniform nuclei, and distinct cell membranes
 - Atypical small lymphocytes
 - Centrocyte-like (cleaved) cells
 - Monocytoid B-cells
 - Immunoblasts
 - Lymphoplasmacytic cells
 - Plasma cells:
 - May be numerous
 - May show intranuclear inclusions (Dutcher bodies) or intracytoplasmic PAS-positive immunoglobulin crystals can be seen.
 - Reactive germinal centers
 - Clusters of epithelioid histiocytes may be present around lymphoepithelial lesions.
 - Ductal dilatation creating a cystic or multicystic appearance not infrequently seen:
 - Presence of cysts vary in size from small to greater than 0.5 cm.
 - Amyloid deposition rarely may be present.
 - Transformation to higher grade lymphoma, usually DLBCL, may occur.
- Immunophenotype (recapitulates that of marginal zone cells)
 - Express CD20, CD79a, CD21, and CD35
 - CD5, CD23, CD10, and cyclin D1 negative
 - Aberrant coexpression of CD43 may be present in approximately 50% of cases:
 - Indicative of neoplastic phenotype
 - Immunoglobulin light chain restriction:
 - Typically IgM; less often IgA or IgG; IgD negative
 - Expressed by lymphocytes and monocytoid B cells, and usually plasma cells
 - Bcl-2 positive (but absent in reactive germinal center cells)
 - Nonreactive for T-cell markers
 - Cytokeratin immunoreactivity limited to lymphoepithelial lesions:
 - May be of assistance in cases where lymphoepithelial lesions are overrun and obscured by lymphoid cells.
- Cytogenetic and molecular genetics:
 - Of chromosomal translocations strongly associated with marginal zone lymphoma, only t(14;18) involving *IgH* and *MALT1* fusion present in proportion of cases ranging from 0 to 18%
 - Other translocations strongly associated with marginal zone lymphoma not seen in salivary gland include:
 - t(11;18) involving *AP1* and *MALT1*; translocation most frequently present in gastric (and lung) MALT lymphoma
 - t(1;14) involving *BCL10* and *IGH*
 - t(3;14) involving *FOXP1* and *IGH*
 - Clonality by itself is insufficient to diagnose lymphoma in setting of LESA as monoclonality in LESA does not necessarily predict clinical or morphologic evidence of lymphoma
 - Nonlymphomatous monoclonal lesions might be considered borderline lesions.
 - Chromosomal abnormalities, including trisomies 3 and 18

Differential Diagnosis

- Lymphoepithelial sialadenitis (LESA):
 - Absence of “halo” formation formed by coalescence of monocytoid and centrocyte-like cells around lymphoepithelial islands, retention of normal salivary gland lobular architecture, absence of increased plasma cells with or without Dutcher bodies assists in differentiating LESA from MALT lymphoma
- Chronic sialadenitis
- HIV-associated salivary gland disease

- Mantle cell lymphoma:
 - Less heterogeneous population of atypical lymphoid cells as compared with EMZBCL
 - CD5, CD43, and cyclin D1 immunoreactivity contrast immunoreactivity of EMZBCL
- Other low-grade lymphomas:
 - Follicular lymphoma:
 - May present diagnostic difficulties with MALT lymphoma when there is follicular colonization
 - CD10, bcl-6, and bcl-2 immunoreactivity contrasts with immunoreactivity of MALT lymphoma
 - In presence of follicular colonization marginal zone neoplastic cells are bcl-2 negative.
- Most often occurs in parotid gland (approximately 75% of all cases)
 - Less often, submandibular gland involvement occurs (from 17% to 20% of cases).
- Majority arise de novo:
 - Some patients may have history of Sjögren syndrome.
 - Rare patients have history of Sjögren syndrome and hepatitis C (HCV) infection.
- Patients present with painless swelling of affected gland(s).
 - Mass is nontender, firm, and often fixed to adjacent tissues.
 - Pain and tenderness uncommonly occur.
- Increased incidence in patients with immunodeficient conditions:
 - Epstein-Barr virus identified in some of these lymphomas

Treatment and Prognosis

- Local therapy including surgery or radiotherapy
- Survival rates include:
 - 5-year survival of 85% to 90%
 - 15-year relative survival was 78.4%
- Relatively indolent behavior usually remains localized:
 - Majority are Ann Arbor stage IE or IIE disease:
 - 54% IE
 - 19% IIE
 - 10% IIIE/IV
 - Relapses not uncommon and may involve:
 - Primary site lymph nodes, especially cervical neck, and extranodal sites
 - Relapses can be treated successfully.
 - Dissemination is slow to occur and may involve cervical lymph nodes and other mucosal sites.
 - Excellent prognosis for low-grade lymphoma with localized disease (IE)
 - Prognosis for nodal involvement (IIE) is similar to that of primary low-grade nodal-based NHL.
- MALT lymphomas may transform to DLBCL:
 - Occurs in approximately 12% of cases
 - Tumors tend to follow a more aggressive course, including death, but may have a more favorable prognosis than comparable nodal disease.

Diffuse Large B-Cell Lymphoma (DLBCL)

Clinical

- Represents approximately 10% of salivary gland PML
- Slight female predilection; wide age distribution but, in general, tendency to occur in elderly people with mean age in mid-seventh decade of life

Pathology

Gross

- Circumscribed to ill-defined and infiltrative lesion
- Cut surface appears tan-white to yellow-tan with a homogeneous (“fish-flesh”) appearance and firm consistency.

Histology

- Characterized by:
 - Diffuse replacement of salivary gland tissue with effacement of the normal lobular architecture:
 - Lymphoma cells infiltrate and replace acini and ducts.
 - Infiltration into adjacent connective tissue structures seen that may include perineural invasion
 - Extraglandular spread into surrounding periglandular soft tissues occurs.
 - Neoplastic cells are large with round to oval enlarged nuclei, vesicular chromatin, and prominent eosinophilic nucleoli.
 - Lymphoepithelial islands (LEIs) not seen
 - Immunophenotype:
 - Express CD45 and various pan-B markers including CD20, CD79a, PAX5
 - CD20 lost in 60% of recurrent tumors treated with rituximab
 - Monotypic surface or cytoplasmic immunoglobulin frequently seen (IgM > IgG > IgA)
 - Melanoma-associated antigen (MIM1) expression (nuclear staining)
 - BCL6 expression in approximately 60%
 - CD10 expression in 20% to 40%
 - CD5 expression in approximately 10%
 - CD30 expression in approximately 10%

- BCL6 expression in approximately 50%
- Ki67 index >20% (mean 55%)
- May be p63 positive
- Cytogenetic and molecular genetics:
 - Clonal rearranged immunoglobulin heavy- and light-chain genes
 - Rearranged germline T-cell receptor (TCR) genes
- Small number of cases of DLBCL have a component of marginal zone lymphoma
 - Likely represent transformation of MALT lymphoma to DLBCL
 - Associated with more aggressive behavior

Differential Diagnosis

- Lymphoepithelial sialadenitis (LESA)
- IgG-related sialadenitis
- Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
- Carcinoma (undifferentiated, others):
 - Immunoreactivity for epithelial markers (cytokeratins, others) and absence of immunoreactivity for hematolymphoid markers allow for differentiation.

Treatment and Prognosis

- Treatment and prognosis similar to histologically identical lymphomas of lymph nodes:
 - Treatment may include combination of surgical resection, radiotherapy, and chemotherapy.
- Most patients have localized disease.

Other Types of Salivary Gland Non-Hodgkin Lymphomas

- Other types of NHLs may involve salivary glands, including:
 - Follicular lymphoma:
 - In different studies varies from second most common (to MALT lymphoma) or third most common (to MALT lymphoma and DLBCL) type of salivary gland lymphoma
 - Mantle cell lymphoma, anaplastic large cell lymphoma, extranodal NK/T cell lymphoma of nasal type, and peripheral T-cell lymphoma

Hodgkin Lymphomas of Salivary Glands

- Primary involvement of salivary glands by Hodgkin lymphoma is rare.
- Classical and nodular lymphocyte predominant type
- Majority occurs in parotid gland and likely represents secondary spread from nodal-based disease.

SARCOMAS OF SALIVARY GLANDS

Clinical

- Sarcomas of salivary glands are extremely uncommon, accounting for less than 2% of all malignant salivary gland tumors and approximately 0.5% of all salivary gland tumors.
- This category excludes carcinosarcoma (previously discussed under Malignant Mixed Tumors).
- Sarcomas of salivary glands tend to occur in older-aged patients.
- Most sarcomas involve the parotid gland.
- Presentation includes mass or swelling with or without pain and/or facial nerve paralysis; a rapidly enlarging mass occurs in a minority of patients.
- Virtually all sarcoma types have been reported to occur in salivary glands; more common types include:
 - Malignant peripheral nerve sheath tumor
 - Fibrosarcoma
 - Undifferentiated pleomorphic sarcoma
 - Rhabdomyosarcoma
 - Angiosarcoma
 - Synovial sarcoma
 - Leiomyosarcoma
 - Kaposi sarcoma:
 - Often occurs in HIV-positive patients
 - Develop in the parotid gland or intra- or periparotid lymph nodes
 - Liposarcoma
 - Alveolar soft part sarcoma
 - Others:
 - Recently rare case of adamantinoma-like Ewing sarcoma reported as primary parotid neoplasm:
 - *EWSR1* and *FLI1* fluorescence in situ hybridization confirmed presence of translocation supporting diagnosis
 - *EWSR1* identified in salivary gland hyalinizing clear cell carcinoma
- Prior to diagnosis of a primary sarcoma of salivary glands, clinical evaluation indicated to:
 - Exclude a history of a histologically similar sarcoma of a separate and/or adjacent (e.g, soft tissues of neck) primary site
 - Exclude metastasis to involved salivary gland from a separate primary site or direct invasion into the salivary gland from an adjacent primary site
 - Confirm origin from within the involved salivary gland
- Diagnosis and differential diagnosis based on light microscopic features often requiring adjunct studies, including histochemistry, immunohistochemistry,

electron microscopy, cytogenetics to confirm the diagnosis

- Depending on tumor type the differential diagnosis may include (but is not limited to) carcinomas (especially in those sarcomas with epithelioid features) and malignant melanoma.
- Treatment usually requires complete surgical resection combined with radiation and chemotherapy.
- Because sarcomas are more likely to spread hematogenously rather than via lymphatic channels, unless there is clinical evidence of neck disease, cervical (nodal) neck dissection would not appear to be warranted.
- Prognosis is dependent on a variety of factors including:
 - Stage of disease
 - Tumor size
 - Sarcoma type
 - Histologic grade
- Recurrence occurs from 40% to 64% of patients:
 - Most recurrences occur within 1 year following treatment.
- Distant metastases occur in 40% to 64% of patients.
- Tumor-related death ranges from 36% to 64%.
- Overall 5-year and 10-year survival rates of 42% and 20%, respectively

SECONDARY TUMORS

Definition: Salivary gland involvement by malignant tumor originating from separate primary site that has spread to involved salivary gland by direct invasion from an adjacent site or via hematogenous or lymphatic spread from a distant site.

Clinical

- Metastatic disease to salivary glands uncommon, representing approximately 5% of all malignant salivary gland tumors.
- Much more common in men than in women; peak incidence is in the seventh to eighth decades of life although may occur in any age group including the

very young (infants and children) and the very old (tenth decade and older).

- Majority of cases involve parotid gland, and to a lesser extent submandibular gland:
 - Metastases may occur to intraparotid lymph nodes and secondarily involve parotid parenchyma.
- Relative to parotid gland, the majority (80%) of secondary tumors originate from head and neck neoplasms.
- Relative to the submandibular gland, the majority (85%) of secondary tumors originate from distant sites.
- Most common secondary tumors involving salivary glands are cutaneous squamous cell carcinoma and malignant melanoma.
- For primary tumors that originate from distant (non-head and neck) sites, most common tumor types metastasizing to salivary glands are of lung (especially small cell neuroendocrine carcinoma), kidney, and breast origin:
 - In contrast to renal clear cell carcinoma, clear cell carcinomas of salivary glands are:
 - Nonreactive for renal cell carcinoma antibody, CD10, PAX2, PAX8, CAIX
 - Demonstrate presence of *EWSR1* translocation.
 - In rare examples of simultaneously occurring salivary duct carcinoma and primary mammary duct carcinoma differentiation can be problematic given overlapping histologic features and immunohistochemical staining:
 - Differentiation possible if primary breast cancer is histologically low grade as salivary duct carcinomas are histologically high grade

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Intraoperative Consultation in Salivary Glands and Biopsy

Diagnosis of Salivary Gland Neoplasms

INTRAOPERATIVE CONSULTATION IN SALIVARY GLANDS

General Considerations

(Figs. 21-1 through 21-12)

- Intraoperative consultation (i.e., frozen section) in salivary gland pathology presents unique diagnostic challenges.
- Majority of salivary gland neoplasms (approximately 80%) originate in parotid and submandibular glands:
 - Approximately 20% to 25% of neoplasms occurring in major salivary glands are malignant.
 - In parotid gland, most neoplasms arise in superficial lobe
- Majority of minor salivary gland neoplasms originate in the oral cavity:
 - 50% to 60% or greater of minor salivary gland tumors are malignant.
- Although any type of salivary gland neoplasm may occur in major and minor salivary glands, a number of salivary gland neoplasms predilect to major glands or to minor glands, including:
 - Predilection to major glands:
 - Warthin tumor (parotid gland)
 - Basal cell adenoma (parotid gland)
 - Oncocytoma (parotid gland)
 - Acinic cell carcinoma (parotid gland)
 - Mammary analogue secretory carcinoma (parotid gland)
 - Basal cell adenocarcinoma (parotid gland)
 - Epithelial-myoepithelial carcinoma (parotid gland)
 - Carcinoma ex pleomorphic adenoma (parotid gland)
 - Salivary duct carcinoma (parotid gland)
 - Oncocytic carcinoma (parotid gland)
 - Others
 - Predilection to minor glands:
 - Canalicular adenoma (lip)
 - Cystadenoma (oral cavity)
 - Polymorphous low-grade adenocarcinoma (palate)
 - Clear cell carcinomas (oral)
 - Cribriform adenocarcinoma of minor salivary glands (base of tongue, oral)
- Major and minor salivary gland neoplasms share similar morphologic features but contrast in other ways that must be considered in their frozen section evaluation:
 - Majority of major salivary gland neoplasms are encapsulated, in part or completely:
 - Major salivary gland benign neoplasms are circumscribed to encapsulated, lacking invasive growth and cytomorphologic features of malignancy:
 - Some benign neoplasms may be multinodular with nodules separate from one another (e.g., pleomorphic adenoma, basal cell adenoma, canalicular adenoma, Warthin tumor).
 - Some benign neoplasms may include foci within soft tissues, in particular recurrent pleomorphic adenomas.
 - Major salivary gland malignant neoplasms show cytomorphologic features of malignancy and/or invasive growth:
 - Cytomorphologically bland-appearing neoplasms may be malignant on the basis of infiltrative growth:
 - ◻ Examples include adenoid cystic carcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, others.
 - Noninvasive neoplasms may be malignant on the basis of identifying specific cell types or the presence of anaplastic cellular features:
 - ◻ Examples of neoplasms with specific cell types diagnostic for malignancy include mucoepidermoid carcinoma, acinic cell carcinoma, others.
 - ◻ Examples of neoplasms with anaplastic cellular features diagnostic for malignancy

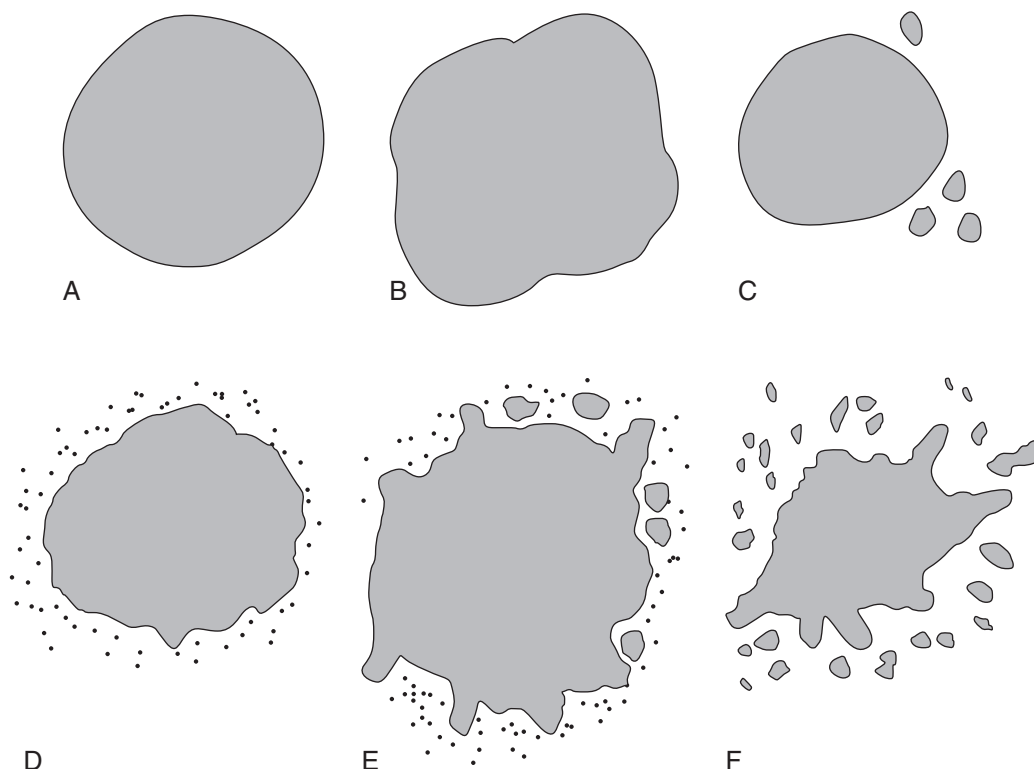


Fig. 21-1. Configuration of benign and malignant salivary gland neoplasms.

Schematic representation of the gross appearance of the configurations of benign (**A** through **C**) and malignant (**D** through **F**) salivary gland neoplasms. The peripheral appearance of benign salivary gland neoplasms is often (**A**) encapsulated to circumscribed with smooth contours; (**B**) lobulated, as may be seen in pleomorphic adenomas; (**C**) multinodular or multifocal, including satellite nodules, as may be seen in pleomorphic adenoma (de novo or recurrent) or monomorphic adenomas, including but not limited to basal cell adenoma, membranous type, or canalicular adenoma. The peripheral appearance of malignant salivary gland neoplasms often includes infiltrative pattern of growth with varying appearances as depicted in **D** through **F**. Ultimately, histologic confirmation of invasion is required and in the presence of invasion the neoplasm is malignant. (Adapted from Ranchod M, Chan JKC, Eisele DW: *Salivary glands*. In Ranchod M, editor: *Intraoperative consultation in surgical pathology*, New York, 2010, Cambridge University Press.)

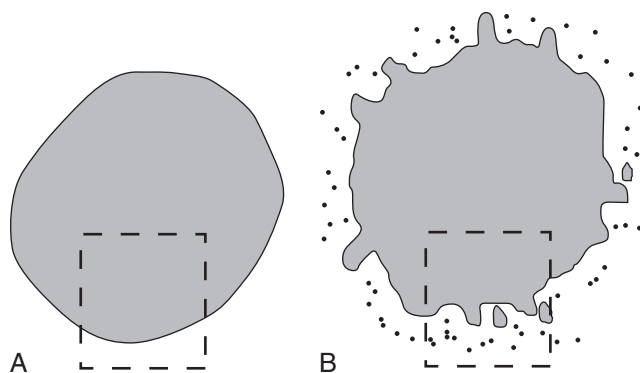


Fig. 21-2. Appropriate sectioning of salivary gland neoplasms.

Schematic representation of proper sampling of salivary gland neoplasms. Whether a given tumor has the peripheral appearance of (**A**) benignancy (smooth contour) or (**B**) malignancy (infiltrative pattern), sectioning as depicted in the illustration should include the interface between the tumor, its periphery, and the surrounding normal tissue. (Adapted from Ranchod M, Chan JKC, Eisele DW: *Salivary glands*. In Ranchod M, editor: *Intraoperative consultation in surgical pathology*, New York, 2010, Cambridge University Press.)

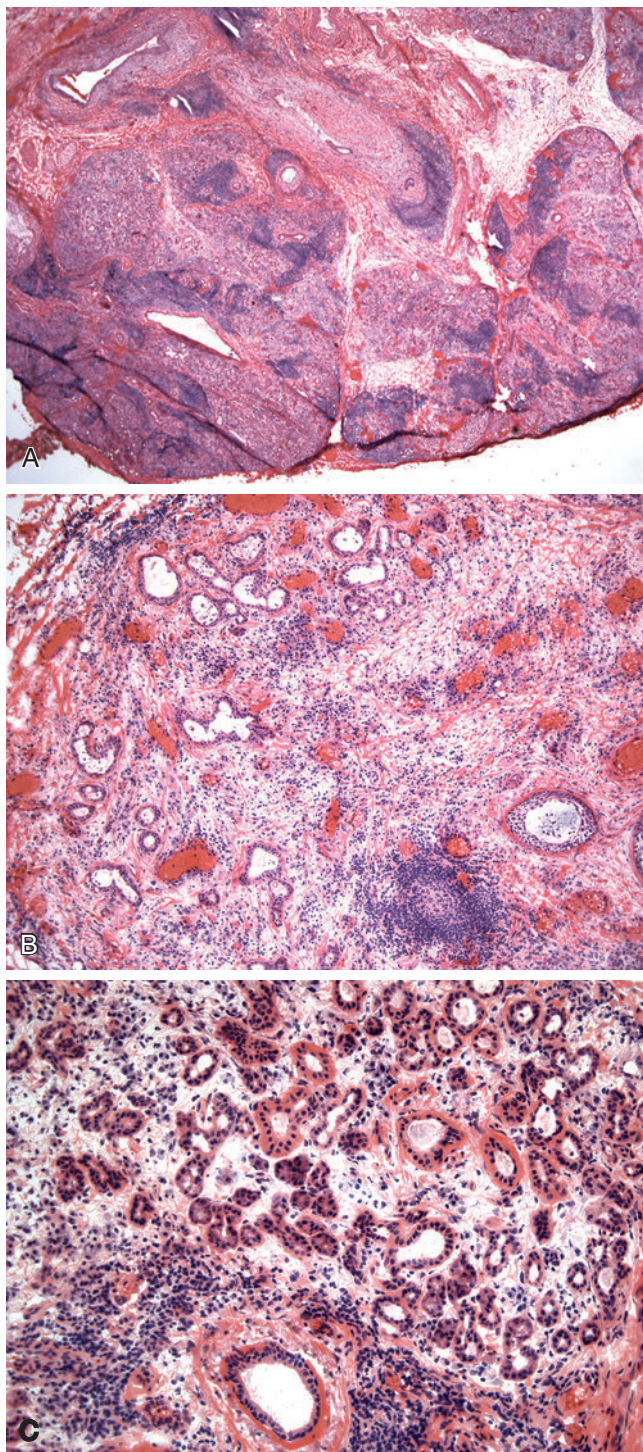


Fig. 21-3. Chronic sialadenitis.

Intraoperative consultation, chronic sialadenitis, parotid gland. **A**, At low magnification the normal lobular architecture of the parotid gland is preserved.

B, Inflammatory cell infiltrate including a lymphoid aggregate with edema, fibrosis, scattered identifiable ducts, and acinar cell atrophy. **C**, Higher magnification shows areas with preservation of parenchymal components with associated lymphoid cell infiltrate.

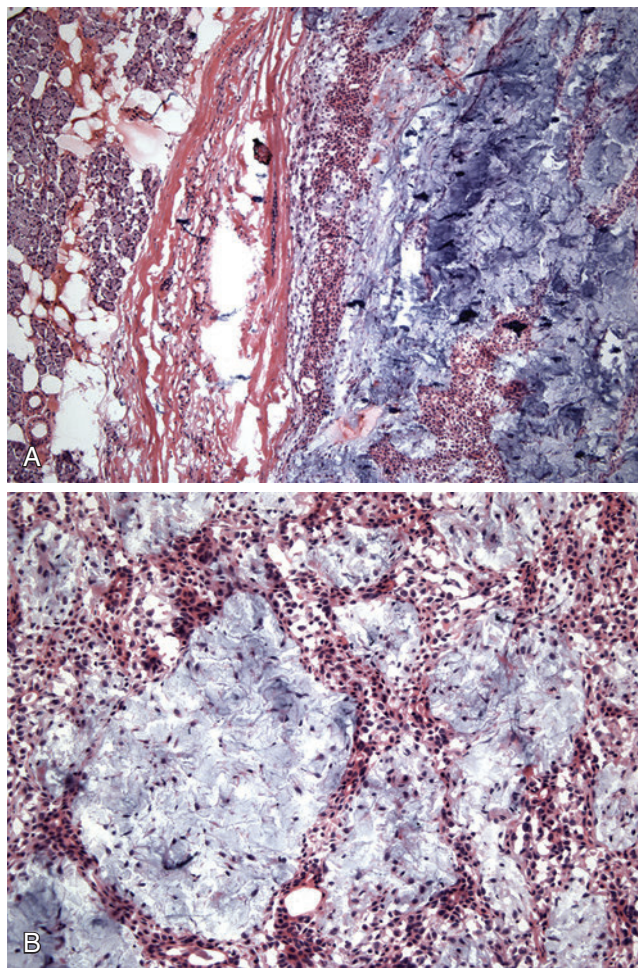


Fig. 21-4. Pleomorphic adenoma.

Intraoperative consultation, pleomorphic adenoma, parotid gland. **A**, Encapsulated tumor separated from adjacent parotid gland (*left*) composed of an admixture of epithelial and chondromyxoid-appearing stroma. **B**, Combination of epithelial cells (glands), myoepithelial cells (spindle and plasmacytoid cells), and chondromyxoid stroma.

include all salivary gland neoplasms composed of histologically high-grade cytomorphology, including salivary duct carcinoma, high-grade carcinoma ex pleomorphic adenoma, high-grade adenocarcinoma, not otherwise specified and high-grade transformation (“dedifferentiation”) of lower grade salivary gland neoplasms.

- All minor salivary gland neoplasms are unencapsulated:
 - Benign minor salivary gland neoplasms are circumscribed without invasive growth.
 - Benign minor salivary gland neoplasms may be multinodular with nodules separate from

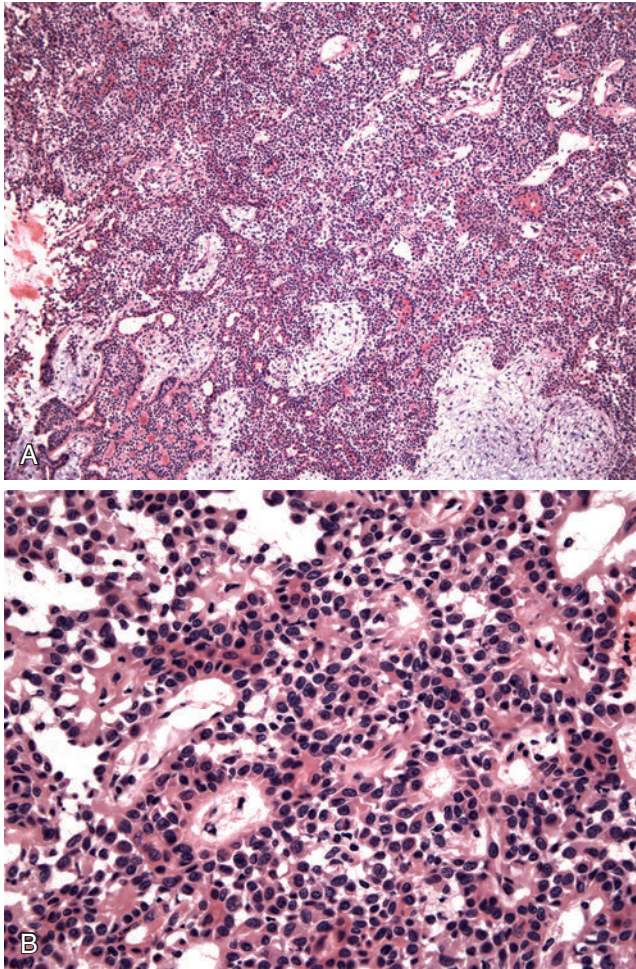


Fig. 21-5. Cellular pleomorphic adenoma.

Intraoperative consultation, cellular pleomorphic adenoma, parotid gland. **A**, This was an encapsulated cellular tumor in which residual foci of chondromyxoid stroma was present (*bottom*). **B**, At higher magnification the cellular components include epithelial (glands) and myoepithelial (plasmacytoid) cells.

- one another (e.g., pleomorphic adenoma, basal cell adenoma, canalicular adenoma).
- Some benign neoplasms may include foci within soft tissues, in particular recurrent pleomorphic adenomas.
- Minor salivary gland malignant neoplasms show cytomorphic features of malignancy and/or invasive growth.
- Cytomorphologically bland-appearing neoplasms may be malignant on the basis of infiltrative growth:
 - Examples include adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, clear cell carcinomas, others.

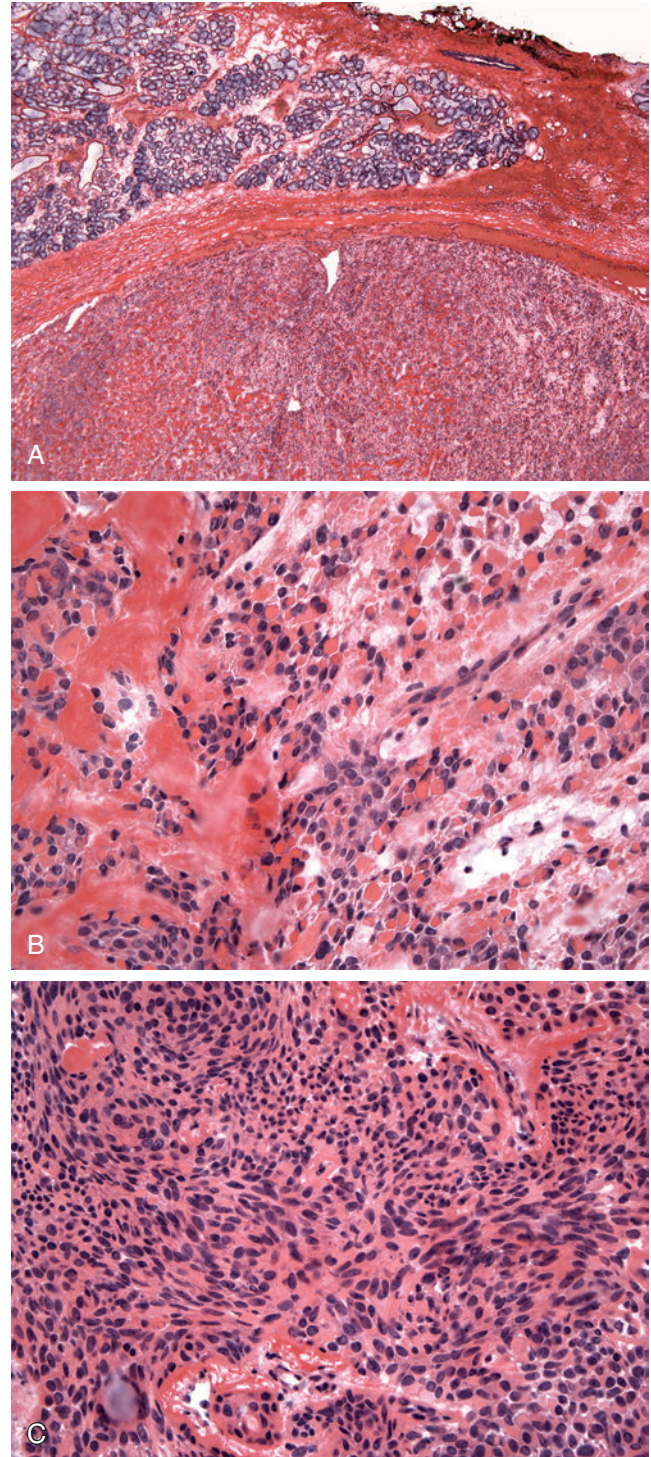


Fig. 21-6. Myoepithelial-predominant PA.

Intraoperative consultation, myoepithelial-predominant pleomorphic adenoma (PA), palate. **A**, Cellular mass that was circumscribed but unencapsulated; residual areas of chondromyxoid stroma (not shown) were present. **B**, Plasmacytoid myoepithelial cells. **C**, Spindle-shaped myoepithelial cells.

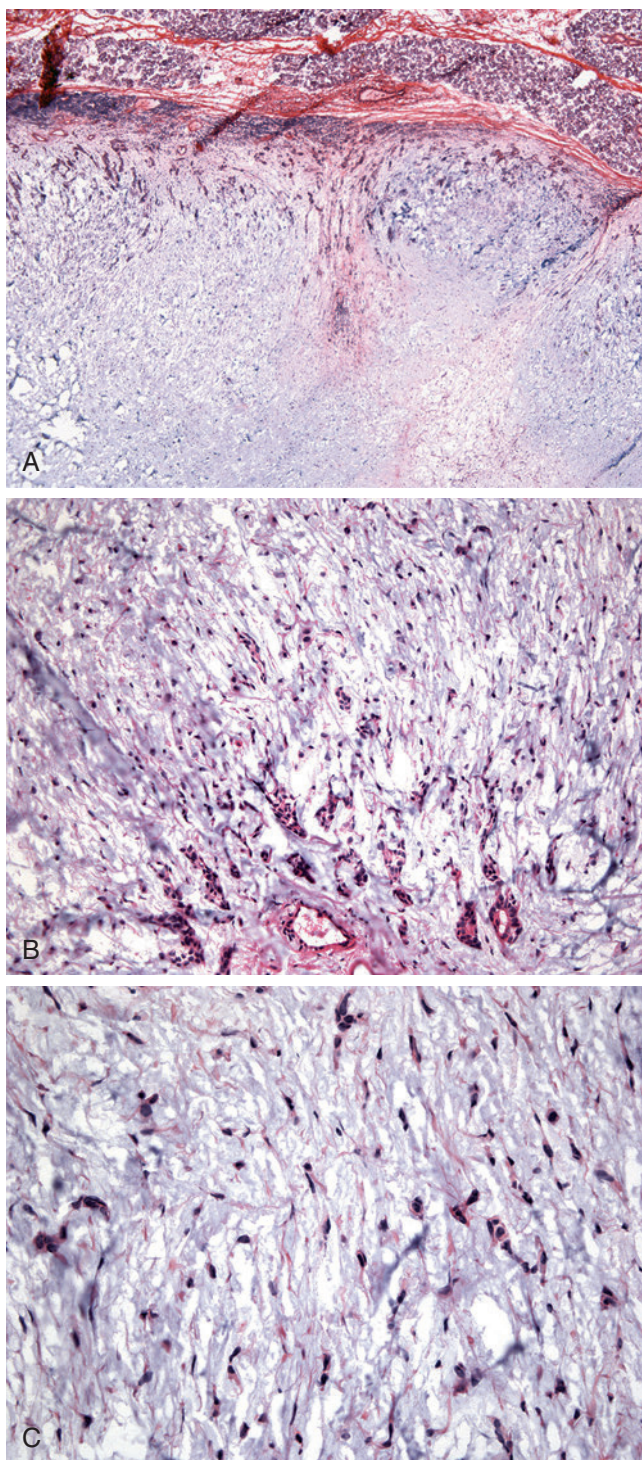


Fig. 21-7. Recurrent pleomorphic adenoma.

Intraoperative consultation, recurrent chondromyxoid-predominant pleomorphic adenoma, parotid gland.

A, Encapsulated tumor separated from adjacent parotid gland (*left*) composed predominantly of chondromyxoid stroma; admixture of epithelial and chondromyxoid-appearing stroma. **B,** Scattered cellular components within the dominant chondromyxoid stroma include epithelial (glands) and myoepithelial (spindle-shaped) cells. **C,** At higher magnification spindle-shaped myoepithelial cells are seen.

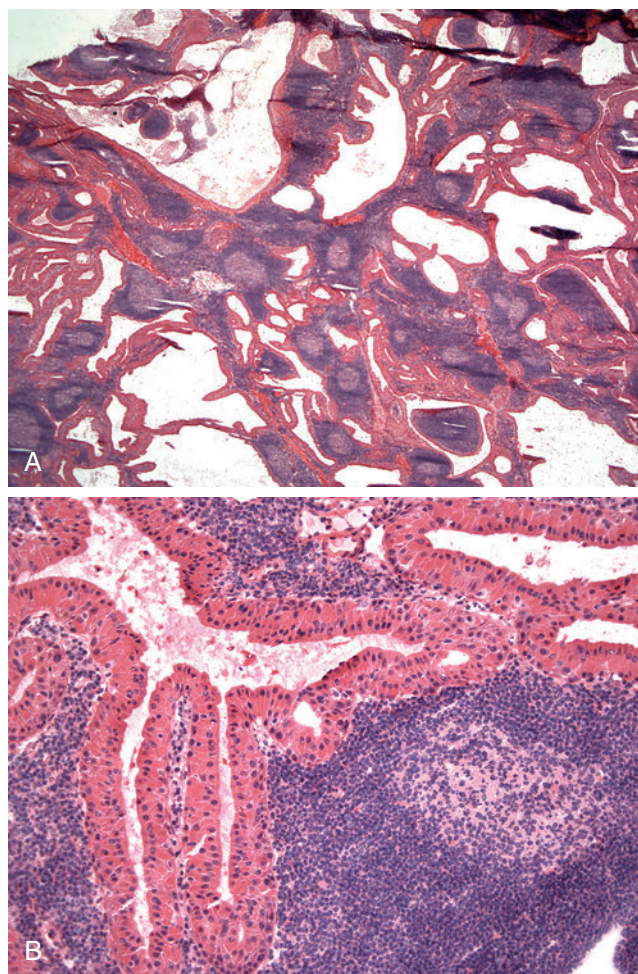


Fig. 21-8. Intraoperative consultation, Warthin tumor, parotid gland.

Classic combination of papillary and cystic growth with dense lymphoid cell infiltrate and oncocytic epithelial cells.

- Noninvasive neoplasms may be malignant on the basis of identifying specific cell types or the presence of anaplastic cellular features:
 - Examples of neoplasms with specific cell types diagnostic for malignancy include mucoepidermoid carcinoma, others.
 - Examples of neoplasms with anaplastic cellular features diagnostic for malignancy include all salivary gland neoplasms composed of histologically high-grade cytormorphology, including salivary duct carcinoma; high-grade carcinoma ex pleomorphic adenoma; high-grade adeno-carcinoma, not otherwise specified and high-grade transformation (“dedifferentiation”) of lower grade salivary gland neoplasms.

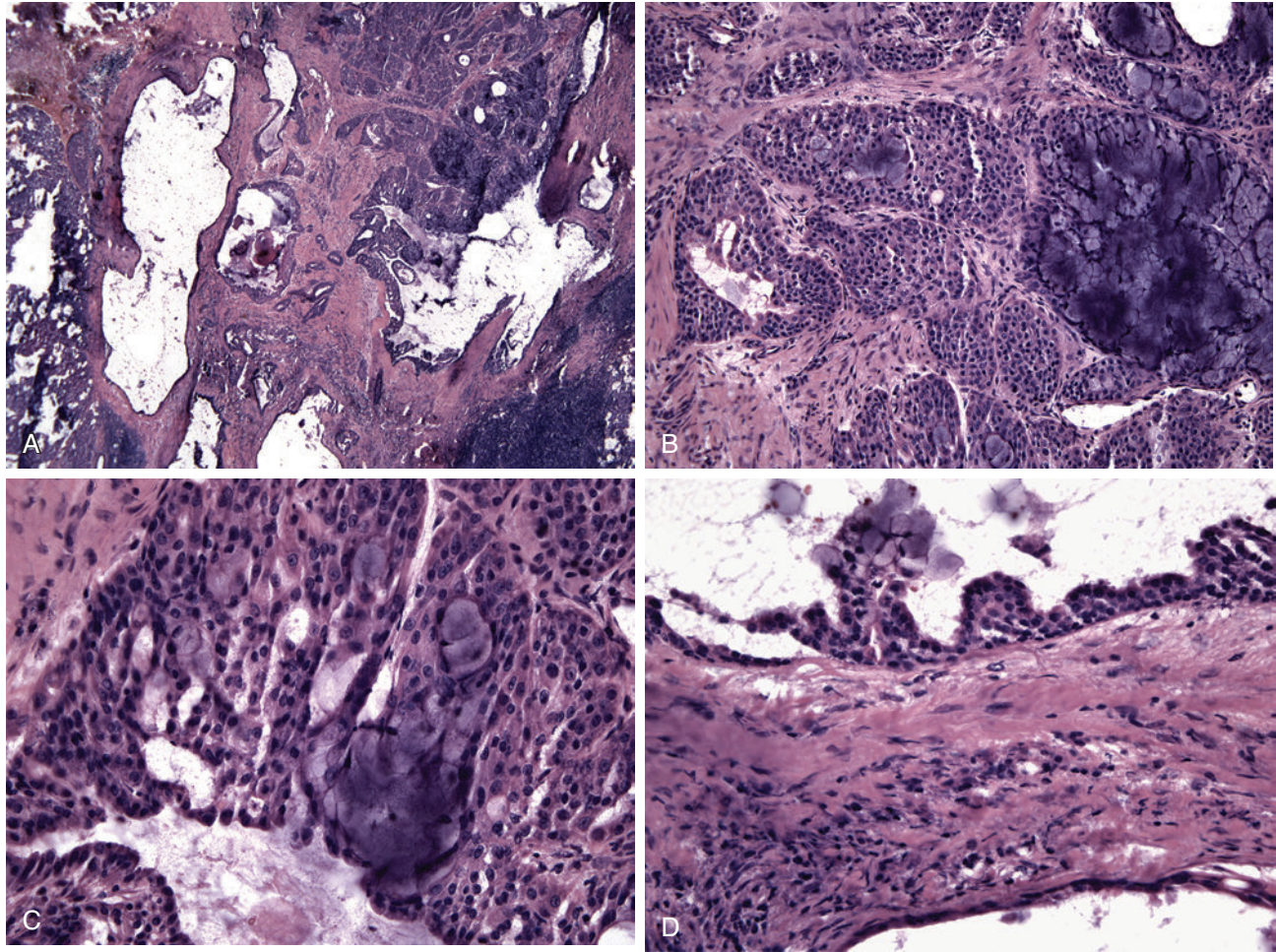


Fig. 21-9. Mucoepidermoid carcinoma, low-grade.

Intraoperative consultation, low-grade mucoepidermoid carcinoma, parotid gland. **A**, At low magnification there is an infiltrative parotid tumor composed of cystic and solid foci. **B** and **C**, Solid foci are composed of a combination of epidermoid cells and mucocytes. **D**, Cysts are also lined by an admixture of epidermoid and mucous cells although attenuated (flattened) epithelium is seen lining the cyst at the bottom. Presence of thickened (proliferative) cellular foci with admixture of cell types should allow for discrimination between low-grade mucoepidermoid carcinoma and benign cystic lesions such as salivary duct cyst with squamous and mucous cell metaplasia.

Indications for Intraoperative Consultation in Salivary Gland Neoplasms

Major Glands

- Indications for intraoperative consultation in major salivary gland neoplasms include:
 - To render a diagnosis (determine tumor type), which may include:
 - Cases in which there has been an equivocal or inconclusive diagnosis by fine-needle aspiration biopsy (FNAB) or core biopsy
 - Cases in which a prior diagnostic procedure (e.g., FNAB, biopsy) has not been attempted
 - To evaluate surgical margins of resection for adequacy of resection:
 - May include measuring distance between tumor and surgical margin(s)
 - To determine if lymph node metastases are present:
 - Identification of nodal metastasis may result in more extensive neck dissection.
 - High-grade malignant salivary gland neoplasms have increased incidence of nodal metastasis at presentation, including:
 - High-grade mucoepidermoid carcinoma, salivary duct carcinoma, others

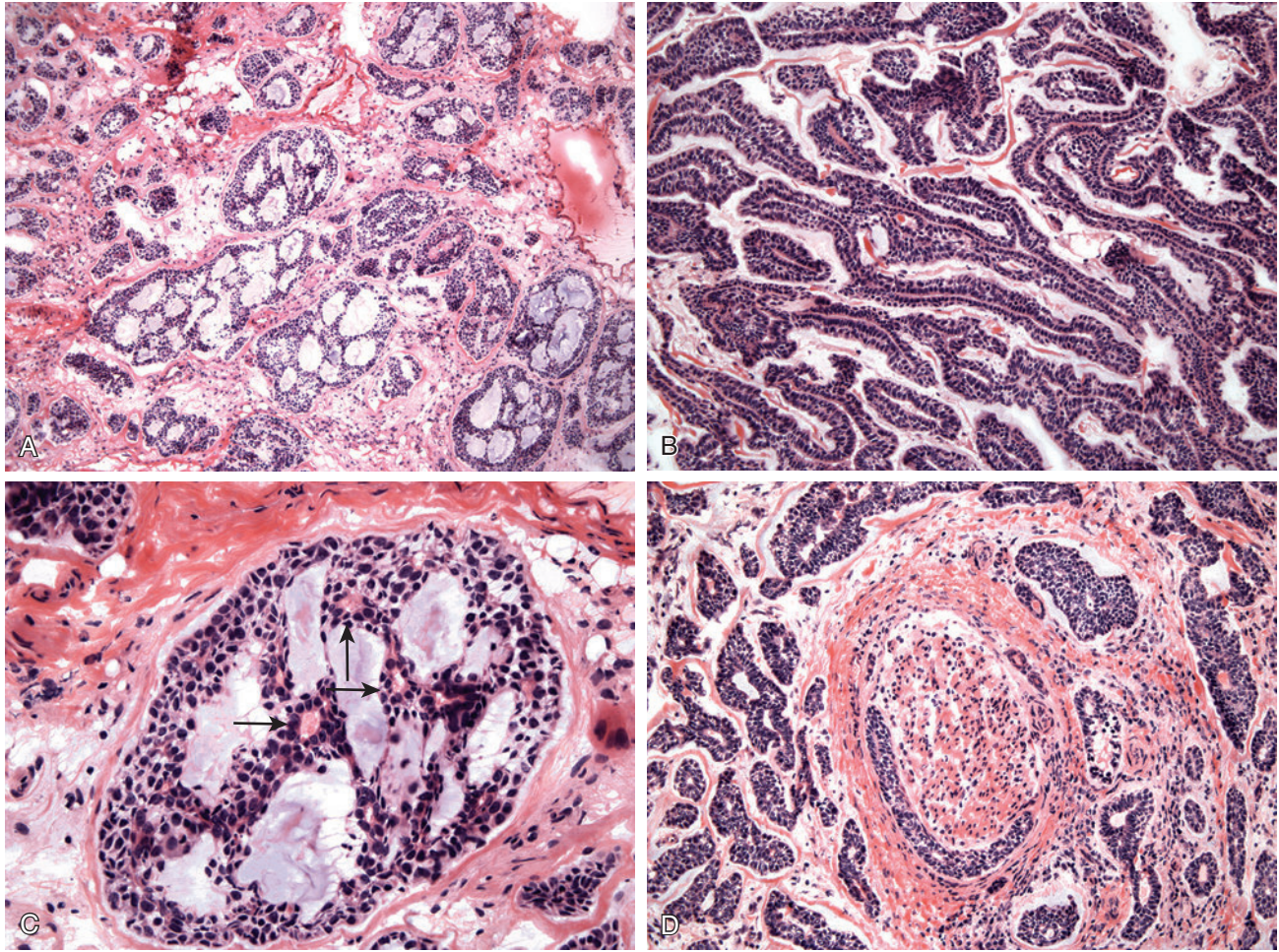


Fig. 21-10. Adenoid cystic carcinoma.

Intraoperative consultation, adenoid cystic carcinoma. **A**, Polymorphic growth, including characteristic cribriform pattern as well as foci showing tubular growth. **B**, Area showing trabecular and canalicular growth patterns. Such findings in intraoral lesions would be reminiscent of canalicular adenoma. **C**, Cribriform areas include pseudocysts filled with mucinous material and surrounded by the dominant abluminal (myoepithelial) cells with small but identifiable true glands (arrows) lined by epithelial cells showing eosinophilic cytoplasm. **D**, Neurotropism would be diagnostic for malignancy that, in combination with cribriform growth and cell types, is diagnostic for adenoid cystic carcinoma.

- To obtain tissue for ancillary studies; examples may include:
 - Lymphoma evaluation
 - Cytogenetic evaluation
 - Less commonly, ultrastructural evaluation

Minor Glands

- Indications for intraoperative consultation in minor salivary gland tumors include:
 - To render a diagnosis (determine tumor type), which may include:
 - Cases in which there has been an equivocal or inconclusive diagnosis by fine-needle aspiration biopsy (FNAB) or core biopsy

- Cases in which a prior diagnostic procedure (e.g., FNAB, biopsy) has not been attempted
- To evaluate surgical margins of resection
- To try to determine the presence of perineural invasion:
 - Involvement of palatine nerves from pterygo-palatine fossa is generally determined pre-operatively by radiographic imaging studies.
- To determine osseous involvement that may necessitate resection of bone (palatine bone or maxilla)
- Usually lymph node dissection is not performed for intraoral minor salivary gland neoplasms

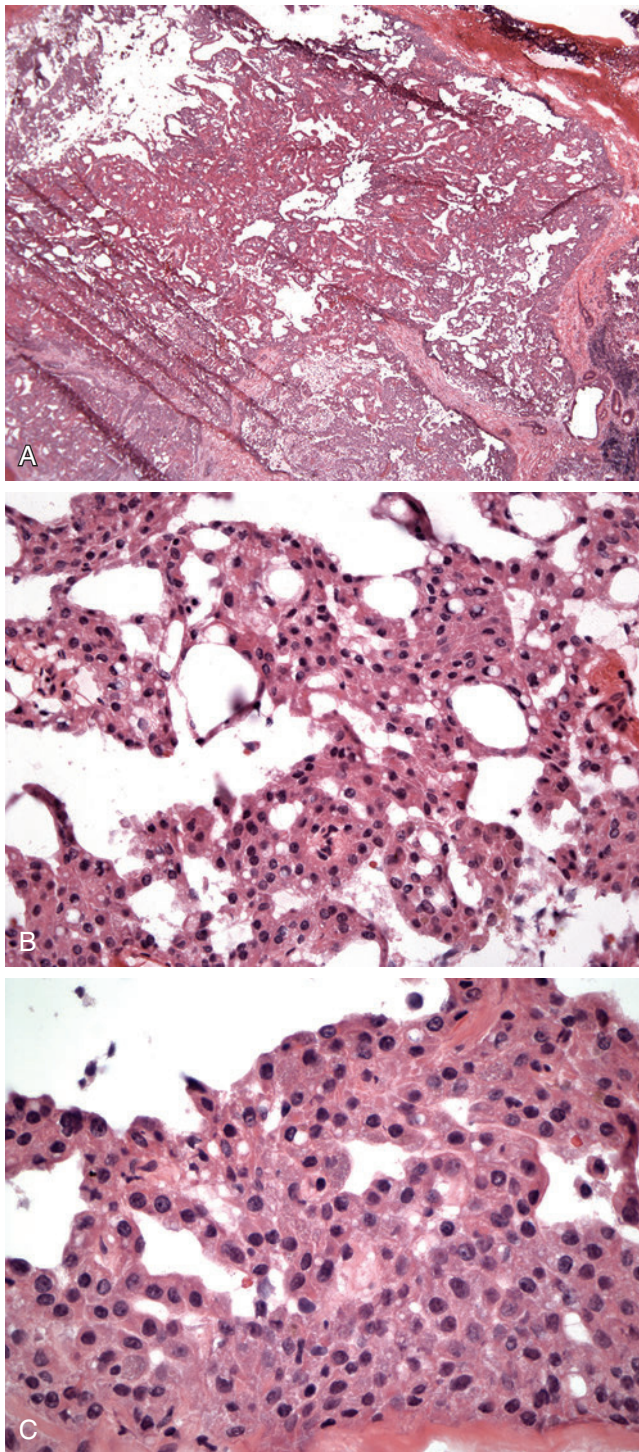


Fig. 21-11. Acinic cell adenocarcinoma.

Intraoperative consultation, acinic cell adenocarcinoma, parotid gland. **A**, Residual parotid gland (*extreme right*) is infiltrated by tumor showing solid, cystic, and papillary architectures. **B**, Microcystic growth composed of a cellular proliferation that includes vacuolated cells; such cells are common in acinic cell carcinoma but not uniquely seen in acinic cell carcinoma. **C**, Diagnostic acinar cells showing intracytoplasmic basophilic granules as well as scattered vacuolated cells.

unless there is preoperative diagnosis of a high-grade malignancy.

- If lymph nodes are excised, then a frozen section may be requested to exclude the presence of metastatic disease.
 - Identification of nodal metastasis may result in more extensive neck dissection.
- To obtain tissue for ancillary studies; examples may include:
 - Lymphoma evaluation
 - Cytogenetic evaluation
 - Less commonly, ultrastructural evaluation

Surgeon's Expectations of the Intraoperative Assessment of Salivary Gland Neoplasms

Major Glands

- Surgeon's expectations at the time of intraoperative consultation include:
 - Distinguish between benign and malignant neoplasms
 - Determine specific type and/or histologic grade of malignancy
 - Assess adequacy of the surgical margins
 - Assess for perineural invasion
- All of the above aid surgeon in deciding extent of surgical resection.

Minor Salivary Gland Tumors

- Surgeon's expectations at the time of intraoperative consultation include:
 - Distinguish between benign and malignant neoplasms
 - Determine specific type and/or histologic grade of malignancy
 - In particular, adenoid cystic carcinoma that may necessitate a wider resection to achieve tumor-free margins
 - Assess adequacy of resection margins and possible extent of disease:
 - Margins for minor salivary gland tumors are similar to those for other mucosal lesions and include the depth and circumferential excision lines.
 - Osseous involvement necessitates resection of the involved bone.
- In the oral cavity, the surgeon must consider the possibility of resecting the lesion with a modest margin.
- Additional surgical treatment can be accomplished immediately if frozen section finding indicates the need.
- As with intraoperative consultation of other body sites, frozen section diagnosis of minor salivary gland

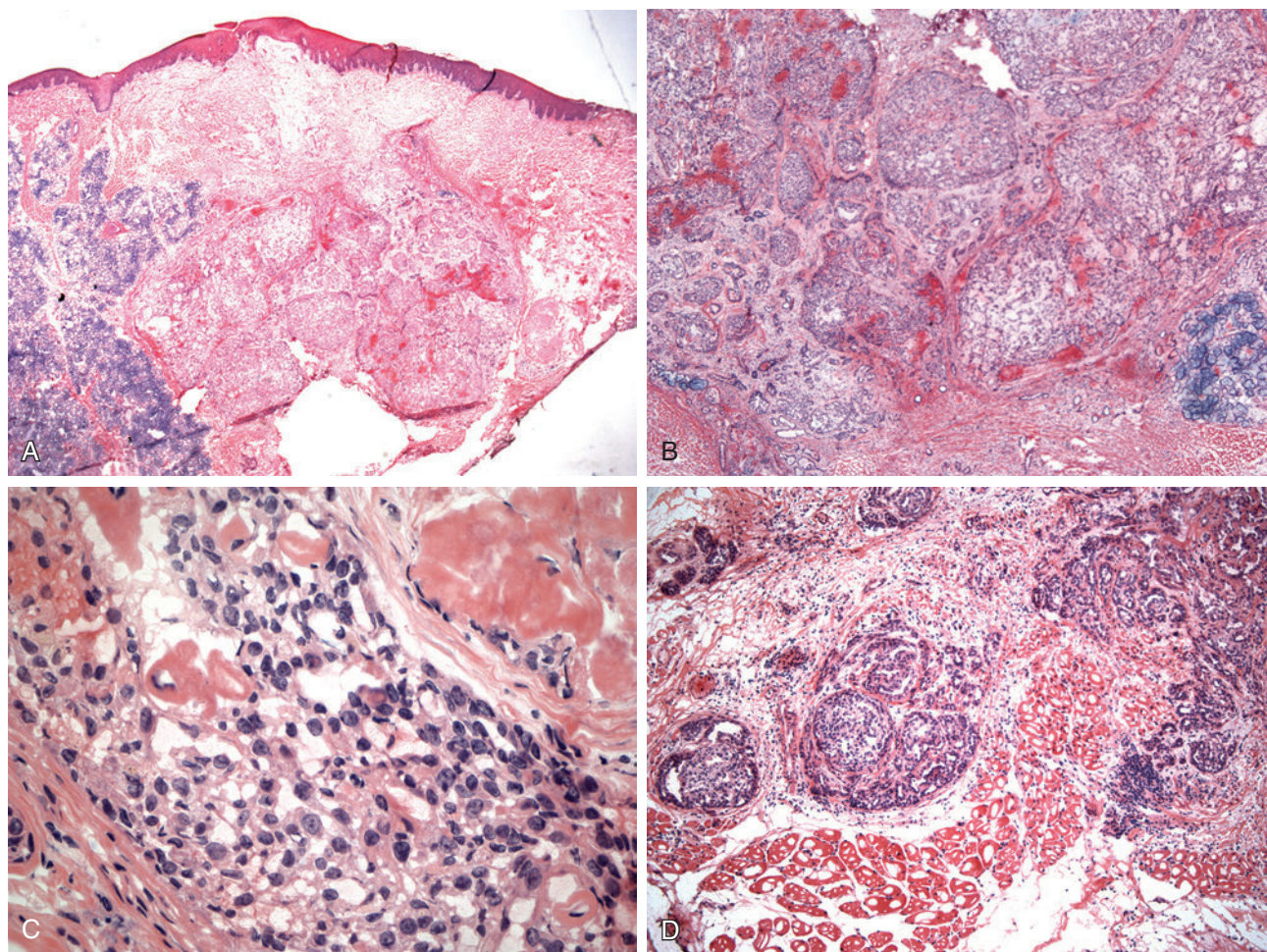


Fig. 21-12. Polymorphous low-grade adenocarcinoma.

Intraoperative consultation, polymorphous low-grade adenocarcinoma of the palate. **A**, Submucosal circumscribed cellular proliferation lying adjacent to seromucous glands and extending to the deep resection margin. **B**, The tumor shows variety of growth patterns, including solid nests, scattered tubules/ducts, and cribriform with a myxoid-appearing stroma; **C**, bland cytology with absence of significant pleomorphism and no mitoses; hyalinized stromal tissue is present. **D**, In its depth the tumor infiltrated soft tissues, including skeletal muscle, indicative of a malignant tumor that, in combination with growth patterns and cytomorphology, is diagnostic for polymorphous low-grade adenocarcinoma.

lesions requires close interaction between the surgeon and the pathologist.

Approach to Handling of Resected Tissue

Major Glands

- Majority of salivary gland tumors are located in parotid gland, in particular the superficial lobe, which is a common specimen at the time of intraoperative consultation, but the following are applicable for handling all specimen types:
 - Orient and ink the specimen.
 - Assess extent and location of tumor.
 - Determine if the tumor is within the confines of the glandular capsule or if it has infiltrated beyond the gland.
 - Assess whether the cut surface (glandular surgical margin) is involved by tumor.
 - Evaluation for facial nerve involvement:
 - Involvement of the facial nerve may be apparent preoperatively; however, facial nerve involvement may not be clinically apparent, which may result in frozen section evaluation for presence of facial nerve invasion.
 - Sampling of the facial nerve for frozen section evaluation usually is a very small tissue fragment and the entire nerve should be embedded for evaluation.

- Parotid “lobes” are only a designation of the portion of the gland that is superficial and deep to the facial nerve; there are no true “lobes” of the parotid gland.

Minor Glands

- Handling of intraoral minor salivary gland lesions is similar to other mucosal-based lesions.
- Careful gross examination of resection specimen is imperative.
- In the evaluation of salivary gland tumors in general the gross inspection of the resection specimen:
 - Should determine what is the relation between the lesion and the adjacent tissues
 - Sections submitted for frozen section should show this relationship.
 - The tissue sample should be taken to include the junction of the tumor and surrounding tissues, not just from the center of the lesion, allowing for evaluation of the relationship of the tumor to surrounding structures.
 - The frozen section should be taken between the tumor and the closest line of excision, which allows for determining how far the tumor is from the surgical resection margin.

For Major and Minor Glands

- Gross appearance (Fig. 21-1):
 - Benign salivary gland neoplasms tend to be circumscribed to encapsulated, lacking invasive growth so that the gross appearance generally shows the presence of smooth-appearing peripheral contours:
 - Periphery in benign neoplasms may vary from smooth to lobulated.
 - One or more separate (satellite) nodules may be present:
 - Each separate nodule has a smooth or lobulated outline.
 - Malignant salivary gland neoplasms tend to have infiltrative margins with irregular peripheral contour(s).
- Tissue sectioning (Fig. 21-2):
 - Most critical portion of any salivary gland neoplasm to sample to try to determine whether the neoplasm is or is not infiltrative is the interface between the tumor and surrounding tissues:
 - Such sampling provides the greatest opportunity to determine invasive growth.
 - Invasion in salivary gland neoplasms includes:
 - Infiltration into residual non-neoplastic salivary gland parenchyma, neurotropism (peri- and/or intraneural), invasion into soft tissues and/or bone, extension beyond the confines of the gland
 - Extension into a capsule is not diagnostic for invasion relative to salivary gland neoplasms.

- Vascular permeation may occur in benign neoplasms (e.g., pleomorphic adenoma), so care must be taken when identifying lymph-vascular invasion that the morphology is not that of a pleomorphic adenoma.

- Other than pleomorphic adenoma, the presence of lymph-vascular invasion generally connotes malignancy.
- There are no specific guidelines to the number of sections to take in any given neoplasm and such a determination should be based on:
 - The specific case
 - Experience of the pathologist
 - Communication with the surgeon
- In general:
 - Benign tumors tend to be well circumscribed and usually grow with a broad-based pushing front.
 - Benign tumors may encircle or displace adjacent normal structures but do not infiltrate these structures.
 - Presence of invasion irrespective of the morphology of the tumor automatically places the tumor in a malignant category.

Diagnostic Considerations

- Multiple growth patterns or polymorphism:
 - Virtually all salivary gland neoplasms show more than one growth pattern, including benign neoplasms and malignant neoplasms:
 - Presence of multiple growth patterns or polymorphic growth does equate to a diagnosis of malignancy:
 - An example of this situation could include a palatal neoplasm with polymorphic growth patterns, raising suspicion for a diagnosis of polymorphous low-grade adenocarcinoma, but pleomorphic adenomas of this (and other) locations also may show polymorphous growth patterns; differentiation in this scenario is predicated on the presence or absence of invasion because both tumors share similar cell types and in the absence of clear-cut invasion (e.g., neurotropism, invasion of bone and soft tissues), a definitive diagnosis cannot and should not be rendered.
 - Specific growth patterns do not necessarily equate to a specific diagnosis:
 - Cribriform growth often associated with adenoid cystic carcinoma may be identified in a variety of other tumor types, including pleomorphic adenoma and basal cell adenoma.
 - Microcystic change can be seen in a variety of lesions/neoplasms (benign and malignant),

and caution should be exercised when identifying microcystic change as it is not diagnostic for any specific lesion or tumor type.

- Caution should be exercised in rendering a diagnosis of malignancy on the basis of growth pattern and should be evaluated in concert with the overall features of the neoplasm.
- Dual cell population:
 - Many benign and malignant salivary gland neoplasms are composed of an admixture of epithelial cells and (modified) myoepithelial/basal cells, including (although not necessarily limited to):
 - Pleomorphic adenoma
 - Basal cell adenoma
 - Adenoid cystic carcinoma
 - Epithelial myoepithelial carcinoma
 - Polymorphous low-grade adenocarcinoma
 - Identification and/or distribution of cell types, in particular myoepithelial/basal cells, does not allow for a specific diagnosis or for discriminating among different neoplasms.
- Neoplasms with clear cells:
 - Presence of cells with clear-appearing cytoplasm may be seen in a wide variety of salivary gland neoplasms, including benign and malignant neoplasms, so identification of clear cells whether in a major gland or minor gland neoplasms is not a pathognomonic finding.
 - Clear cells may be seen focally in many salivary gland neoplasms or may be the predominant/exclusive cell type:
 - Evaluation of the entire tumor is required to determine if there are features that may allow classification into a specific tumor type.
 - Histochemical and immunohistochemical evaluation may be required to further determine the tumor type.
 - Primary salivary gland neoplasms with clear cells (wholly or in part) include:
 - Benign neoplasms:
 - Oncocytoma
 - Myoepithelioma
 - Pleomorphic adenoma
 - Monomorphic adenomas
 - Malignant neoplasms:
 - Epithelial-myoepithelial carcinoma
 - Clear cell carcinoma (hyalinizing and non-hyalinizing)
 - Mucoepidermoid carcinoma
 - Acinic cell carcinoma
 - Mammary analogue secretory carcinoma
- Myoepithelial carcinoma
- Oncocytic carcinoma
- Sebaceous carcinoma
- Metastatic neoplasms with clear cells include:
 - Renal cell carcinoma
 - Malignant melanoma
 - Others
- Odontogenic neoplasms represent another class of neoplasms that may include clear cells (wholly or in part), and a diagnosis of an odontogenic neoplasm with clear cells should be taken into consideration when dealing with an intraoral lesion:
 - Generally related to teeth and/or gnathic bone
 - Preoperative clinical and radiologic correlation should alert the pathologist to the possibility of an odontogenic neoplasm.
 - Close working relationship with the surgeon is imperative.
- Neoplasms with vacuolated cells:
 - Vacuolated cells can be seen in a variety of neoplasms (benign and malignant), including:
 - Pleomorphic adenoma
 - Monomorphic adenomas
 - Acinic cell carcinoma
 - Mammary analogue secretory carcinoma
 - Caution should be exercised in rendering a diagnosis of malignancy when identifying vacuolated cells because they are not diagnostic for any specific tumor type.
- Changes secondary to fine-needle aspiration biopsy (FNAB) or core tissue biopsy:
 - Prior FNAB or biopsy may result in degenerative and reactive changes, creating difficulties in the frozen section (and permanent section) evaluation.
 - Post-FNAB or biopsy degenerative and reactive changes may include:
 - Extensive tumor infarction and/or necrosis
 - Squamous metaplasia
 - Mucous cell metaplasia
 - Such degenerative and reactive changes may result in erroneous diagnosis of a malignant neoplasm, especially low-grade mucoepidermoid carcinoma; in contrast to mucoepidermoid carcinoma:
 - Squamous metaplasia typically includes presence of keratinization and intercellular bridges, features not typically seen in mucoepidermoid carcinoma.
 - Findings, especially metaplastic changes, usually are focal and not spread throughout the neoplasm.
 - Absence of invasive growth

- Close communication with the surgeon, including questioning if the lesion had previously been needled or biopsied, may assist in preventing misdiagnosis.
- Among the more common benign neoplasms that may undergo such degenerative and reactive changes include (but are not limited to):
 - Warthin tumor
 - Pleomorphic adenoma
 - Oncocytoma
- Cystic change:
 - Many salivary gland lesions/neoplasms may be cystic and/or undergo cystic change.
 - Cystic low-grade mucoepidermoid carcinoma may be problematic to differentiate from non-neoplastic cystic lesions (e.g., salivary duct cyst), especially with associated squamous and mucous cell metaplasia.
 - Presence of more solid/cellular foci composed of admixture of mucocytes, epidermoid cells, and intermediate cells supports a diagnosis of mucoepidermoid carcinoma, distinguishing it from salivary duct cyst with squamous and mucous cell metaplasia.
 - Cystic change may be seen and predominate in acinic cell carcinoma, but the identification of characteristic cells with basophilic granular cytoplasm allows for a diagnosis.
- Multifocal neoplasms:
 - Some primary salivary gland neoplasms may be multifocal within a single gland or in multiple (bilateral) glands or may be multinodular, including:
 - Warthin tumor (most common):
 - May be bilateral in approximately 12% of cases
 - Pleomorphic adenoma:
 - De novo or recurrent
 - Monomorphic adenomas:
 - Basal cell adenoma, in particular membranous type
 - Canalicular adenoma
 - Metastatic tumors to salivary glands, a rare occurrence, may be multifocal.
- Metastatic tumors:
 - Rarely, metastatic neoplasms may spread to salivary glands.
 - Usually not an issue for frozen section evaluation as a diagnosis established by fine-needle aspiration biopsy or core biopsy
 - Most metastases to salivary glands occur from primary malignancies in the head and neck, including:
 - Squamous cell carcinoma
 - Malignant melanoma
 - Less commonly, metastatic tumor from a non-head and neck malignancy may occur to salivary glands
 - Most common scenario is widespread metastasis in a patient with known nonsalivary gland primary malignancy.
 - Less often, metastatic tumor may occur from an occult primary malignancy.
 - At frozen section some issues/considerations include:
 - Presence of keratinization and intercellular bridges in a malignant neoplasm that may include mucocytes generally indicative of a squamous cell carcinoma and not mucoepidermoid carcinoma
 - Difficulties in classifying a given tumor within the spectrum of salivary gland tumor classification should raise the possibility of the presence of metastatic disease.

Accuracy of Intraoperative Diagnosis

- Among a variety of studies evaluating accuracy of frozen section diagnosis in large numbers of salivary gland neoplasms, it has been shown that frozen section diagnosis of salivary gland tumors is reliable and clinically valuable, with accuracy rates ranging from 90% to 98%.
 - Reported sensitivity and specificity of a malignant diagnosis include 98.5% and 99.0%, respectively.
- False-positive, false-negative, and deferral rates are reported to be as high as 2%, 12%, and 10%, respectively.
- Sampling errors represent a primary reason for false-negative errors.
- Clinically significant error rates are probably lower than reported because a proportion of these tumor “errors” are classification changes within the same category.
- Accuracy of fine-needle aspiration biopsy (FNAB) versus frozen section include:
 - For FNAB, sensitivity 73%, specificity 87%, positive predictive value 61%, and negative predictive value 90%
 - For frozen section, sensitivity 80%, specificity 98%, positive predictive value 92%, and negative predictive value 94%
 - Meta-analysis studies of frozen section diagnosis of salivary gland neoplasm to be consistently accurate across study centers
- Frozen section pathology for salivary gland lesions, in particular parotid lesions, has high accuracy and utility in intraoperative decision making, facilitating timely complete procedures.

BIOPSY DIAGNOSIS OF SALIVARY GLAND NEOPLASMS (Figs. 21-13 through 21-18)

- Initial diagnostic modality for a patient with a salivary gland mass often includes fine-needle aspiration biopsy (FNAB) or incisional biopsy.
- Biopsy sampling of salivary gland neoplasms frequently consists of lesional material without surrounding tissues:
 - In such a scenario:
 - Differentiation neoplasms with overlapping histologic features, including growth patterns and bland cytomorphology, may be problematic.
 - Sole determinant may be presence or absence of invasive growth that in presence of only lesional tissue without surrounding tissues on biopsy precludes assessment of relationship of neoplasm to surrounding tissues and may not allow for definitive diagnosis:
 - S100 protein may be of assistance in trying to identify neurotropism.
 - ◻ Absence of neurotropism does not exclude a diagnosis of malignancy.
- ◻ Many neoplasms included in this specific differential diagnosis (see below) have lesional cells that are S100 protein positive:
 - Utility of S100 protein is in trying to identify presence of perineural invasion because it is not specific to any single salivary gland neoplasm
- Among more common benign and malignant (major or minor) salivary gland neoplasms that may create problems in a definitive diagnosis and ability to differentiate one from another include:
 - Pleomorphic adenoma (PA), “usual” and cellular types
 - Basal cell adenoma (BCA)
 - Basal cell adenocarcinoma (BCAdC)
 - Adenoid cystic carcinoma (AdCC)
 - Polymorphous low-grade adenocarcinoma (PLGA)
- Shared pathologic features of above neoplasms may include:
 - Growth patterns:
 - All salivary gland neoplasms are characterized by more than one growth pattern, so presence of polymorphous growth is not a definitive diagnostic finding for malignancy:
 - Polymorphism does not equate to polymorphous low-grade adenocarcinoma.

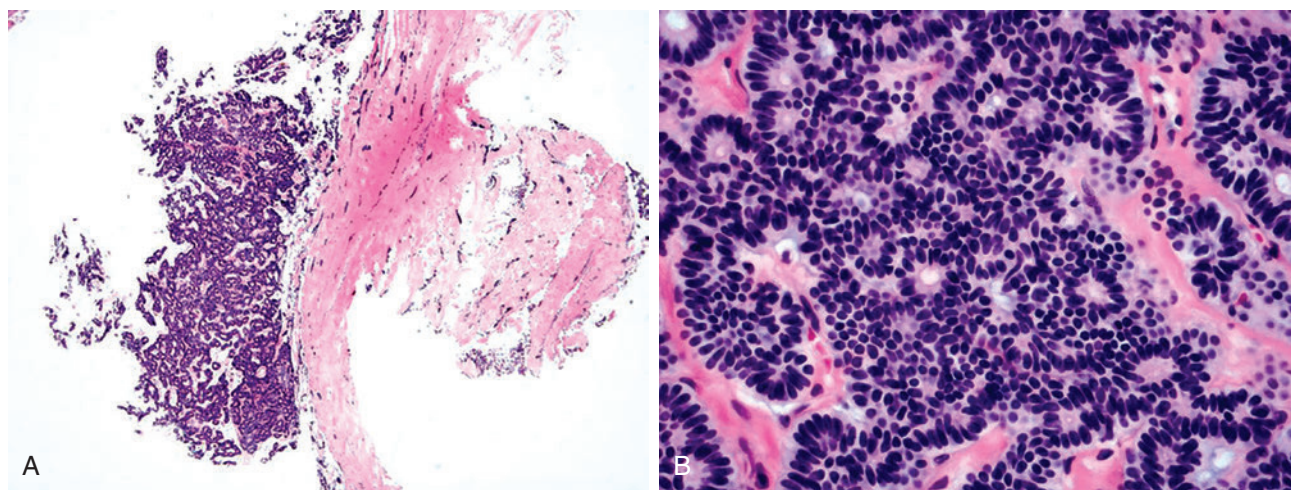


Fig. 21-13. Incisional biopsy of oral cavity submucosal lesion.

A, Biopsy includes tissue fragment entirely composed of lesion (*left*) and adjacent hyalinized tissue, the latter is part of the lesion rather than representing surrounding nonlesional tissue. **B**, Higher magnification shows solid and tubular growth (polymorphism) composed of bland-appearing basaloid cells with hyperchromatic nuclei without significant nuclear pleomorphism or increased mitotic activity. Immunohistochemical staining (not shown) included reactivity with cytokeratins and myoepithelial markers. The overall biopsy findings could be those of a cellular pleomorphic adenoma, basal cell adenoma, or a low-grade carcinoma. A diagnosis of “salivary gland neoplasm, not further specified” was rendered with the recommendation for conservative but complete excision. Following complete excision, the tumor was not invasive with findings diagnostic for basal cell adenoma.

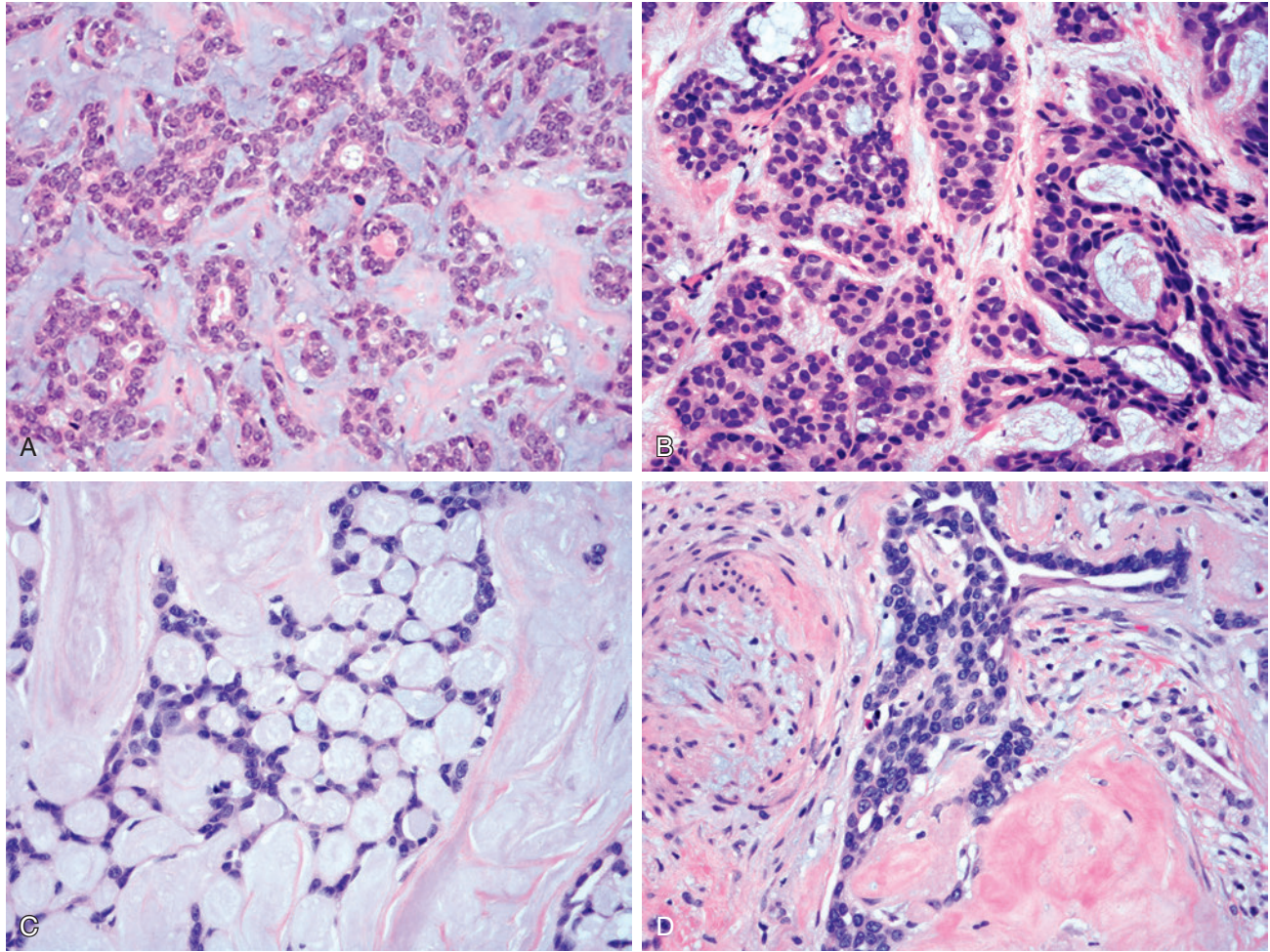


Fig. 21-14. Overlapping features in benign and malignant salivary gland neoplasms.

Shared histologic findings that can be seen in benign and malignant salivary gland neoplasms include **(A)** tubular growth with myxoid-appearing stroma and bland cytologic features; **(B)** tubular and solid growth composed of basaloid nuclei lacking significant nuclear pleomorphism and increased mitotic activity; **(C)** cribriform growth; **(D)** hyalinized and myxoid stroma surrounding lesion with solid and focally glandular growth composed of bland-appearing cells with basaloid nuclei. Although these examples may suggest a specific diagnosis, in the absence of surrounding tissues to evaluate for the presence (or absence) of invasive growth an unequivocal diagnosis cannot be rendered and a diagnosis of “salivary gland neoplasm, not further specified” may be prudent with a recommendation for conservative but complete resection.

- No single growth pattern or combination of growth patterns defines any specific neoplasm or distinguishes among salivary gland neoplasms.
- Specific patterns may suggest a specific diagnosis:
 - Cribriform growth characteristically associated with adenoid cystic carcinoma but may be seen in other tumors, including pleomorphic adenoma and basal cell adenoma
 - Nuclear palisading of basaloid cells along the stromal interface is often seen in BCA and BCAdC but is not specifically diagnostic.
 - Presence of squamous differentiation a feature seen in BCA and BCAdC can be seen in PA and PLGA but generally not in AdCC.
 - Swirling or whorling patterns often at lesion’s periphery characteristic, although not pathognomonic for polymorphous low-grade adenocarcinoma
 - Single filing of tumor cells (akin to lobular carcinoma of the breast) another characteristic (although not pathognomonic) finding associated with polymorphous low-grade adenocarcinoma

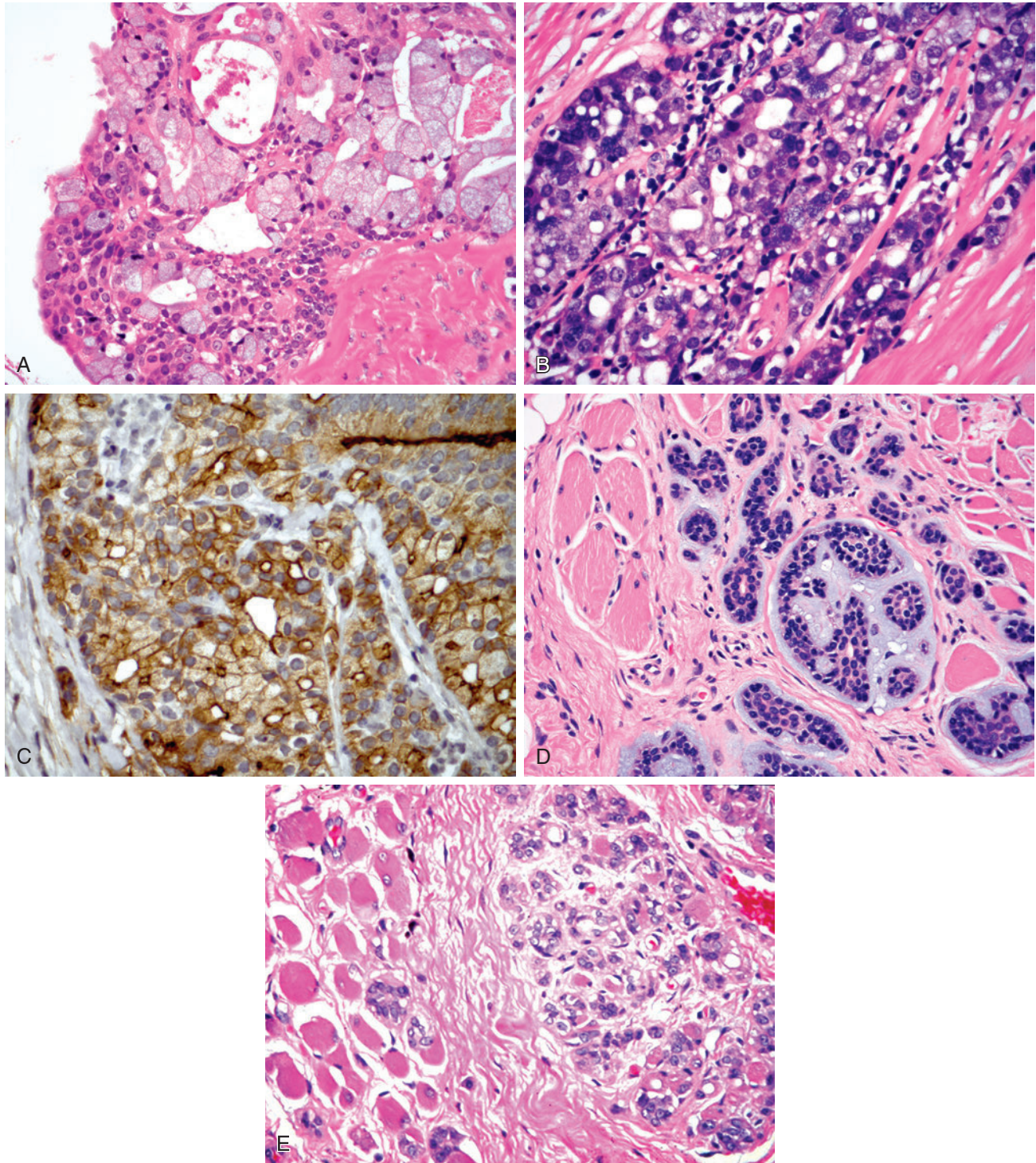


Fig. 21-15. Diagnostic findings for malignancy in salivary gland neoplasms.

Definitive diagnostic findings for a salivary gland carcinoma in incisional biopsies may include cell types and invasive growth: **(A)** cell types diagnostic for mucoepidermoid carcinoma include an admixture of mucocytes, epidermoid cells, and intermediate cells; **(B)** cell type diagnostic for acinic cell carcinoma includes presence of cells with basophilic granular cytoplasm confirmed by **(C)** presence of DOG-1 immunoreactivity (apical, cytoplasmic, and membranous); invasive growth includes **(D and E)** invasion into skeletal muscle (**D** representing adenoid cystic carcinoma; **E** representing polymorphous low-grade adenocarcinoma).

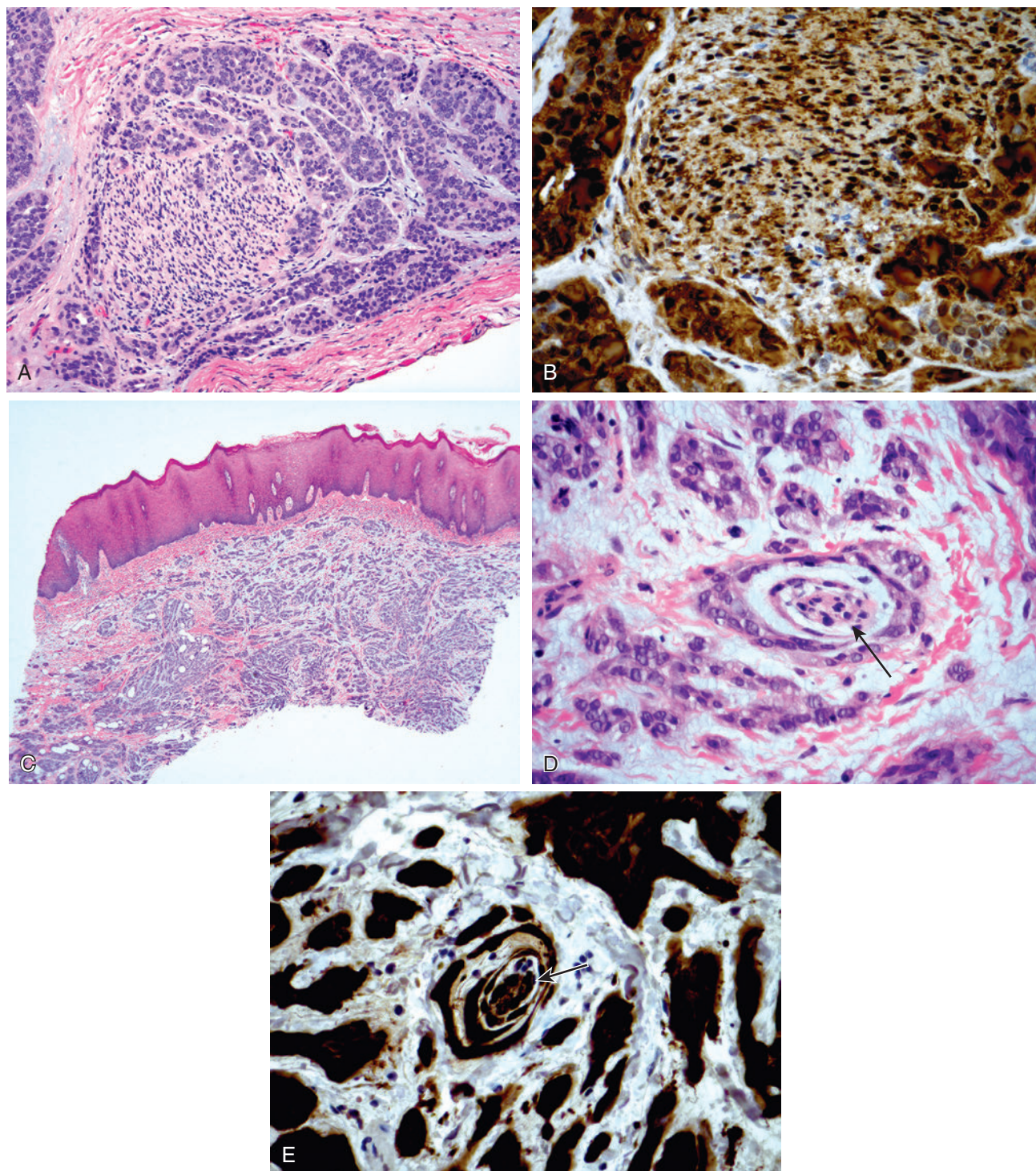


Fig. 21-16. Perineural invasion.

Neurotropism in biopsies of salivary gland neoplasms is diagnostic for carcinoma. The following examples are from separate cases of polymorphous low-grade adenocarcinoma. **A**, Readily apparent peri- and intraneural invasion seen on light microscopic evaluation. **B**, Although unnecessary given the light microscopic findings, S100 protein highlights the nerve surrounded and infiltrated by neoplastic cells which are also S100 protein positive. **C**, Incisional biopsy of a palate lesion with a submucosal neoplastic proliferation showing **(D)** more subtle (*arrow*) and potentially overlooked perineural invasion. **E**, S100 protein highlights the small nerve (*arrow*) surrounded by neoplastic cells, which are also S100 protein positive.

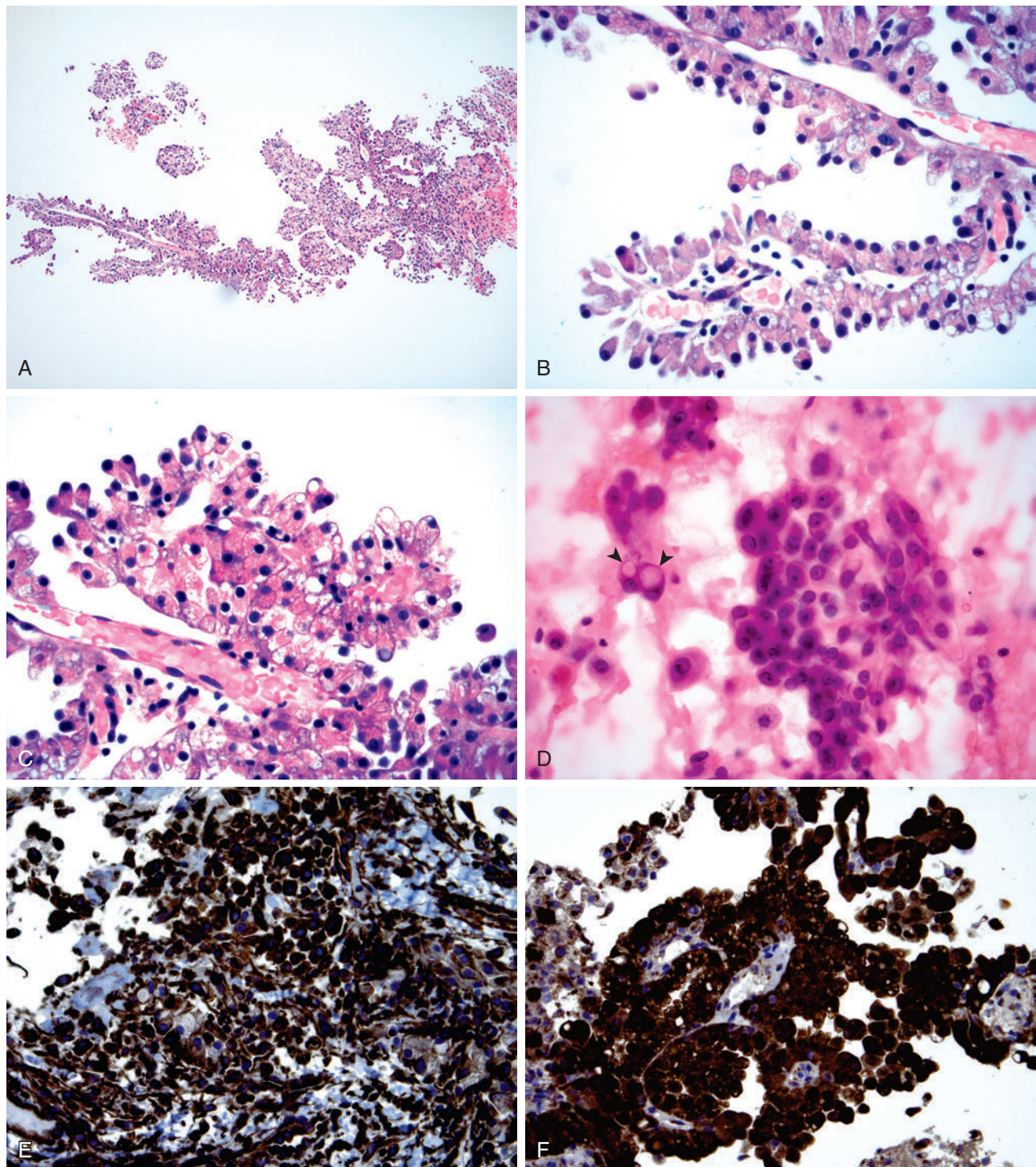
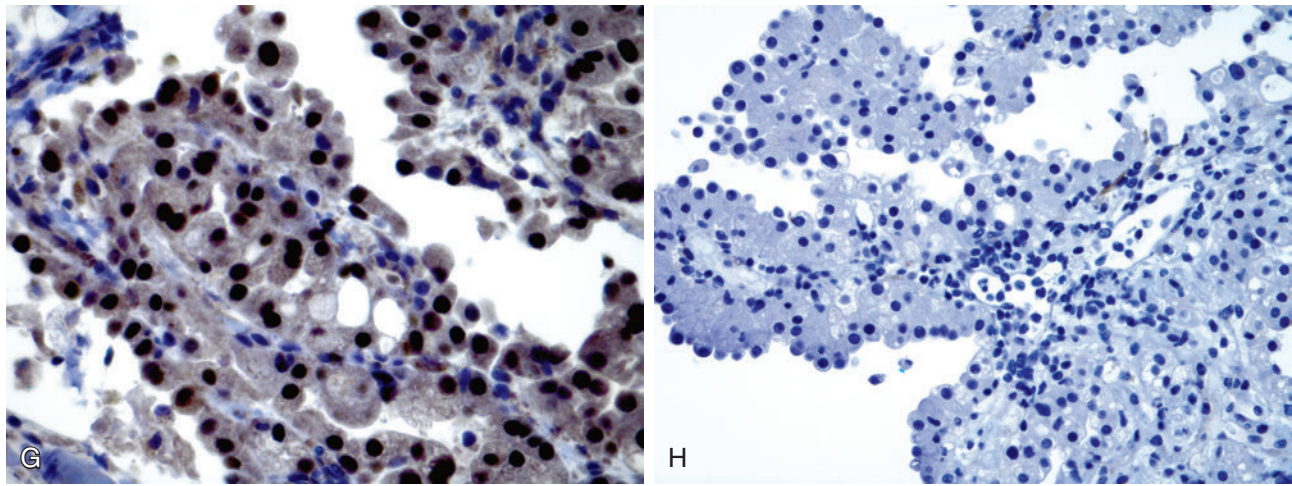


Fig. 21-17. Acinic cell adenocarcinoma vs mammary analogue secretory carcinoma.

Needle biopsy of submandibular gland tumor diagnostic for carcinoma. **A** and **B**, Limited biopsy material that at low magnification shows a neoplastic proliferation with papillary, hobnail, and solid growth. **C**, At higher magnification vacuolated cells and cells with vague-appearing intracytoplasmic granules are present. **D**, A smear of the tumor prepared during the biopsy procedure showed the presence of cells with vacuolated-appearing cytoplasm (*arrowheads*). The overall findings are most suggestive for either an acinic cell carcinoma or mammary analogue secretory carcinoma. Immunohistochemical staining showed the lesional cells to be reactive for **(E)** mammaglobin, **(F)** S100 protein, and

**Fig. 21-17, cont'd**

(G) GATA-3 but negative for (H) DOG-1. The findings are diagnostic for mammary analogue secretory carcinoma.

- Despite purportedly specific growth patterns, PA, BCA, BCAdC, PLGA, and AdCC share too many architectural features to permit definitive diagnosis based on any single or combination of growth patterns.
- Limited sampling may not be representative of entire neoplasm, and more definitive diagnostic features not seen in biopsy material may be present only with availability of entire neoplasm following complete resection:
 - Features suggestive of benign neoplasm on biopsy (e.g., PA or BCA) may prove to be malignant based on invasive growth (e.g., perineural invasion) only seen following complete resection, providing availability of entire tumor and surrounding tissues; conversely, features suggestive of malignant neoplasm on biopsy (e.g., PLGA, AdCC) may prove to be benign only following complete resection with absence of invasive growth
- Cytomorphologic findings:
 - PA, BCA, AdCC, PLGA, and BCAdC may share bland cytomorphologic findings, including limited nuclear pleomorphism and absent to rare mitotic figures
- Dual cell population:
 - Many salivary gland neoplasms, especially more common ones, including PA, BCA, AdCC, PLGA, BCAdC, are composed of epithelial cells and myoepithelial cells, so identification of both cell types by light microscopy and/or immunohistochemical staining does not allow for their differentiation.
- Tumor stroma:
 - Chondromyxoid stroma represents a histologic component of PA
 - Even in limited quantity, chondromyxoid stroma facilitates distinction of pleomorphic adenoma from basal cell adenoma
 - Chondromyxoid stroma derives from neoplastic (modified) myoepithelial cells and often includes myoepithelial cells “streaming” through the matrix.
 - Due to limitations of tissue sampling, the chondromyxoid stroma of pleomorphic adenoma may not be present in an incisional biopsy specimen.
 - Absence of chondromyxoid stroma does not preclude a diagnosis of pleomorphic adenoma nor should absence of chondromyxoid stroma prompt a diagnosis of basal cell adenoma
 - Hyalinized (collagenized) stroma:
 - Can be seen in PA, BCA (membranous subtype), BCAdC, and AdCC:
 - Sometimes show small “droplets” of matrix within nests of neoplastic cells, whereas AdCC exhibits a combination of mucoid basophilic pseudocysts and hyaline eosinophilic pseudocysts.
 - Stromal features are potentially useful within the appropriate context, but definitive diagnosis of salivary gland tumors generally depends upon additional considerations.
- Mitotic activity and proliferation indices:
 - PA, BCA, PLGA, AdCC, and BCAdC are frequently devoid of mitotic activity, although for benign and malignant neoplasms scattered mitotic figures may be identified.
 - Malignant neoplasm sometimes shows increased mitotic activity, including atypical mitoses, but mitotic figures do not distinguish

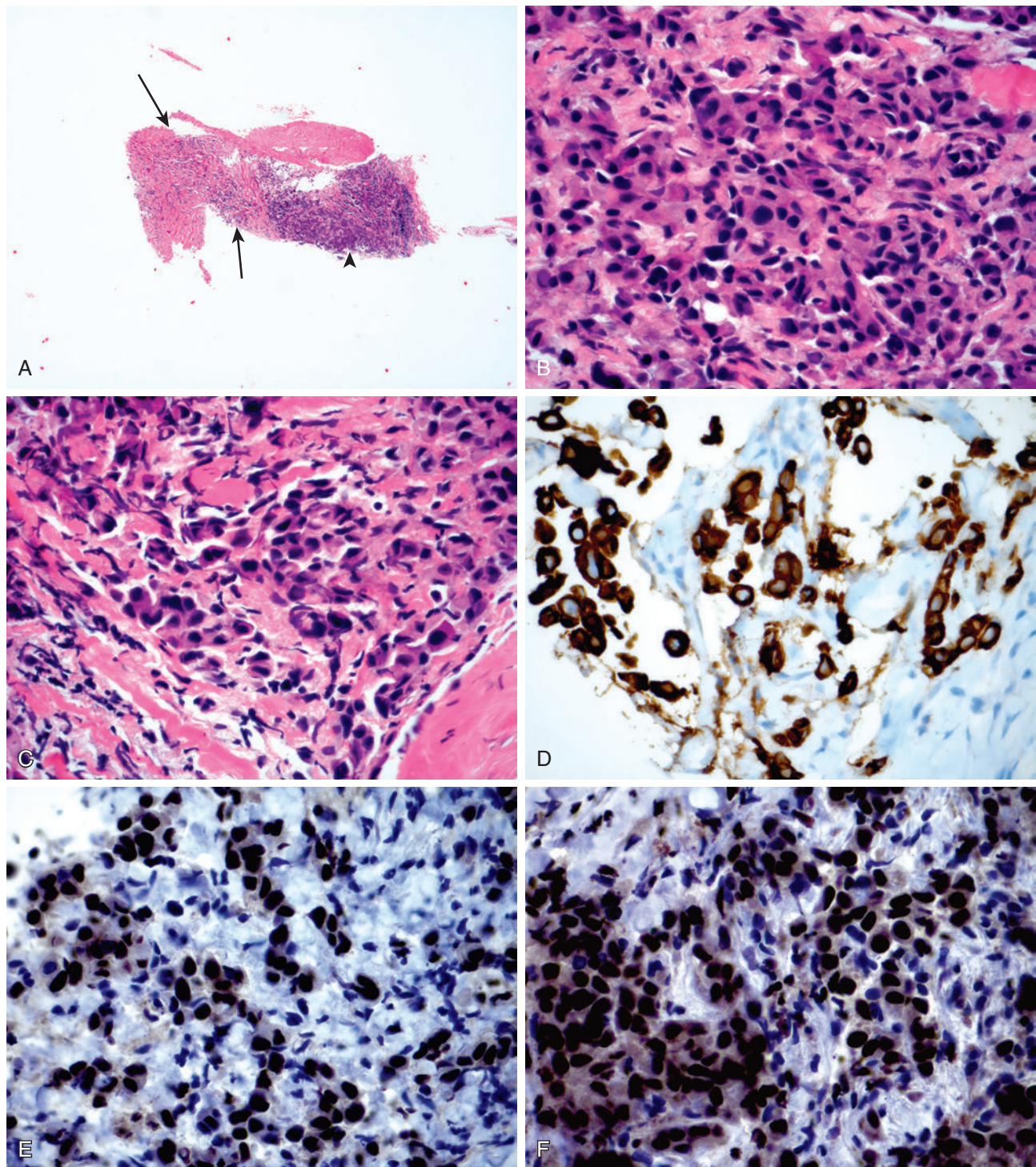


Fig. 21-18.

Needle biopsy of parotid gland tumor diagnostic for carcinoma. **A**, Small tissue fragment showing a densely cellular proliferation (*arrowhead*) with scattered cells within fibroconnective tissue (*arrows*). **B** and **C**, Neoplastic cells in densely cellular area (**B**) and less cellular area (**C**) show moderate to marked nuclear pleomorphism with hyperchromatic nuclei. On the basis of the cytomorphic features, the findings are those of a malignant undifferentiated neoplasm. Immunohistochemical staining showed the lesional cells to be reactive for (**D**) cytokeratin (AE1/AE3); (**E**) androgen receptor (nuclear); (**F**) GATA-3 (nuclear). The findings are diagnostic for salivary duct carcinoma (either occurring *de novo* or possibly the malignant component of a carcinoma ex pleomorphic adenoma). Radical excision of the tumor and neck dissection were subsequently performed confirming a diagnosis of a (*de novo*) salivary duct carcinoma with nodal metastasis.

- malignant lesions from their benign counterparts.
- Although there may be slightly higher proliferation indices in malignant neoplasm as determined by Ki67 (MIB1) immunoreactivity, proliferation indices do not definitively distinguish low-grade malignant salivary gland neoplasm from benign salivary gland neoplasm.
 - Immunohistochemical findings:
 - PA, BCA, BCAdC, AdCC, and PLGA share many similar immunohistochemical findings (Table 21-1) to allow for differentiation solely based on their immunohistochemical staining characteristics.
 - Unique staining patterns have been suggested as allowing for discriminating among salivary gland neoplasms:
 - C-kit (CD117) has been investigated as a potential marker of AdCC, in particular the intensity of C-kit staining of luminal cells in AdCC, but c-kit expression is not unique to AdCC, as this marker may be seen in other salivary gland neoplasms, including PLGA, PA, and BCA.
 - Pairing p63 and p40 reported to assist in differentiating PA from PLGA and AdCC:
 - PA: p63+, p40+; discordant p63+/p40– staining pattern identified in overtly mesenchymal-rich chondromyxoid stroma
 - PLGA: consistent p63+ and p40–
 - AdCC: p63+ and p40+:
 - Although p63/p40 immunohistochemical pairing can be a valuable tool for differentiating PA, PLGA, and AdCC, it is not infallible, and any given example may demonstrate divergence from reported p63/p40 immunophenotype.
 - When can a definitive diagnosis be established in incisional biopsy (or FNAB)?
 - Identification of specific cell types diagnostic for specific neoplasms:
 - Admixture of epidermoid cells, mucocytes, and intermediate cells:
 - Support diagnosis of MEC but caution should be exercised as metaplastic changes, including squamous metaplasia and mucous cell metaplasia, can be seen in benign neoplasms, including PA and Warthin tumor

TABLE 21-1 Immunohistochemistry* of Selective Salivary Gland Neoplasms

Tumor	PanK	LMWK	HMWK	p63	p40	S100	DOG-1	MGB	AR	GATA-3	Her-2	CD117	PLAG1
PA	+	+	+	+	+	+	–	–	–	v	–	v	+
BCA/BCAdC	+	+	+	+	+	+	–	–	–	v	–	v	v
MYO	+	+	+	+	+	+	–	–	–	v	–	v	+
MEC	+	+	+	+	+	–	–	–	–	v	–	v	–
ACC	+	+	+	–	–	–	+	–	–	–	–	–	–
MASC	+	+	+	–	–	+	–	+	–	+ (n)	–	–	–
AdCC	+	+	+	+	+	+	+ [†]	–	–	–	–	+ (lum)	–
PLGA	+	+	+	+	–	+	–	–	–	–	–	v	v
SDC	+	+	+	–	–	–	–	–	+ (n)	+ (n)	v (memb)	–	–
EMC	+	+	+	+	+	+	+ [†]	–	–	–	–	–	–
CCC/HCCC	+/+	+/+	+/+	–/+	–	–/–	–/–	–/–	–/–	–/–	–/–	–/–	–/–

*Staining characteristics vary widely among tumor types and even within the same tumor type. This table details ideal staining characteristics per tumor type, and although these staining patterns generally remain consistent, any given tumor listed may defy “convention” and show reactivity for a marker usually not associated with that tumor or may lack a marker usually associated with that tumor (e.g., p63 in myoepithelial cells).

†Frequently positive, often showing distinctive combined apical ductal and membranous/cytoplasmic myoepithelial staining profile.

ACC, Acinic cell carcinoma; AdCC, adenoid cystic carcinoma; AR, androgen receptor; BCA, basal cell adenoma; BCAdC, basal cell adenocarcinoma; CCC, clear cell carcinoma, including hyalinizing type; DOG-1, discovered on GIST1; EMC, epithelial-myoepithelial carcinoma; GATA-3, GATA binding protein 3; HCCC, hyalinizing clear cell carcinoma; HMWK, high molecular weight cytokeratin (e.g., CK5/6, CK14); LMWK, low molecular weight cytokeratin (e.g., CK7, CK8, CK19); lum, strong staining luminal cells; MASC, mammary analogue secretory carcinoma; MEC, mucoepidermoid carcinoma; memb, membranous; MGB, mammaglobin; MYO, myoepithelioma; n, nuclear; PA, pleomorphic adenoma; PanK, pancytokeratin (e.g., AE1/AE3; CAM5.2); PLAG1, pleomorphic adenoma gene 1; PLGA, polymorphous low-grade adenocarcinoma; SDC, salivary duct carcinoma; V, variably positive.

Specific staining characteristics:

DOG1: should be admixture of strong apical membranous, cytoplasmic and complete membranous staining

Mammaglobin: should be strong and diffuse cytoplasmic staining in MASC (same for S100 protein in this tumor)

PLAG1 immunohistochemical staining may not be confirmed by FISH analysis even for PA.

- Neoplastic acinar cells:
 - In presence of a mass, especially of parotid gland including cells with prominent intracytoplasmic basophilic granules, a diagnosis of acinic cell carcinoma can be rendered, especially when coupled with DOG-1 immunoreactivity:
 - DOG-1 immunoreactivity in ACC includes complex mixture of intense (3+) apical membranous, cytoplasmic, and complete membranous staining; strong staining used to support diagnosis of acinic cell carcinoma
 - Other tumor types that may express DOG-1 include adenoid cystic carcinoma and epithelial-myoepithelial carcinoma, showing distinctive combined apical ductal and membranous/cytoplasmic myoepithelial staining profile but lack intensity associated with ACC.
- Vacuolated cells:
 - Not pathognomonic for any neoplasm but often identified in acinic cell carcinoma, mammary analogue secretory carcinoma (MASC), and mucoepidermoid carcinoma (MEC):
 - Vacuolated cells with DOG-1 reactivity, absence of mammaglobin and GATA-3 reactivity, and absent or weak focal S100 protein reactivity supports diagnosis of acinic cell carcinoma
 - Vacuolated cells with strong mammaglobin, S100 protein, and GATA-3 (nuclear) reactivity and absent DOG-1 reactivity support diagnosis of MASC.
- Clear cells:
 - Not uniquely diagnostic for any specific salivary gland neoplasm as may be seen in a wide variety of tumor types, including benign and malignant neoplasms
 - Immunohistochemical staining may assist in trying to determine nature of neoplasm.
 - Unique *EWSR1* translocation seen in hyalinizing clear cell carcinoma and some clear cell myoepithelial carcinomas but limited tissue sampling may preclude cytogenetic evaluation
- Presence of cytomorphologically high-grade features:
 - Support diagnosis of malignancy, which would be sufficient to plan for definitive treatment (e.g., radical extirpation, neck dissection):
 - In general treatment for all high-grade salivary gland carcinomas is similar irrespective of specific tumor type
 - Definitive diagnosis can be suggested in conjunction with certain immunohistochemical findings:
 - Neoplasm with cytomorphologically high-grade nuclear features (with or without increased mitotic activity and necrosis) coupled to diffuse and strong immunoreactivity for androgen receptor (with or without HER-2 staining) and GATA-3 supports diagnosis of salivary duct carcinoma (SDC), which in turn may be a:
 - De novo SDC
 - Malignant component in carcinoma ex pleomorphic adenoma
 - In presence of cells/nuclei with high-grade features, confirmation of epithelial origin achieved with cytokeratin staining:
 - Absence of reactivity with epithelial markers may suggest malignant lymphoma, latter confirmed by presence of reactivity with hematolymphoid markers (e.g., CD45, CD20, others)
 - Attention to nuclear chromatin may suggest presence of neuroendocrine differentiation that can be confirmed by presence of reactivity for neuroendocrine-related markers (e.g., synaptophysin, chromogranin); within group of neuroendocrine carcinomas of salivary gland origin, diagnosis of Merkel cell type can be confirmed by presence of immunoreactivity for CK20 and Merkel cell polyomavirus (MCPyV)
 - Generally, treatment for all high-grade salivary gland malignant neoplasms is similar, including radical surgical excision plus neck dissection so that a diagnosis of “high-grade carcinoma” irrespective of more specific classification will prompt similar therapeutic approach.
- Presence of invasive growth:
 - Invasion of residual nonlesional salivary gland parenchyma:
 - Perineural/intraneural invasion:
 - Either by light microscopy and/or use of S100 protein to highlight nerve surrounded/infiltrated by tumor confers a diagnosis of malignancy (i.e., carcinoma) but may not differentiate among tumor types:
 - Overlapping features shared by such neoplasm as AdCC, PLGA, and BCAdC
 - Angioinvasion or lymph-vascular invasion
 - Invasion of other soft tissue structures, including:
 - Skeletal muscle
 - Bone

TABLE 21-2 Salivary Gland Neoplasms: Chromosomal Translocations

Tumor	Chromosomal Translocation	Gene Fusion	Percentage of Cases
Pleomorphic adenoma	Rearrangement of 8q12: t(3;8)(p21;112) t(5;8)(p13;q12) Rearrangement of 12q13-15: t(3;12)(p14.2;q14-5) ins(9;12)(p23;q12-15)	<i>PLAG1</i> <i>HMGA2</i>	Approximately 70%
Mucoepidermoid carcinoma	t(11;19)(q21;p13) t(11;15)(q21;q26)	<i>CRTC1-MAML2</i> <i>CRTC3-MAML2</i>	60%-80% 6% or less
Adenoid cystic carcinoma	t(6;9)(q22-23;p23-24)	<i>MYB-NFIB</i>	80%-90%
Mammary analogue secretory carcinoma	t(12;15)(p13q25)	<i>ETV6-NTKR3</i>	Translocation 80% ETV6 break 99%
Hyalinizing clear cell carcinoma (HCCC) Clear cell variant of myoepithelial carcinoma (CCMC) [†]	t(12;22)(q13;q12)	<i>EWSR1-ATF1</i>	For HCCC 80% For CCMC 39% [†]
Cribiform cystadenocarcinoma of salivary glands	t(1;14)(p36.11;q12) t(X;14)(p11.4;q12)	<i>ARID1A-PRKD1</i> <i>DDX3X-PRKD1</i> Other abnormalities of <i>PRKD2</i> , <i>PRKD3</i>	To be determined but could be as high as 80%
Epithelial-myoepithelial carcinoma	No translocation but a mutation	<i>HRAS</i> exon3, codon 61	27%*

*Chiosea SI, Miller M, Seethala RR: *HRAS* mutations in epithelial-myoepithelial carcinoma, Head Neck Pathol 8:146-150, 2014.

[†]Includes de novo CCMC and CCMC ex pleomorphic adenoma. From Skalova A, Weinrib I, Hycza M, et al: Clear cell myoepithelial carcinoma of salivary glands showing EWSR1 rearrangement, Am J Surg Pathol 39:338-348, 2015.

- Noted caveats to above findings include:
 - In general, presence of neurotropism and invasion of residual salivary gland parenchyma are diagnostic for malignancy:
 - Relative to salivary gland neoplasms, benign neoplasms are not neurotropic and do not invade (efface) non-neoplastic salivary gland tissues.
 - Occasionally, benign neoplasms may permeate into lymph-vascular spaces:
 - Noted example would be pleomorphic adenoma
 - Occasionally, benign neoplasms may be identified within soft tissues, including skeletal muscle (but not usually bone):
 - Noted example would be recurrent pleomorphic adenoma (chondromyxoid predominant or usual type)

Conclusions

- In summary, FNAB and incisional biopsy diagnosis of salivary gland lesions, including major glands and minor glands (e.g., intraoral), can be difficult to differentiate a benign from malignant neoplasm, especially histologically low-grade carcinomas, including

adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma:

- Often biopsy material is too limited to allow for differentiation given absence of surrounding tissues to evaluate for presence of infiltrative growth.
- Overlapping immunohistochemical findings, including reactivity with epithelial and myoepithelial markers:
 - S100 protein may be most useful stain in trying to establish presence of neurotropism that, if found, would be diagnostic for carcinoma, although differentiation among low-grade carcinomas may still be problematic.
- Presence of specific chromosomal translocation/gene fusion linked to specific neoplasms and would allow for specific diagnosis when identified (Table 21-2), but limited sampling in FNAB or incisional biopsy may not yield sufficient material to perform molecular analysis
- Treatment for benign neoplasms (e.g., PA, BCA) and low-grade salivary gland carcinomas generally similar, including complete resection to include tumor-free margins without sacrifice of nerves and without neck dissection in absence of clinical evidence of neck disease

- In absence of definitive diagnostic findings, better to render a diagnosis of “salivary gland neoplasm, not further specified” with recommendation for complete resection, including tumor-free margins
 - Neoplasms appearing benign on FNAB/biopsy may prove malignant following complete resection.
 - Neoplasms appearing malignant on FNAB/biopsy may prove benign following complete resection.
- Following complete resection and availability of entire neoplasm for histologic evaluation, a definitive diagnosis can be established, and any adjunct therapy, if needed, can be instituted.

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Embryology, Anatomy, Histology, and Physiology of the Thyroid Gland

EMBRYOLOGY OF THE THYROID (Fig. 26-1)

- Thyroid gland is the first endocrine gland to appear during embryonic development.
- Thyroid gland derives from three primordium, median anlage, and lateral anlagen:
 - Median anlage develops around the twenty-fourth day of gestation as a small, median endodermal thickening on primitive pharynx.
 - This thickening forms a diverticulum, which attaches to tongue by a narrow tube referred to as thyroglossal duct.
 - Opening in base of tongue constitutes foramen cecum
 - Lateral anlagen correspond to ultimobranchial body, which derives from pharyngeal pouches:
 - Ultimobranchial body from which C-cells originate fuses and incorporates into thyroid gland.
- As result of further cellular proliferations, hollow thyroid diverticulum obliterates and divides into right and left lobes, connected by isthmus around seventh week of gestation.
- During development thyroid descends and assumes a definitive position in anterior neck, at which time:
 - Thyroglossal duct undergoes atrophy
 - In approximately 40% to 50% of individuals, inferior end of thyroglossal duct persists as pyramidal lobe, which is attached to hyoid bone by fibrous or muscular tissue.
 - Faulty migration (of medial anlage) or persistence of thyroglossal duct may give rise to thyroid ectopia (e.g., lingual thyroid, other) or thyroglossal duct cysts.
- Proximal opening persists as foramen cecum of tongue.
- Development of thyroid gland controlled by coordinated action of specific transcription factors, including:
 - Thyroid transcription factor 1 (TTF-1), TTF-2, paired box gene 8 (PAX8), and hematopoietically expressed homeobox (HHEX)
 - Altered expression of transcription factors play a role in thyroid dysgenesis.
- Thyroid follicular cells:
 - Endodermal cell mass constituting thyroid primordium is separated into cords by invasion of vascular mesenchyme and divide into smaller groups around tenth week of gestation.
 - A single layer of cells becomes arranged around a lumen, and primitive follicles make their appearance around the eleventh week of gestation.
 - At the time colloid is stored, iodine concentrates and hormone synthesis can be demonstrated.
 - By week 14, follicles with central lumen containing colloid are well developed.
 - Follicular cells and colloid are thyroglobulin positive.
- Thyroid C-cells:
 - Neuroendocrine cells presumed to be of neural crest derivation
 - Originate from ultimobranchial body that migrates into pharyngeal pouches from branchial arches:
 - Reach thyroid via ultimobranchial body, which originates from fourth and fifth branchial pouch complex
 - While still attached to pharynx, ultimobranchial bodies start migration downward on each side of neck together with parathyroid fourth anlage.
 - At 7 to 8 weeks, ultimobranchial bodies separate from pharynx and parathyroids.
 - At weeks 8 to 9 appear as solid masses fusing with dorsolateral aspects of median thyroid anlage incorporated into developing lateral thyroid lobes
 - C-cells are largely restricted to middle and upper thirds of lateral thyroid lobes.
 - C-cells produce calcitonin, which regulates normal calcium levels in body.
 - Solid cell nests are believed to be remnants of ultimobranchial body

ANATOMY OF THE THYROID (Fig. 26-2)

- Thyroid gland is a reddish tan organ located in lower part of the neck on either side of the larynx and trachea placed anteriorly at level of fifth cervical to first thoracic vertebrae.
- Thyroid gland is ensheathed by pretracheal layer of deep cervical fascia consisting of right and left lobes

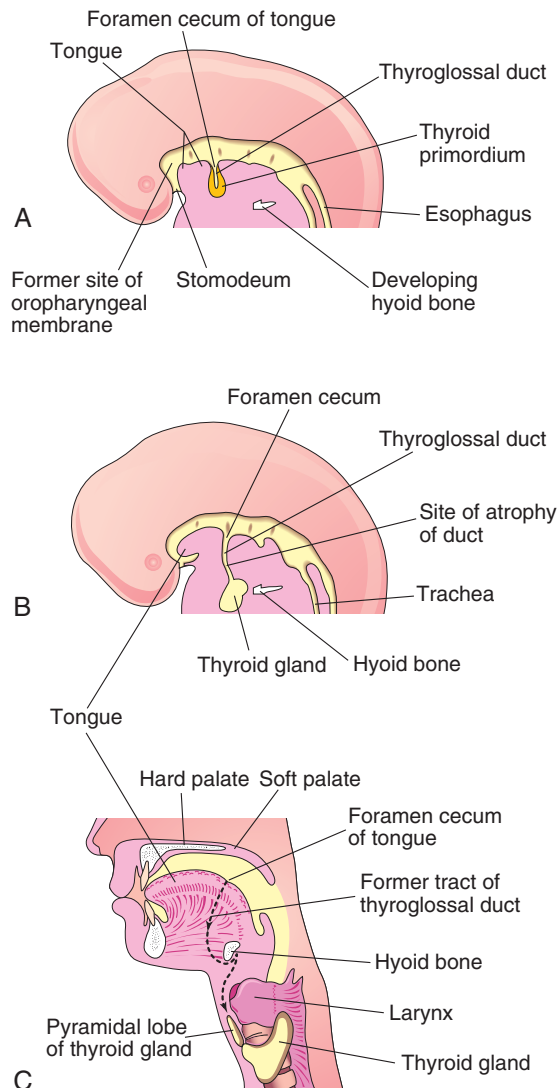


Fig. 26-1. Development of the thyroid gland.

A and B, Schematic sagittal sections of the head and neck regions of embryos at 5 and 6 weeks, illustrating successive stages in the development of the thyroid gland. **C,** Similar section of an adult head and neck showing the path taken by the gland during its embryonic descent (indicated by the former tract of the thyroglossal duct). (From Moore KL, Persaud TVN, Torchia M: *The developing human: clinically oriented embryology*, ed 10, Philadelphia, 2015, Elsevier.)

connected by a narrow median band of tissue referred to as the isthmus, which overlies the three tracheal rings below cricoid cartilage.

- Weight of thyroid gland varies from 15 to 25 g in adults, is heavier in women than in men, and varies during pregnancy, iodine intake, and other pathologic conditions.
- Lateral thyroid lobes have a conical shape, measuring 5 cm long, 3 cm transversally, and 2 cm anteroposteriorly:

- Their ascending apices diverge laterally to level of oblique lines on laminae of thyroid cartilage, and their bases are level with fourth and fifth tracheal rings.
- Each lobe, in posteromedial aspect, is attached to side of cricoid cartilage by a lateral thyroid ligament.
- Isthmus connects both lobes, measures 1.25 cm transversely and vertically, and extends anterior to the second and third tracheal rings.
- Pyramidal thyroid lobe:
 - Present in approximately 40% to 50% of the population
 - Conical shaped, projecting upwards from isthmus ascending to hyoid bone
 - Appears generally as a fibrous tract, but in pathologic conditions becomes prominent or cystic
- Thyroid gland capsule:
 - Thyroid gland invested by thin connective tissue capsule firmly attached to gland
 - Numerous fibrous septa penetrate thyroid parenchyma, dividing gland into lobules.
 - Although gland grossly may appear completely encapsulated, microscopically capsule is incomplete in majority of population.
- Surfaces and relations:
 - Convex lateral (superficial) surface of thyroid gland is covered by sternothyroid muscle.
 - Medial surface is adapted to larynx and trachea.
 - Superior pole contacts inferior pharyngeal constrictor and posterior part of cricothyroid, which separate it from posterior part of thyroid lamina and side of cricoid cartilage.
 - Inferiorly, trachea and more posteriorly recurrent laryngeal nerve (running in the tracheoesophageal space) and esophagus (closer on the left side) are medial relations.
 - Posterolateral surface of thyroid gland is close to carotid sheath and overlaps common carotid artery.
 - Anterior border is thin and near anterior branch of superior thyroid artery it slants down medially.
 - Rounded posterior border is related inferiorly to inferior thyroid artery and its anastomosis with posterior branch of superior thyroid artery.
 - On left side, lower end of posterior border of thyroid lies near thoracic duct.
 - Parathyroid glands are usually related to posterior border.
 - Isthmus is covered by sternothyroid muscle from which it is separated by pretracheal fascia; more superficially isthmus is covered by sternohyoid muscle, anterior jugular veins, fascia, and skin.

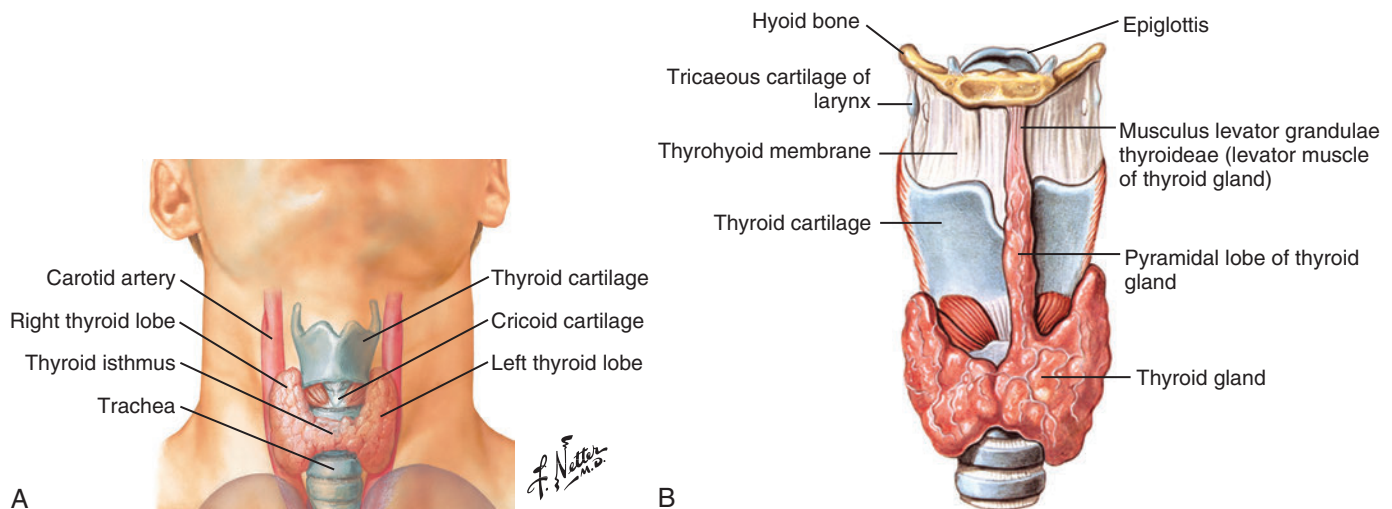


Fig. 26-2. Anatomy of the thyroid gland.

A, Frontal view drawing of the neck with the chin raised shows the typical location of the thyroid gland in relationship to the larynx and trachea. **B**, Frontal drawing of the thyroid gland showing the position of the gland relative to the trachea and larynx. Also shown is a pyramidal lobe and the musculus levator glandulae thyroideae. (A, Modified from www.netterimages.com. B, Modified from Sobota Atlas of Human Anatomy © Elsevier GmbH, Urban & Fischer, Munich.)

Vascular Supply and Lymphatics of the Thyroid

Arteries and Veins

- Thyroid gland is a richly vascularized organ with vascular supply derived from superior and inferior thyroid arteries:
 - Arteries are large and branches anastomose frequently on and in thyroid gland ipsilaterally and contralaterally.
 - Arteria thyroidea ima from brachiocephalic trunk or aortic arch sometimes provides vascular supply.
- Superior thyroid artery:
 - Arises from external carotid artery and is closely related to external branch of superior laryngeal nerve; descends forward and downward to superior pole of the thyroid gland, pierces thyroid fascia, and divides into anterior and posterior branches
 - Anterior branch supplies anterior surface, runs down over anterior surface of thyroid gland to isthmus, and anastomoses with superior thyroid artery of contralateral side.
 - (Smaller) posterior branch supplies lateral and medial surface, courses posterolateral surface of gland and through small ramus communicans, and anastomoses with inferior thyroid artery from same side.
- Inferior thyroid artery:
 - Larger than superior thyroid artery originates from thyrocervical trunk, branch of the subclavian artery, passes behind and close to carotid sheath and under common carotid artery, approaches base of thyroid gland, and divides into superior (ascending) and inferior branches at level of junction of inferior and middle thirds of thyroid gland to supply inferior and posterior surfaces of thyroid gland:
 - Superior branch also supplies parathyroid glands.
 - Relationship of inferior thyroid artery and recurrent laryngeal nerve is highly variable and of clinical importance as iatrogenic injury to nerves supplying larynx is a potential major complication of thyroid surgery.
 - Recurrent laryngeal nerve usually related to posterior branch of inferior thyroid artery
- In thyroid gland arteries penetrate substance and divide into numerous branches throughout parenchyma, giving origin to a rich capillary network that ends in capillaries around follicles.
- Venous drainage of thyroid gland usually via superior, middle, and inferior thyroid veins:
 - Superior thyroid vein emerges from upper part of gland, runs with superior thyroid artery towards carotid sheath, and drains into internal jugular vein.
 - Middle thyroid vein collects blood from lower part of gland, emerges from lateral surface of gland, and drains into internal jugular vein.
 - Inferior thyroid vein arises in glandular venous plexus, which also connects with middle and superior thyroid veins.

- Efferent vessels anastomose frequently and accompany arteries to surface of gland, forming a large venous (pretracheal) plexus in fascia covering gland from which:
 - Left inferior vein descends to join left brachiocephalic vein and right descends obliquely across brachiocephalic artery to join right brachiocephalic vein at its junction with superior vena cava.
 - Inferior thyroid vein often opens via a common trunk into superior vena cava or left brachiocephalic vein.
- Thyroid lymphatics may drain directly with no intervening node to thoracic duct.
- Thyroid endowed with rich lymphatic network that may not be readily evident in hematoxylin and eosin staining requiring immunostaining with podoplanin (D2-40) for identification
- Regional lymph nodes include: (Fig. 26-3)
 - Pericapsular lymph nodes:
 - Intraglandular lymph vessels penetrate capsule merging with pericapsular lymph nodes to form plexus around thyroid gland.
 - Pretracheal, paratracheal, and prelaryngeal lymph nodes:
 - Drain inferior portion of gland
 - Prelaryngeal lymph node referred to as Delphian node:
 - Along with para- and pretracheal make up level VI
 - Lies adjacent to thyroid gland once regarded as sentinel for thyroid disease and drains thyroid gland and larynx lying anterior to cricothyroid ligament
 - Enlargement may be indicative of metastasis from thyroid or laryngeal carcinoma.
 - Name originates from Oracle of Delphi, whose prophecy in this case would be unpleasant death secondary to laryngeal cancer
 - Internal jugular chain lymph nodes:
 - Includes subdigastic nodes
 - Collecting lymph vessels draining superior portion of thyroid lobes and isthmus

Lymphatics

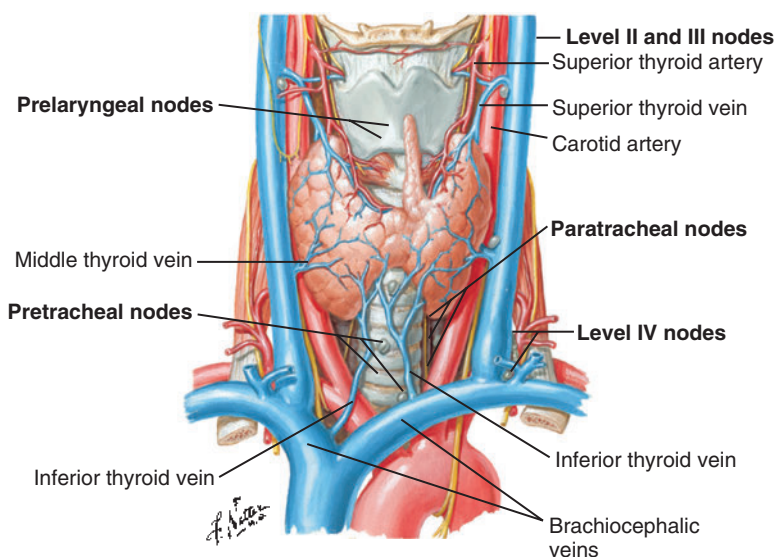


Fig. 26-3. Regional lymph nodes of the thyroid gland.

Frontal view of the thyroid gland shows its vascular supply. Also shown are the primary drainage lymph nodes of the thyroid gland. Not shown are the level I and retropharyngeal nodes. (Modified from www.netterimages.com.)

- Recurrent laryngeal nerve chain lymph nodes
- Retropharyngeal and retroesophageal lymph nodes
- Drainage from thyroid gland may also include anterosuperior mediastinal lymph nodes.

Nerves

- Thyroid gland receives innervation from superior, middle, and inferior cervical sympathetic ganglia.
- In thyroid gland through perivascular and interfollicular plexus, nerves end near follicular basement membrane, influencing thyroid secretion indirectly by action in blood vessels.
- Small paraganglia normally present close to thyroid and occasionally found beneath thyroid capsule

HISTOLOGY (Fig. 26-4)

- Thyroid gland capsule:
 - A thin fibrous capsule completely envelops thyroid gland with septa that divide thyroid gland incompletely into lobules:
 - Capsule includes sizable vascular spaces as well as small peripheral nerves and is continuous with pretracheal fascia.
 - In practice, a fibrous capsule of thyroid gland is often not identifiable by microscopic examination.
 - Criteria for defining (minimal) extrathyroidal extension may be problematic and subjective; see later in Chapter 28 for more detailed discussion.
- Thyroid gland is divided by connective tissue septae into lobules, each one of these containing from 20 to 40 follicles:
 - Each follicle is considered a functional unit of thyroid gland.
- Thyroid follicular epithelial cells:
 - Thyroid follicles consist of rounded structures of variable size lined by a single layer of flattened (inactive) to cuboidal or rarely columnar (cylindrical) cells and a lumen containing a proteinaceous colloid material representing storage product of secretory activity of follicular cells:
 - Cuboidal cells are most numerous and major function is to secrete colloid.
 - Single follicle may have flattened cells on one side and cuboidal cells on other side.
 - Follicular cells have a central rounded or ovoid nucleus with delicate chromatin, a single (eccentric) nucleolus, and an eosinophilic or amphophilic cytoplasm:
 - Nuclear chromatin is coarse, appearing finely granular or clumped.
 - Uncommonly normal follicular cells may have deeply eosinophilic cytoplasm referred to as oncocytes (so-called Hürthle cells).
 - Lipofuscin appearing as an intracytoplasmic golden brown pigment may be present.
- Follicles are separated by loose fibroconnective tissue.
- Follicles have an average diameter of 200 microns.
 - Size varies according functional status of gland or patient age.
- Follicles are surrounded by a basement membrane:
 - Remain in close relationship with lymphatics, a rich capillary network, and nerves present around individual follicles
- Colloid is:
 - Pale eosinophilic with scalloped borders in actively secreting gland and deeply eosinophilic in resting follicles
 - Variably periodic acid Schiff (PAS) and alcian blue positive
 - Calcium oxalate crystals may be visualized in colloid in normal and pathologic conditions.
- Immunohistochemistry: follicular cells are immunoreactive for:
 - Thyroglobulin (intraluminal colloid is also reactive):
 - Dedicated and specific marker of thyroid follicular cells including tumors of thyroid follicular cell origin:
 - Represents single best marker for determination of thyroid follicular cell origin
 - Follicular cells with cytoplasmic oncocytic change (so-called Hürthle cells) show much lesser degree of thyroglobulin reactivity.
 - Tends to leak out from cytoplasm of follicular cells and may diffuse into cytoplasm of other (nonfollicular) cells, including non-thyroid tumors potentially resulting in diagnostic misinterpretation
 - Thyroid transcription factor 1 (TTF-1) (nuclear staining):
 - Homeodomain transcription factor expressed in thyroid, diencephalon, and lung
 - Necessary in thyroid organogenesis and differentiation:
 - Regulates expression of thyroid peroxidase (TPO) and thyroglobulin genes
 - Extremely useful marker for thyroid follicular cells, including tumors of thyroid follicular cell origin but unlike thyroglobulin may be reactive in other tumor types, including tumors of thyroid C-cell origin (i.e., medullary thyroid carcinoma)
 - Reactive in a broad spectrum of tissue types and tumors, therefore not as dedicated and

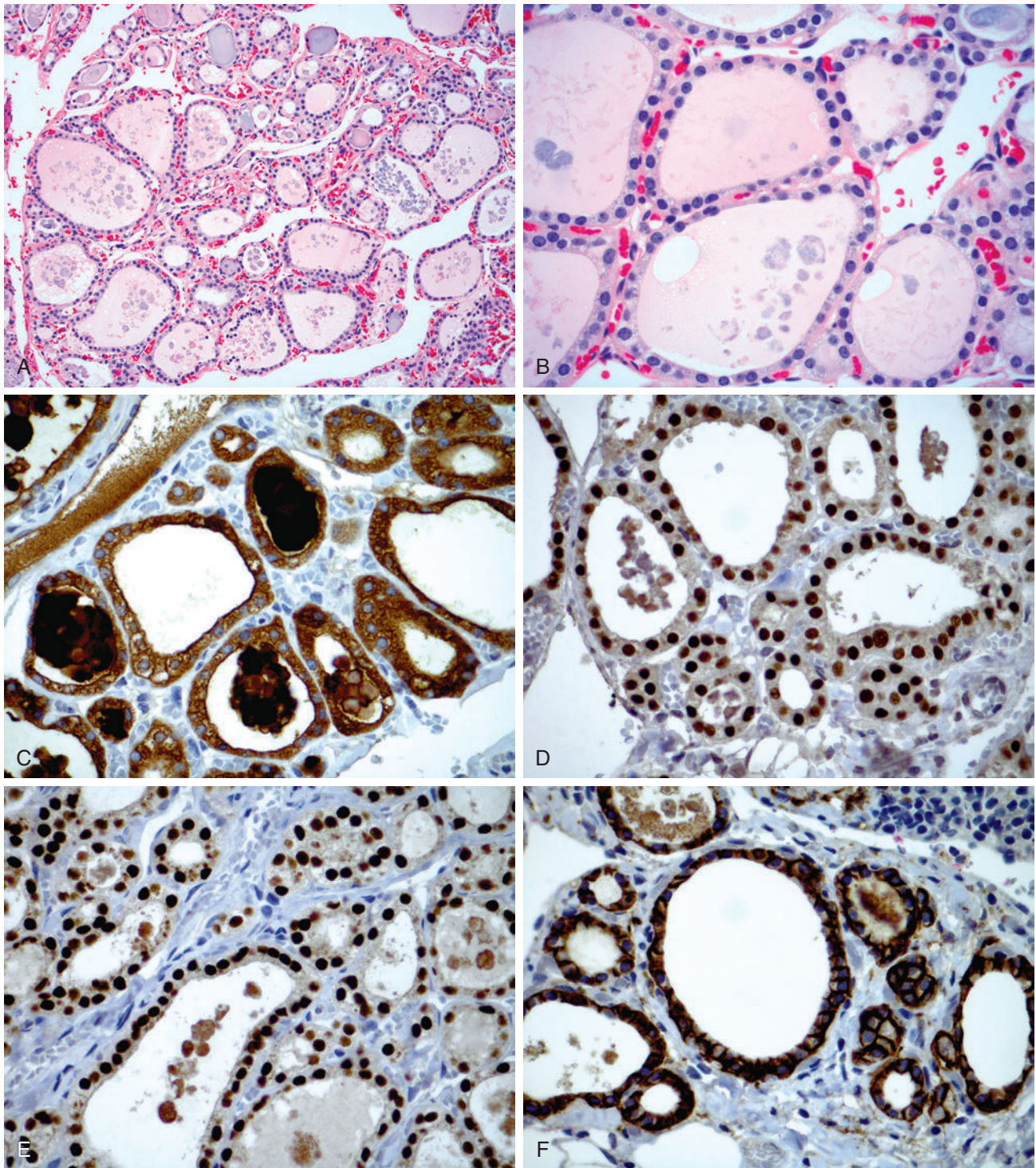


Fig. 26-4. Normal thyroid follicular epithelial cells.

A, Thyroid gland lobule containing numerous colloid-filled follicles; each follicle is considered a functional unit of thyroid gland. **B**, Variable-sized colloid-filled follicles lined by single layer of flattened (inactive) to cuboidal follicular cells with round or ovoid nuclei and coarse nuclear chromatin. Immunohistochemical staining of follicular cells includes reactivity for **(C)** thyroglobulin (colloid is also immunoreactive), **(D)** thyroid transcription factor 1 (TTF-1; nuclear staining), **(E)** PAX8 (nuclear staining), and **(F)** CD56 (membranous staining).

- specific as thyroglobulin relative to thyroid follicular cells and lesions/tumors derived from follicular cells
- Paired box gene 8 (*PAX8*) (nuclear staining):
 - Member of Pax family of transcription factors defined by common element, the Paired (Prd) domain, by which they bind to specific DNA sequences
 - *PAX8* gene located on human chromosome 2q12-q14
 - Along with TTF-1 (and TTF-2) necessary in thyroid organogenesis and differentiation
 - CD56 (membranous staining):
 - May be present in thyroid follicular cells and lesions/tumors of follicular cell origin
 - Low molecular weight keratins:
 - CK7, CK18, CK8, CK19
 - Epithelial membrane antigen
 - Vimentin
 - Galectins:
 - Implicated in cell growth and differentiation, intercellular recognition, and adhesion
 - Galectin-3 (GAL-3) stains normal follicular cells and carcinomas
 - Estrogen and progesterone receptors may be identified.
 - Laminin and type IV collagen stain basement membrane of the follicles.
 - Electron microscopy:
 - Numerous microvilli are seen in the luminal surface of the follicular cells.
 - Cells are joined tight junctions containing occludin and various claudins.
 - Cytoplasm has abundant rough endoplasmic reticulum, a well-developed Golgi apparatus in a supranuclear or paranuclear position, and lysosomes in the apical cytoplasm.
 - Thyroid C-cells (parafollicular cells) (Fig. 26-5)
 - Represent a second population of distinct cells in thyroid gland
 - Have neuroendocrine function responsible for production of calcitonin
 - Are encountered at junction of upper third and middle thirds of lateral thyroid lobes:
 - Tend to aggregate in vicinity of solid cell nests
 - Not present in isthmus portion of gland
 - Are difficult to identify in routine stain sections but can be recognized due to their location in follicles and their morphologic characteristics:
 - Located individually or in small groups within thyroid follicles:
 - Found at periphery of follicular wall within its basement membrane without contact with follicular lumen
 - Ultrastructurally C-cells occupy an intrafollicular position separated from thyroid interstitium by follicular basal lamina
 - Are round, polyhedral, or spindle shaped with round to oval nuclei and granular weakly eosinophilic to clear cytoplasm and are larger and paler than follicular cells
 - Number of C-cells varies from neonatal period to adulthood:
 - Numerous cells found at birth to single cells or smaller groups in adult thyroid parenchyma
 - Histochemistry:
 - C-cells can be selectively stained by silver techniques, including:
 - Grimelius (argyrophilic) stain, Churukian-Schenk, and the silver nitrate of Cajal revealing brown to black cytoplasmic granules
 - Immunohistochemistry: C-cells are immunoreactive for:
 - Calcitonin (cytoplasmic staining)
 - Calcitonin-gene-related peptide (CGRP)
 - Cytokeratins:
 - Pankeratins, CK7
 - Neuroendocrine markers, including synaptophysin, chromogranin
 - Thyroid transcription factor-1 (TTF-1) (nuclear stain)
 - Carcinoembryonic antigen (CEA)
 - CD56, CD57
 - Neuron-specific enolase
 - Somatostatin and serotonin
 - Electron microscopy:
 - Characteristic of C-cells is presence of round electron dense membrane bound neuroendocrine-type granules, which range in size from 60 to 550 nm in diameter:
 - 2 types of granules identified, including type I and type II
 - Most C-cells have type I rather than type II secretory granules.
 - C-cells are enclosed in the basement membrane of follicular cells without reaching the lumen of the follicles due to interposition of follicular cells.
 - Solid cell nests (SCN):
 - Consist of collection of cells with a squamoid appearance lacking intercellular bridges, most probably representing remnant of ultimobranchial body from which the C-cells originate; see Chapter 27 for discussion

Thyroid Stroma

- Thyroid stroma includes:
 - Blood vessels
 - Lymphatics
 - Fibrous tissue
- Lymphocytes are not normally a component of thyroid stroma and presence of lymphocytes is

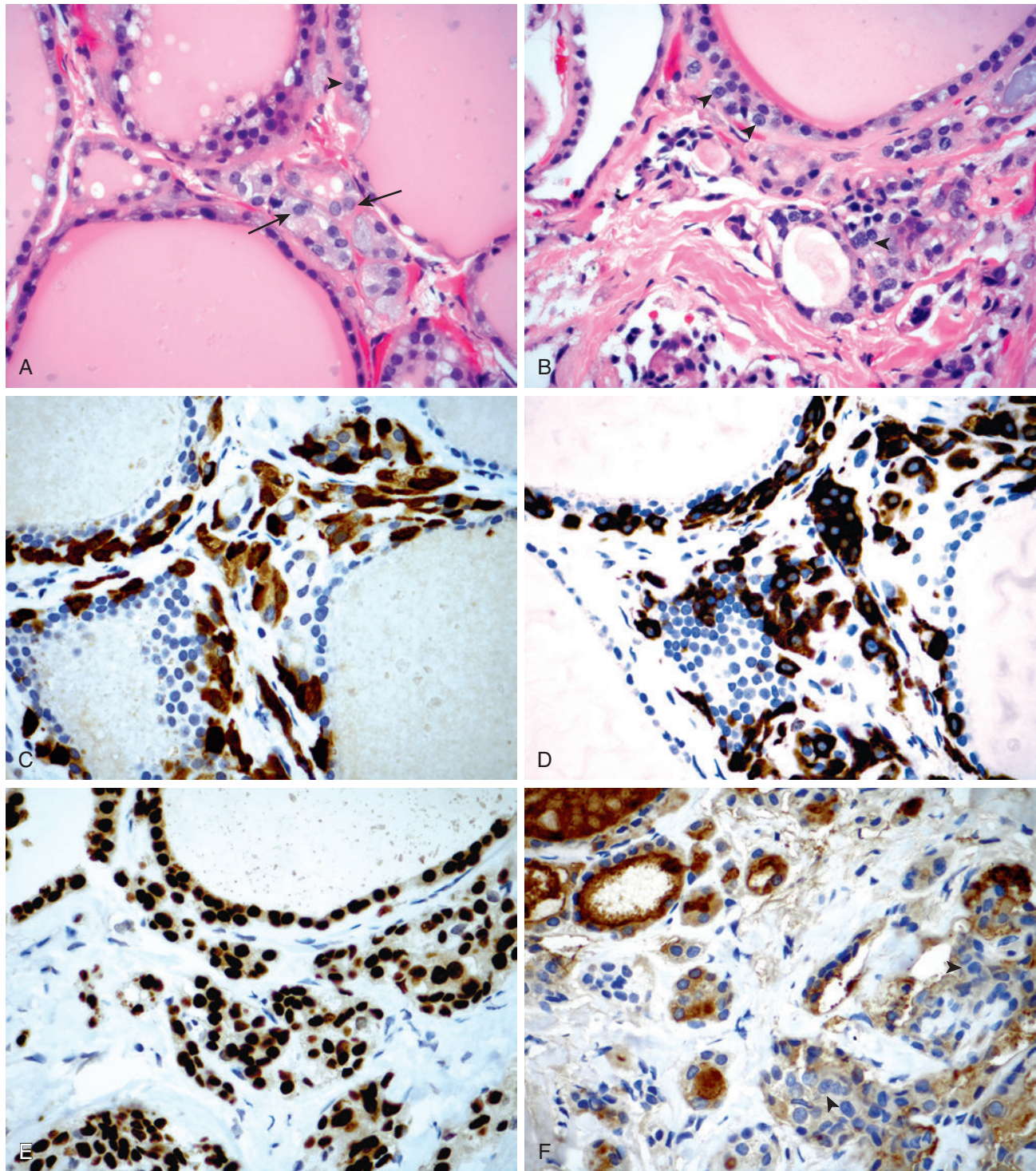


Fig. 26-5. Normal thyroid C-cells.

A, C-cells identified in between follicles (*arrows*) and associated with thyroid follicular cells (*arrowhead*) in a para-follicular location without contact with follicular lumen. **B**, Another example of para-follicular location of C-cells (*arrowheads*). Note in both images the C-cells are larger with more dispersed-appearing nuclear chromatin as compared to follicular epithelial cells. Immunohistochemical staining of C-cells includes reactivity for **(C)** calcitonin, **(D)** synaptophysin, **(E)** TTF-1 (nuclear staining) present in C-cells and follicular epithelial cells but **(F)** negative for thyroglobulin staining (*arrowheads*), which is reactive in the follicular epithelial cells.

abnormal; see Chapter 27 for discussion of lymphocytic infiltrates in thyroid gland parenchyma.

- Typically, normal thyroid gland is devoid of mature adipose tissue and skeletal muscle but either or both of these mesenchymal tissues can be found in thyroid gland as anatomic variation or metaplasia; see Chapter 27 for discussion of fat and muscle in thyroid gland parenchyma.

PHYSIOLOGY

- Main function of thyroid gland is production of thyroid hormones, including:
 - Thyroxine (T_4)
 - Triiodothyronine (T_3)
- Thyroid hormones regulate metabolism, increase protein synthesis throughout the body, and increase oxygen consumption:
 - Also important for body development and normal maturation of central and peripheral nervous systems
- Thyroid hormones:
 - Are stored in thyroglobulin
 - Stimulate metabolism, increase oxygen consumption, and cause a rise in heart production, cardiac output and heart rate
 - Essential for normal development, growth, and maturation
- Thyroid biosynthetic and secretory activities controlled by blood level of thyroid-stimulating hormone (TSH), a glycoprotein secreted by anterior pituitary gland:
 - TSH release regulated thyrotropin-releasing hormone (TRH), a tripeptide secreted by hypothalamus
 - TSH and TRH release regulated by circulating levels of T_3 and T_4 via negative feedback on pituitary and hypothalamus:
 - Low levels of T_3 and T_4 stimulate release of TSH and TRH.
 - High levels of T_3 and T_4 inhibit release of TSH and TRH.
 - Prolonged high levels of circulating TSH induce follicular cell hypertrophy, progressive resorption of colloid, and increased stromal vascularity.
- Exogenous iodine required for synthesis of T_4 :
 - Iodine balance maintained by dietary sources
 - Many conditions modify iodine intake, including medications, dietary supplements, and food additives.
- Calcitonin:
 - 32 amino acid peptide
 - Secretion regulated primarily by extracellular calcium concentration
 - Main function is regulation of level of calcium in plasma by feedback mechanism via inhibition of osteoblastic activity:
 - Increase in serum calcium concentration above normal physiologic levels activates calcium-sensing receptor, a G-protein coupled receptor that facilitates increased calcitonin secretion from the thyroid gland
 - Binding of calcitonin to its receptor on osteoclast inhibits bone resorption, lowering blood calcium by inhibiting bone resorption and calcium recovery from renal tubule ultrafiltrate
 - Resulting reduction in calcium concentration leads to lower calcitonin secretion.
 - Other stimuli enhancing calcitonin secretion include supraphysiologic concentrations of glucagon, gastrin (and pentagastrin), and cholecystokinin.

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Embryology, Anatomy, and Histology of the Ear

EMBRYOLOGY

External Ear

- External ear develops from the first brachial groove.
- Auricle (pinna) develops from the auricular hillocks, a group of six mesenchymal swellings, from the first and second branchial arches lying around the first branchial groove.
- Mesenchymal structures of the auricle arise from the mesoderm of the first and second branchial arches.
- Epithelium of the external auditory canal develops from the ectoderm at the dorsal end of the first branchial groove or cleft.
- Tympanic membrane forms from the first and second branchial pouches and the first branchial groove:
 - Ectoderm of the first branchial groove gives rise to the epithelium on the external side.
 - Endoderm from the first branchial pouch gives rise to the epithelium on the internal side.
 - Mesoderm of the first and second branchial arches gives rise to the connective tissue lying between the external and internal epithelial surfaces.

Middle Ear

- Middle ear space develops from invagination of the first branchial pouch (pharyngotympanic tube) from the primitive pharynx.
- Endoderm of the tubotympanic recess, a derivative of the first pharyngeal pouch, gives rise from its distal portion to the epithelium of the tympanic cavity and the mastoid antrum, and from its proximal portion to the epithelium of the auditory tube (eustachian or pharyngotympanic tube).
- Middle ear ossicles have different derivations:
 - Malleus and incus develop from the mesoderm of the first branchial arch cartilage (Meckel cartilage).
 - Stapes develops from the mesoderm of the second branchial arch cartilage (Reichert cartilage).
- Tensor tympani muscle, attached to the malleus, derives from the first branchial arch; stapedius muscle attached to the stapes, derives from the second branchial arch.

Inner Ear

- First of the three anatomic divisions of the ear to develop beginning toward the end of the first month of gestation.
- Membranous labyrinth, including the utricle, saccule, semicircular ducts, and cochlear duct, arises from the otic vesicle (otocyst), an invagination from the surface ectoderm, which migrates into its position, losing its connection to the surface ectoderm.
- Otic vesicle forms from the invagination of the surface ectoderm, located on either side of the neural plate, into the mesenchyme:
 - Invagination eventually loses its connection with the surface ectoderm.
- Bony labyrinth including the vestibule, semicircular canals, and cochlea arises from the mesenchyme around the otic vesicle.

ANATOMY (Figs. 22-1 through 22-3)

- The ear can be considered as three distinct regions or compartments to include:
 - External ear
 - Middle ear and temporal bone
 - Inner ear

External Ear

- Consists of the auricle (pinna), external auditory canal (or meatus), and the tympanic membrane at the medial end of the auditory canal.
- Outer portion of the external ear includes the auricle or pinna leading into the external auditory canal:
 - Skeleton of the auricle consists of a single plate of elastic cartilage conforming to the shape of the ear.
 - Lobule is the only part of the auricle that is devoid of skeletal support.
 - Cartilage of the auricle is continuous with that of the external auditory canal.
- External auditory canal or meatus extends from the concha to its medial limit, which is the external aspect of the tympanic membrane:
 - Lateral portion of external canal wall consists of cartilage and connective tissue.

- Medial portion of external canal wall consists of bone.
- Cartilaginous part of the external auditory canal constitutes slightly less than half its total length.
- Inconstant fissures referred to as the fissures of Santorini occur in the cartilage; these fissures may

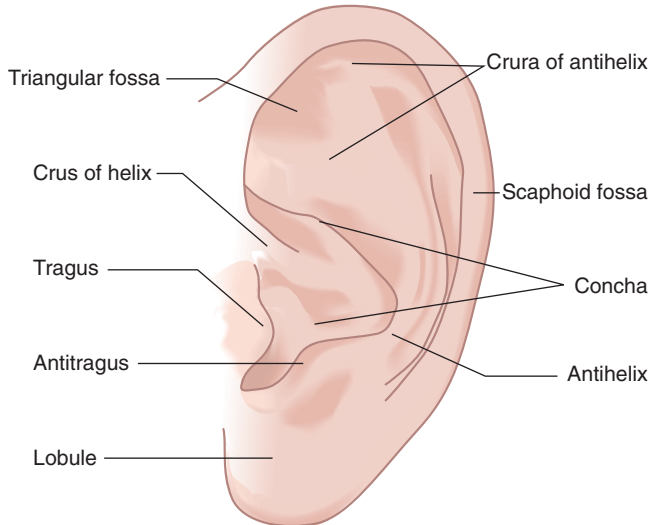


Fig. 22-1. Anatomy of the external ear.

- transmit infection from the canal to the parotid gland and superficial mastoid regions, or vice versa.
- Bony part of the canal is formed by both the tympanic part and the petrous part of the temporal bone.
- In adults, anterior and inferior walls of the cartilaginous canal are closely related to the parotid gland.
- Anterior wall of the bony canal is closely related to the mandibular condyle, the posterior wall to the mastoid air cells, and the medial portion of the superior wall to the epitympanic recess.
- Tympanic membrane (eardrum) is situated obliquely at the end of the external auditory canal sloping medially from above downward and from behind forward:
 - Tympanic membrane is a fibrous sheet interposed between the external auditory canal and the middle ear cavity.
 - Connective tissue interposed between these two layers consists of radiating fibers attached to the manubrium of the malleus that are reinforced peripherally by circular fibers
 - In the upper portion of the tympanic membrane there is a limited area where the connective tissue

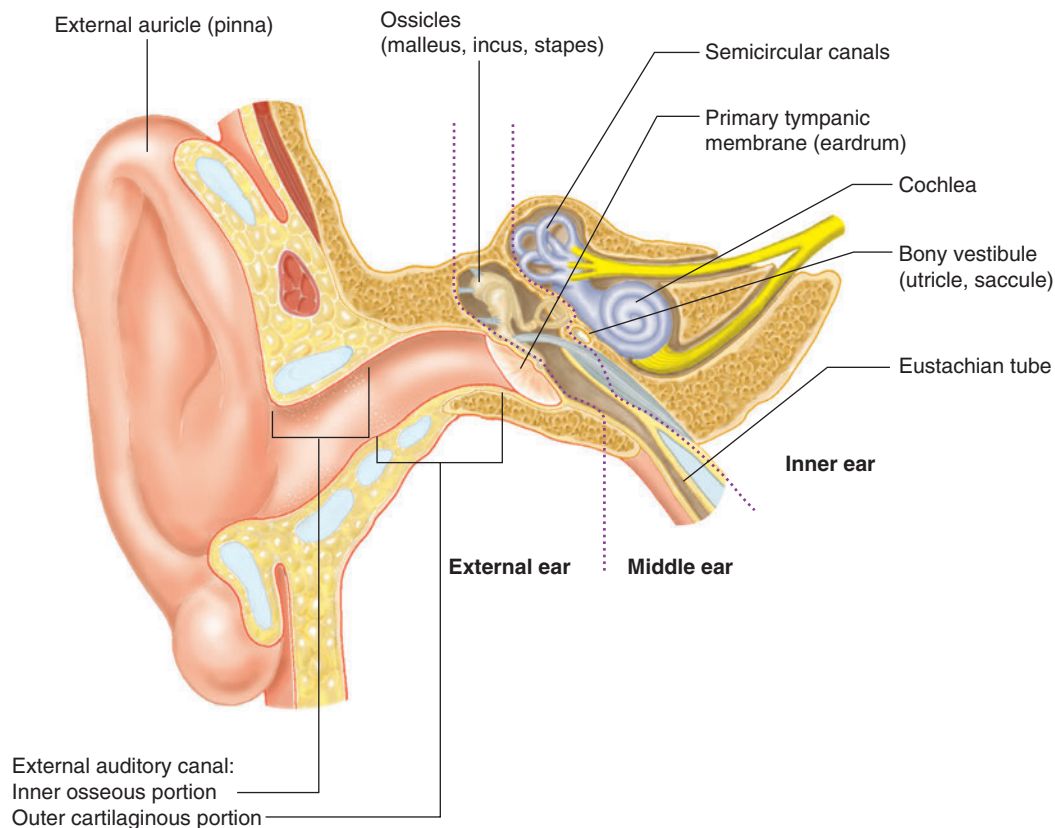


Fig. 22-2. Anatomy of the middle ear and temporal bone.

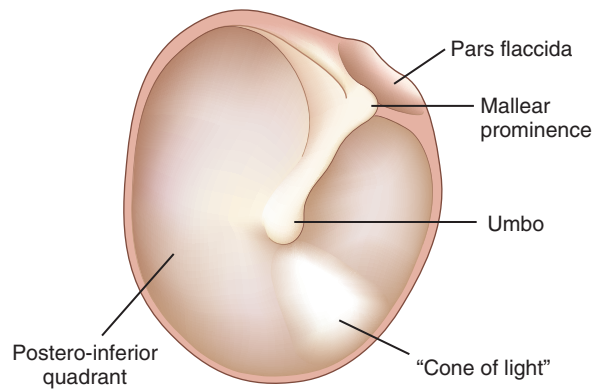


Fig. 22-3. External (lateral) aspect of the tympanic membrane (eardrum).

(Modified from Mills, Stacy E: *Histology for pathologists*, ed 3, Philadelphia, 2007, Lippincott, Williams, and Wilkins, Fig. 14-5.)

fibers are lacking; this area is referred to as the pars flaccida or Shrapnell membrane. In this area the tympanic portion of the temporal bone is deficient; this gap is referred to as the tympanic incisure or the notch of Rivinus, where the tympanic membrane attaches to the temporal bone.

- Remainder of the tympanic membrane in which there are intact connective tissue fibers is referred to as the pars tensa.
- Outer aspect of the tympanic membrane is concave:
 - Center of the concavity is referred to as the umbo, which is the strong point of attachment of the manubrium of the malleus to the tympanic membrane.
 - In otoscopic examinations of the tympanic membrane, the bright area of light reflection present downward and forward from the umbo is referred to as the “cone of light.”

Borders

- Medial border:
 - Limited medially by the external aspect of the tympanic membrane

Middle Ear (Tympanic Cavity)

- Middle ear or tympanic cavity lies within the temporal bone between the tympanic membrane and the squamous portions of the temporal bone laterally and the petrous portion of the temporal bone surrounding the inner ear medially.
- Contents include:
 - Ossicles (malleus, incus, and stapes), ligaments of the ossicles, tendons of the ossicular muscles,

eustachian tube, tympanic cavity proper, epitympanic recess, mastoid cavity, and the chorda tympani of the facial (VII) nerve

Eustachian (Auditory) Tube

- Extends from its tympanic ostium high on the anterior wall of the tympanic cavity to a nasopharyngeal ostium situated posterior to the inferior nasal concha.
- Can be divided into an osseous portion and cartilaginous portion:
 - Osseous portion or canal has a bony wall and is the lateral or tympanic third of the tube.
 - Anteromedial two thirds has a cartilaginous and connective tissue wall and is referred to as the cartilaginous portion of the tube.
 - Cartilaginous and osseous tubes meet at an obtuse angle.
- Eustachian tube is not straight but slightly S-shaped:
 - In adults:
 - Tympanic ostium is approximately 2 to 2.5 cm higher than is the nasopharyngeal end and runs downward, medially, and anteriorly to the nasopharynx.
 - Length of the tube in adults varies from 31 to 38 mm.
 - In infants:
 - Tube is shorter, relatively wider, and more horizontal in its course and therefore an easier pathway for infections ascending from the nasopharynx to the tympanic cavity.

Borders

- Lateral (internal) border:
 - Internal aspect of the tympanic membrane and squamous portion of the temporal bone
- Medial border:
 - Petrous portion of the temporal bone
- Superior border (roof):
 - Delimited by the tegmen tympani, a thin plate of bone that separates the middle ear space from the cranial cavity
- Inferior (floor):
 - Thin plate of bone separating the tympanic cavity from the superior bulb of the internal jugular vein
- Anterior border:
 - Delimited by the thin plate of bone separating the tympanic cavity from the carotid canal housing the internal carotid artery
- Posterior border:
 - Petrous portion of the temporal bone containing the mastoid antrum and mastoid air cells
- Tympanic cavity communicates anteriorly with the nasopharynx by way of the eustachian (auditory or pharyngotympanic) tube and communicates posteriorly with the mastoid air cells by way of the aditus and mastoid antrum.

Function

- Middle ear as well as the external ear function as conduits for sound conduction for the auditory part of the internal ear.

Inner Ear (Labyrinth)

- Embedded within the petrous portion of the temporal bone and composes the medial portion of the temporal bone adjacent to the cranial cavity
- Consists of the structures of the membranous (otic) labyrinth that is surrounded by an osseous layer or bony shell termed the osseous (bony) labyrinth (otic capsule), and the internal auditory canal in which the vestibulocochlear nerve (VIII) runs

Function

- Membranous labyrinth contains the cochlea, which is the organ of hearing and the vestibular system, which is the system of balance (equilibrium).
- Complexity of the anatomy of the inner ear is beyond the scope of this book, and the reader is referred to specific texts for more details.

INNERVATION**External Ear**

- Overlapping innervation including auriculotemporal branch of the mandibular branch of trigeminal (V) nerve; cutaneous branches of the cervical plexus, primarily the greater auricular and lesser occipital nerves from C2 and C3; and the auricular branches of the vagus (X) (nerve of Arnold), glossopharyngeal (IX), and facial (VII) nerves
- External aspect of the tympanic membrane is innervated from the auriculotemporal branch of cranial nerve V and the auricular branches of cranial nerves X, IX, and VII.

Middle Ear

- Nerve supply is chiefly from the tympanic plexus formed by the tympanic branch of the glossopharyngeal nerve (nerve of Jacobson) and from the carotico-tympanic nerves derived from the internal carotid plexus.

Inner Ear

- Nerve to the inner ear is the vestibulocochlear nerve or the eighth cranial nerve; these nerves run together in the internal auditory canal until the lateral end, at which point they separate into three parts, two vestibular and one cochlear.
- Fibers of the vestibular nerve arise from Scarpa ganglion.

BLOOD SUPPLY AND LYMPHATIC DRAINAGE**External Ear**

- Arteries and veins:
 - Blood supply to the auricle comes from branches of the external carotid artery.
 - Blood supply to the external auditory canal is the same as that to the auricle and in addition receives blood from the deep auricular artery, a branch of the internal maxillary artery.
 - Veins from the auricle and external auditory canal are the superficial temporal and posterior auricular veins, which join with the jugular veins and sometimes to the sigmoid sinus.
- Lymphatics:
 - From the auricle and external auditory canal to the parotid lymph nodes, the superficial cervical nodes, and the retroauricular lymph nodes

Middle Ear

- Arteries and veins:
 - Arterial supply to the middle ear is mostly derived from branches of the external carotid artery, including the internal maxillary, posterior auricular, and ascending pharyngeal arteries.
 - Veins of the middle ear parallel those of the arteries and empty into the pterygoid venous plexus and the superior petrosal sinus.
- Lymphatics:
 - To the retropharyngeal and parotid lymph nodes

Inner Ear

- Arteries and veins:
 - Primary arterial supply to the internal ear is via the labyrinthine or internal auditory artery, a branch of the anterior inferior cerebellar artery, or from the basilar artery.
 - Veins parallel those of the arteries and empty into the superior petrosal sinus or the transverse sinus.
- Lymphatics:
 - Internal ear is not usually described.

HISTOLOGY**External Ear (Fig. 22-4)**

- Auricle is essentially a cutaneous structure composed of keratinizing, stratified squamous epithelium with associated adnexal structures including hair follicles, sebaceous glands, and eccrine sweat glands; its subcutaneous tissue is composed of fibroconnective

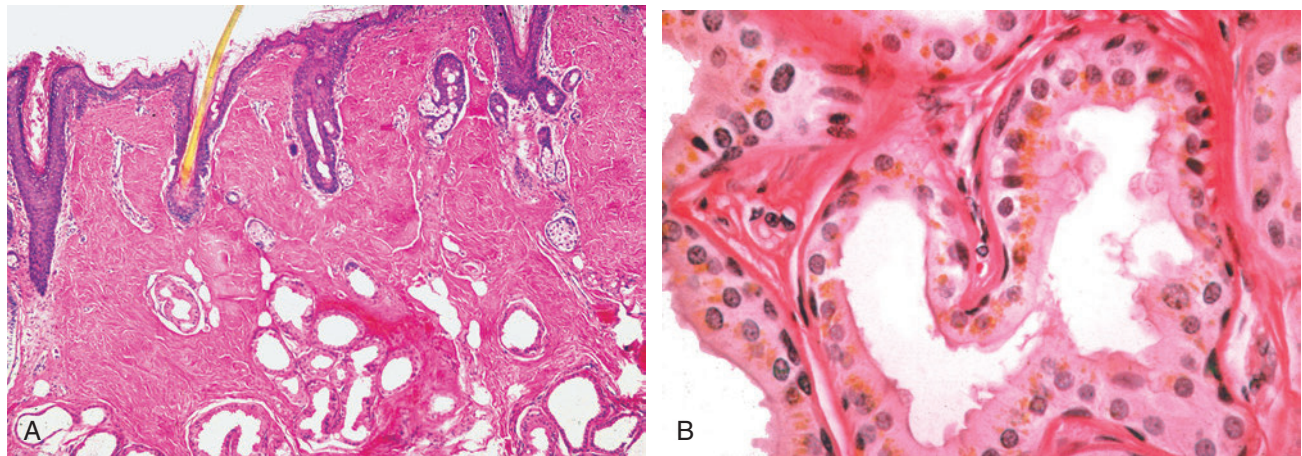


Fig. 22-4. Histology of external auditory canal.

A, The external ear is a cutaneous structure composed of keratinizing stratified squamous epithelium with associated adnexal structures including hair follicles, sebaceous glands, and eccrine sweat glands; keratinizing squamous epithelium lines the entire external auditory canal and covers the external aspect of the tympanic membrane. **B**, The outer third of the external canal includes the presence of ceruminous glands (modified apocrine glands), which are submucosal in location, arranged in clusters or lobules, and composed of a two-cell layer, including the inner or secretory cells containing intracytoplasmic cerumen appearing as granular, golden-yellow pigmentation, and flattened-appearing myoepithelial cells located peripheral to the secretory cells; the secretory cells show holocrine (decapitation) type secretion.

- tissue, fat, and elastic-type fibrocartilage, which gives the auricle its structural support.
- Outer third of the external canal is noteworthy, in addition to the other adnexal structures, for the presence of modified apocrine glands called ceruminous glands, replacing the eccrine glands seen in the auricle:
 - Ceruminous glands:
 - Produce cerumen
 - Are submucosal and arranged in clusters
 - Are composed of two cell layers:
 - Inner or secretory cells appear cuboidal with eosinophilic cytoplasm often containing intracytoplasmic granular, golden-yellow pigment (cerumen); secretory cells show holocrine (decapitation) type secretion characterized by secretory droplets along their luminal border.
 - Myoepithelial cells lie peripheral to the secretory cells and appear as flattened cells.
 - Ducts of the ceruminous glands terminate in the hair follicle or on the skin.
 - Ducts of ceruminous glands lack apocrine or myoepithelial cells.
 - In the inner portion of the external auditory canal, ceruminous glands, as well as the other adnexal structures, are absent.
 - Like the auricle, the external auditory canal is lined by keratinizing squamous epithelium, which runs throughout the canal and covers the external aspect of the tympanic membrane.
 - Tympanic membrane has a central bilaminated zone, including lateral radially arranged and medial circularly arranged collagenous fibers.
 - Inner two thirds of the external auditory canal contains bone instead of cartilage.
 - Due to the absence of adnexal structures there is relatively close apposition of the epithelium to the subjacent bone.

Auditory Epithelial Migration

- Represents the mechanism by which keratin is removed from the tympanic membrane; without such a self-cleaning process the keratin squames normally produced by the stratified squamous epithelium of the tympanic membrane would continuously build up and interfere with the conduction of sound via the tympanic membrane.
- Entire epithelium including keratin moves from the tympanic membrane onto the deep external auditory canal; from the deep external auditory canal the epithelium moves laterally to the junction of the deep (osseous) canal and the cartilaginous canal, where it is desquamated.
- Auditory epithelial migration occurs in two separate and discrete pathways:
 - Epithelium moves upward over the handle of the malleus then moves posterosuperiorly across the pars flaccida moving laterally over the deep canal.
 - Other pathway is radially moving centrifugally away from the handle of the malleus and pars

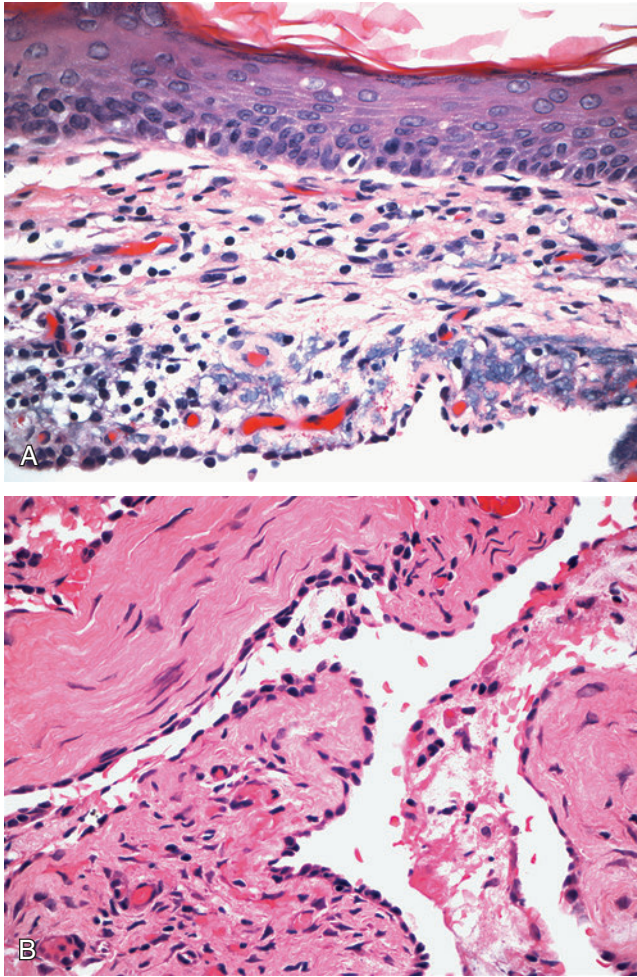


Fig. 22-5. Histology of tympanic membrane.

A, The tympanic membrane is covered externally by keratinizing squamous epithelium and **B**, internally (middle ear or tympanic cavity side) by a single layer of flattened cuboidal epithelium. The presence of chronic inflammatory cells between the two types of epithelium represents a component of chronic otitis media. The tympanic cavity, including mastoid air cells (not shown), is also lined by cuboidal epithelium.

flaccida to the periphery of the tympanic membrane and then to the deep canal.

- Process of auditory epithelial migration has been felt to represent a possible pathogenesis for the development of cholesteatoma; however, there is no definitive evidence linking auditory epithelial migration to the development of cholesteatoma.

Middle Ear (Figs. 22-5 and 22-6)

- Epithelial lining of the tympanic cavity, including internal aspect of the tympanic membrane (i.e., eardrum) is composed of:

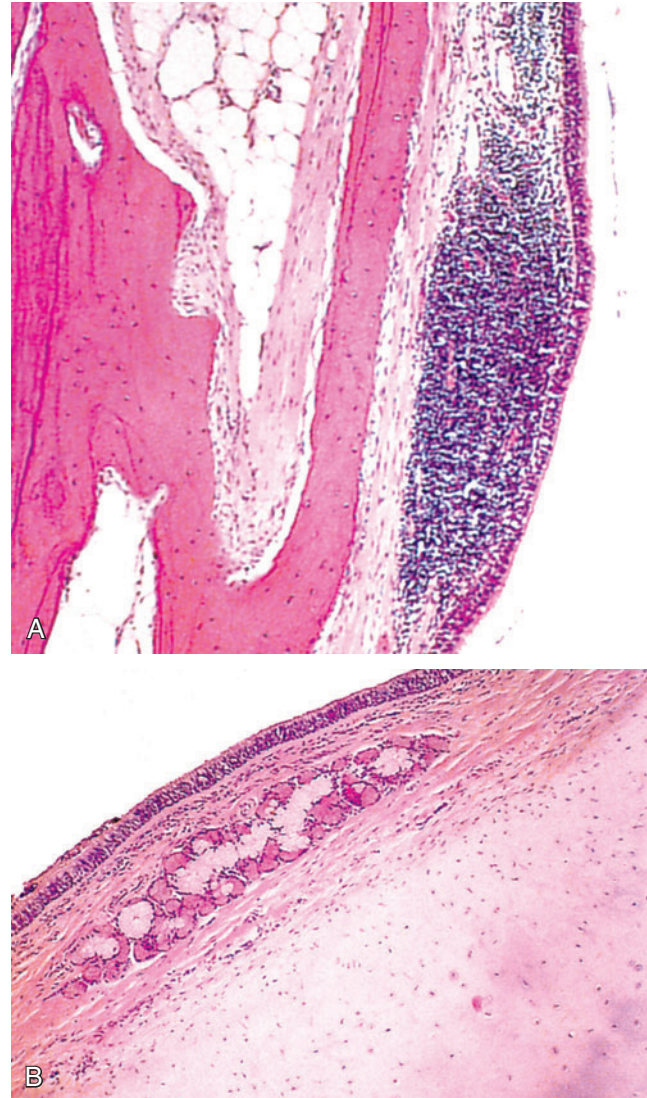


Fig. 22-6. Histology of eustachian tube.

A, The eustachian tube is lined by ciliated pseudostratified columnar epithelium. The presence of lymphoid aggregates, in particular in children, may become hyperplastic, closing off the eustachian tube and providing a milieu for otitis media. **B**, In the cartilaginous portion of the eustachian tube (*bottom right*) seromucinous glands can be identified lying immediately below the ciliated pseudostratified columnar epithelium.

- Single flat layer of cuboidal epithelium lining the tympanic cavity and mastoid
- Low ciliated epithelium from much of its length of the eustachian tube except as it approaches its nasopharyngeal end, where it becomes ciliated pseudostratified columnar epithelium containing goblet cells
- Epithelial lining the eustachian tube becomes pseudostratified as it approaches the pharyngeal end.

- Under normal conditions, there are no glandular elements within the middle ear; the presence of glandular epithelium in the middle ear is abnormal (e.g., metaplastic in otitis media, middle ear adenoma).
- Ciliated pseudostratified columnar epithelium may be found in limited patches among the flattened or cuboidal epithelium.
- Eustachian tubes contain:
 - A lymphoid component, particularly in children, referred to as Gerlach's tubal tonsil:
 - Reactive hyperplasia of this lymphoid component particularly in children may close off the eustachian tube, providing a milieu for otitis media.
 - Seromucinous glands in its cartilaginous portion
- Persistence of cartilage in each of the ossicles and the bifurcation of the stapes to form the crura with the obturator foramen between them distinguishes the middle ear ossicles from other long bones.
- Head of the stapes is formed of endochondral bone with a cartilaginous cap at the incudostapedial joint.
- Crura of the stapes are formed of periosteal bone only.
- From the middle ear aspect of the stapes footplate to its vestibular surface the histologic findings include the flattened to cuboidal epithelium of the tympanic cavity, a thin layer of bone, cartilage, and a single flattened (perilymphatic) epithelial cell layer.
- Malleus and incus, similar to long bones, have an outer covering of periosteal bone layer and an inner core of endochondral bone with well-formed haversian systems:
 - Manubrium (handle) of the malleus is covered predominantly by retained cartilage instead of periosteal bone.
 - Entire inner core of the manubrium, as well as the rest of the malleus, is composed of endochondral bone.
 - Short process of the incus shows a tip of unossified cartilage.

Mastoid Air Cells

- Represent a network of intercommunicating spaces that emanate from the tympanic cavity
- Each air cell is lined by flattened to cuboidal epithelium, which rests on periosteum that covers a thin frame of lamellar bone.

Pneumatization of the Temporal Bone

- In the newborn the rudimentary mastoid bone contains a single air space, the antrum, surrounded by diploic bone containing hematopoietic elements.
- As the mastoid process develops, the marrow spaces hollow out.
- Mesenchymal component occupying the space is resorbed and the developing air-containing cells become lined by the advancing endodermal epithelium.
- Mastoid process is constantly pneumatized in adults, although not in the infant:
 - Cells grow out from the antrum, as well as from each other, forming complex interlocking chains of thin-walled cavities opening into each other.
 - Antrum apparently always has air cells; the mastoid process is usually one of several types including pneumatized (containing air cells), diploic (containing marrow), mixed (containing air cells and marrow), or sclerotic.
 - Approximately 80% of people the mastoid is well pneumatized by the age of 3 or 4, but in approximately 20% of people normal pneumatization fails to occur.

Middle Ear Ossicles

- Middle ear ossicles develop from cartilage with a single center of ossification for bone; there is no epiphyseal ossification.

Middle Ear Joints

- Both the incudomalleal and incudostapedial joints are diarthrodial.
- Ossicular articulations are typical synovial joints.
- Middle ear epithelium is present on the outer surface of the joint capsule and synovial membrane is present on its inner surface.
- Joint capsule is composed of fibrous tissue with a high elastic fiber content.
- Articular disk representing the space in between the articular ends is composed predominantly of fibrocartilage.
- Articular processes of the malleus and the incus are covered by cartilage.

Inner Ear

- Complexity of the anatomy of the inner ear is beyond the scope of this book, and the reader is referred to specific texts for more details.

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Non-Neoplastic Diseases of the Ear

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE EAR

BOX 23-1 Classification of Non-Neoplastic Lesions of the Ear and Temporal Bone

External Ear

- Developmental (accessory tragi; first branchial cleft anomalies, others)
- Infectious and inflammatory
- Keloid
- Epidermal and sebaceous cysts
- Idiopathic cystic chondromalacia
- Chondrodermatitis nodularis helices chronicus
- Autoimmune systemic diseases:
 - Relapsing polychondritis
 - Gout
 - Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
 - Others

- Exostosis
- Synovial chondromatosis

Middle and Inner Ear Including Temporal Bone

- Developmental and congenital anomalies
- Infectious (otitis media) and inflammatory
- Otic or aural polyp
- Cholesteatoma
- Langerhans cell histiocytosis
- Heterotopias (central nervous system tissue; salivary gland)
- Otosclerosis
- Paget disease
- Ménière disease
- Others

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES OF THE EAR

- The ear, including the external, middle, and internal ear, often is the target organ for congenital anomalies.
- Congenital abnormalities occur as an isolated defect or in combination with other aural and extra-aural abnormalities and vary from cosmetic defects to complete hearing loss.
- A complete discussion of the developmental defects of the ear is beyond the scope of this chapter; the interested reader is referred to other texts that detail this subject.
- This section includes the more common developmental abnormalities that the surgical pathologist is likely to be confronted with in daily practice.

- Located on the skin surface often anterior to the auricle and may clinically be mistaken for a papilloma
- Thought to be related to second branchial arch anomalies
- May occur independent of other congenital anomalies but may occur in association with cleft palate or lip, mandibular hypoplasia, or in association with other anomalies such as Goldenhar syndrome (oculoauriculovertebral dysplasia)

Pathology

- Histologically, accessory tragi recapitulate the normal external auricle and include skin, cutaneous adnexal structures, and a central core of cartilage.

Differential Diagnosis

- Squamous papilloma:
 - The absence of cutaneous adnexal structures and cartilage differentiates squamous papilloma from accessory tragi.

Treatment and Prognosis

- Simple surgical excision is curative.

EXTERNAL EAR

Accessory Tragi (Figs. 23-1 and 23-2)

Synonyms: Supernumerary ears, accessory auricle, polyotia

Clinical

- Appear at birth
- Unilateral or bilateral, solitary or multiple, sessile or pedunculated, soft or cartilaginous, skin-covered nodules or papules.



Fig. 23-1. Accessory tragus.

Accessory tragus appearing as pedunculated, skin-covered papules located on the skin surface anterior to the auricle; these lesions may be mistaken clinically for a papilloma.

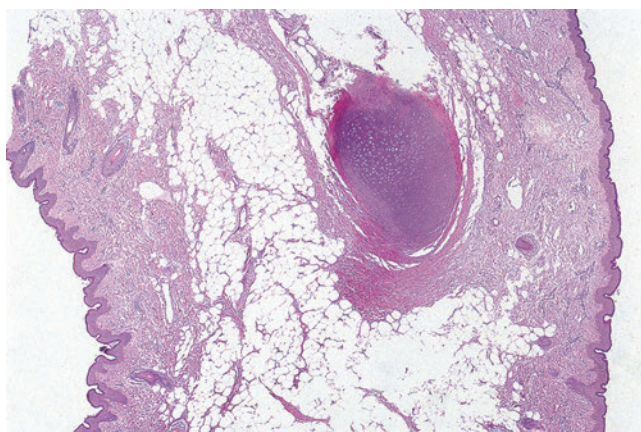


Fig. 23-2. Accessory tragus.

Histologically, accessory tragi recapitulate the normal external auricle as evidenced by the presence of skin, including keratinizing squamous epithelium, cutaneous adnexal structures, and a central core of cartilage.

Branchial Cleft Anomalies

- First branchial cleft anomalies typically occur in the area of the external ear and include cysts, sinuses, and fistulas.
- See the Section on the Neck for more complete discussion.

MIDDLE AND INNER EAR

Developmental Defects

- Numerous developmental or congenital anomalies affect the middle ear and temporal bone; a complete discussion of the developmental defects of the ear is beyond the scope of this chapter. The interested reader is referred to other texts.
- In brief, developmental or congenital anomalies of the middle ear and temporal bone include a variety of anatomic variations and anomalies, hereditary deafness (primarily conductive) occurring in syndromes, deafness caused by noxious prenatal influences, first and second branchial arch syndromes, dysplasias of the osseous and membranous cochlea and vestibular labyrinth, and hereditary/genetic sensorineural hearing loss.
- Other dysplasias of the external, middle, and inner ear include a combination of hypertelorism, microtia, and clefting, and 18q syndrome.
- Anatomic variations and anomalies may involve the facial nerve, jugular bulb, and intratemporal carotid artery:
 - Facial nerve anomalies include congenital bony dehiscence of the facial canal, anatomic variation, or anomalies in the course of the facial nerve, mastoid segment anomalies, anatomic variation of the chorda tympani nerve, and abnormal facial artery and vein.
 - Jugular bulb anomalies include superolateral extension of the bulb or superomedial enlargement of the bulb.
 - Abnormalities of the intratemporal carotid artery include aneurysm, aberrant location, abscess and inflammatory necrosis, traumatic lacerations, and atherosclerotic changes.
- Hereditary deafness primarily conductive occurring in syndromes include:
 - Mandibulofacial dysostosis (Treacher Collins syndrome)
 - Acrofacial dysostosis (Nager syndrome)
 - Craniofacial dysostosis (Crouzon syndrome)
 - Klippel-Feil syndrome (fused vertebra, short neck, facial asymmetry, visceral abnormalities, deafness)
 - Marfan syndrome (arachnodactyly, ectopia lentis, deafness)

- Pierre Robin syndrome (cleft palate, micrognathia, glossoptosis, low-set ears, deformed pinna, and hearing loss)
- Other hereditary diseases causing conductive hearing loss, include osteoporosis (Albers-Schönberg disease or marble bone disease), otosclerosis, osteogenesis imperfecta
- Deafness caused by noxious prenatal influences (embryopathic atresias) include:
 - Maternal rubella
 - Birth injuries
 - Hyperbilirubinemia (erythroblastosis fetalis)
 - Drugs, including thalidomide, quinine
 - Cretinism
- First and second branchial arch syndromes include a variety of abnormalities with nonotologic and otologic manifestations
- Otologic abnormalities include:
 - Malformed or absent external ears
 - Atretic external auditory canal and impaired hearing
- Nonotologic features include:
 - Asymmetric facies
 - Temporomandibular joint
 - Neuromuscular abnormalities
 - Associated abnormalities of the cardiovascular, renal, and central nervous systems; Goldenhar syndrome, also known as oculoauriculovertebral dysplasia, is a first and second branchial arch syndrome characterized by ear tags and preauricular pits and fissures, epidermoids and lipodermoids, and vertebral column abnormalities.
- Of the approximately 2000 to 3000 profoundly deaf infants born yearly in the United States, 35% to 50% have a defined genetic origin for their hearing impairment.
- In approximately one third the hearing loss is syndromal or associated with other anomalies.
- In adults, approximately 20% of sensorineural hearing loss has a genetic cause.
- Etiologic factors vary with age.
- More than 50% of early-onset hearing loss is due to genetic factors, of which:
 - 60% to 70% are autosomal recessive (both parents carry the affected gene, involvement of the offspring is 25%)
 - 20% to 30% autosomal dominant (one parent carries the affected gene and the incidence of involvement of the offspring is approximately 50%)
 - 2% are X-linked
- In patients with late-onset hearing loss:
 - Approximately 20% are due to infections
 - About 7% due to trauma
 - 35% due to old age, heredity, and noise trauma
 - Approximately 35% of unknown cause

Hereditary sensorineural hearing loss includes the following categories:

- Autosomal-recessive hereditary sensorineural hearing loss:
 - Hereditary recessive sensorineural hearing loss without associated defects (about 50% of recessive hereditary deafness), including recessive congenital severe deafness, high-frequency deafness, mid-frequency deafness)
- Inborn errors of metabolism and deafness:
 - Albinism and deafness
 - Hurler syndrome (abnormality of mucopolysaccharide metabolism)
 - Tay-Sachs disease (ganglioside lipidoses and deafness)
 - Wilson disease (hepatolenticular degeneration and deafness)
- Degenerative diseases of the nervous system and deafness:
 - Friedrich ataxia (spinocerebellar ataxia, deafness)
- Congenital heart disease and deafness:
 - Jervell and Lange-Nielsen syndrome (cardiac conduction anomaly, deafness)
- Endocrine system disorders and deafness:
 - Pendred syndrome (nonendemic goiter and deafness)
- Ocular diseases and deafness
 - Usher syndrome (retinitis pigmentosa, deafness)
 - Cockayne syndrome (retinitis pigmentosa, mental retardation, dwarfism, retinal atrophy, deafness)
 - Alström syndrome (retinitis pigmentosa, obesity, diabetes mellitus, deafness)

Autosomal-dominant hereditary sensorineural hearing loss:

- Inborn errors of metabolism and deafness:
 - Tietze syndrome (albinism, deafness, abnormality of tyrosine metabolism)
 - Waardenburg syndrome (partial albinism, deafness, abnormality of tyrosine metabolism)
 - Schäfer syndrome (hereditary mental retardation, deafness, abnormality of tyrosine metabolism)
 - Hereditary mental retardation, homocystinemia, deafness, abnormality of methionine metabolism
- Nephropathies and deafness:
 - Alport syndrome (hereditary nephritis, deafness)
 - Muckle-Wells syndrome (hereditary nephritis, urticaria, amyloidosis, deafness)
 - Herrmann syndrome (hereditary nephritis, mental retardation, epilepsy, diabetes, and dominant nerve deafness)
- Ectodermal defects and deafness:
 - von Recklinghausen disease (vestibular schwannomas [unilateral, bilateral] and deafness)

- Dysplasia of the inner ear may be inherited, sporadic, or the result of chromosomal aberrations:
 - Typically, both ears are involved but perhaps not to a similar extent.
 - The classification of dysplasias of the osseous and membranous cochlea and vestibular labyrinth are divided into eight types:
 - Type I: isolated aplasia or dysplasia of the lateral semicircular canal
 - Type II: type I plus cochlear dysplasia
 - Type III: type I plus aplasia or rare club-shaped distension of the vestibule with rudimentary superior or posterior semicircular canals; a normal cochlea is present
 - Type IV: aplasia or dysplasia of all three semicircular canals plus severe cochlea dysplasia
 - Type V: aplasia or dysplasia of all three semicircular canals plus normal cochlea
 - Type VI: aplasia of all three semicircular canals plus cochlea aplasia
 - Type VII: normally configured vestibular labyrinth with aplasia of the cochlea
 - Type VIII: aplasia of the vestibular labyrinth and cochlea
- Above subclassifications of dysplasias of the osseous and membranous cochlea and vestibular labyrinth are based on earlier reports detailing the morphologic changes involving the cochlear modiolus, osseous spiral lamina, and contents of the vestibule and endolymphatic sac and duct. The original designations for the dysplasias of the cochlea and vestibular labyrinth in patients with profound congenital hearing loss include Michel type, Mondini type or Mondini-Alexander type, Scheibe type, and Siebenmann-Bing type:
 - Michel type includes bilateral aplasia of the cochlear and vestibular capsule with bilateral aplasia of the eighth cranial nerve.
 - Mondini type includes anomalies of the cochlea; this may include the presence of a single coil and/or flattening and underdevelopment
 - Scheibe type, referred to as cochleosaccular dysplasia, includes morphologic changes limited to the membranous cochlea and saccule. The utricle and semicircular canals are not involved.
 - Siebenmann-Bing type includes dysplasia of the membranous cochlea and vestibular labyrinth with a well-formed bony labyrinth (cochlear capsule).

Heterotopias (Choristomas) of the Middle Ear and Mastoid

Definition: Heterotopias include the presence of normal-appearing tissue(s) in an anatomic location in which they normally are not found.

Synonyms: Choristomas; ectopias

- Heterotopias that occur in the middle ear include salivary gland tissue and neuroglial tissue:
 - Presence of glial tissue in the middle ear may represent acquired encephalocele rather than heteropia; see next section.

Middle Ear Salivary Gland Heterotopia (Fig. 23-3)

- May present with unilateral conductive hearing loss, tend to occur more often in women and occurs over a wide age range

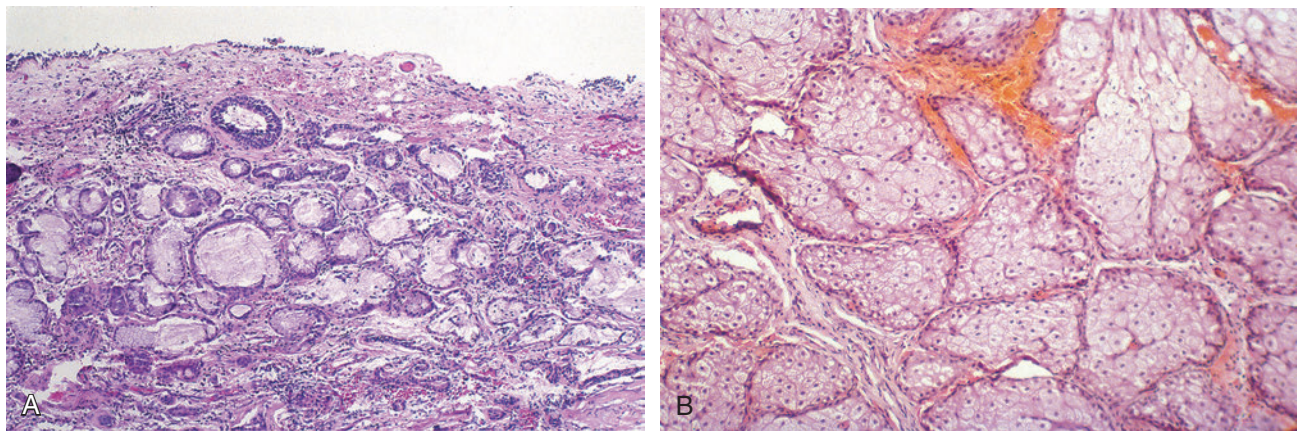


Fig. 23-3. Middle ear heterotopia.

- A,** Heterotopic salivary gland tissue within the middle ear composed of seromucous glands. Note the presence of middle ear attenuated cuboidal-appearing epithelium overlying the heterotopic salivary gland tissue at the top of the image.
- B,** Heterotopic sebaceous glands in the middle ear.

- Often arise in conjunction with facial nerve and ossicular chain anomalies:
 - The combination of facial nerve and ossicular chain anomalies may be explained on the basis of a second branchial arch developmental abnormality.
- Salivary choristomas of the middle ear may be associated with branchial arch abnormalities, most commonly the second arch, as well as abnormalities of the facial nerve, including:
 - Bilateral preauricular pits, conchal bands, an ipsilateral facial palsy, and bilateral Mondini-type deformities

Pathology

Gross

- Choristomas appear as a lobulated, nonpulsatile soft tissue mass lying in the middle ear space with an intact tympanic membrane.

Histology

- Salivary gland tissues include an admixture of seromucous glands and adipose tissue.

Treatment and Prognosis

- Conservative surgical removal is the preferred treatment.
- Choristomas often adhere to dehiscent facial nerve; if complete surgical resection will compromise the integrity of the facial nerve, then incomplete resection is justified.
- Biopsy for diagnostic purposes followed by observation is an alternative to surgical excision.

- Rarely, salivary gland ectopia may produce a salivary gland neoplastic proliferation (e.g., pleomorphic adenoma).

Middle Ear Neuroglial Heterotopia

- True neuronal heterotopias in which isolated neuroglial tissue is located in the middle ear and temporal bone without continuity with the central nervous system is rare.
- More common occurrence in which glial-type tissue is present within the middle ear/temporal bone is seen in association with an acquired encephalocele.

Acquired Encephalocele (Fig. 23-4)

- Represent herniation of the brain into the middle ear and mastoid via compromise of the tegmen, a thin bony shell that separates the middle ear and mastoid cavity from the temporal lobe:
 - Tegmen may be compromised or destroyed secondary to trauma or prior surgery, by a complication of otitis media, or due to a congenital defect.
 - Fracture of the temporal bone may also result in herniation of the brain into the middle ear and mastoid.
 - Some cases appear to have occurred spontaneously without known association with an underlying cause and/or without a history of trauma, tumor, cholesteatoma, or surgery of the mastoid or cranium.
- No gender predilection; may occur over a wide age range but tends to occur in older individuals
- Often represent an incidental finding in patients requiring surgery for chronic otitis media

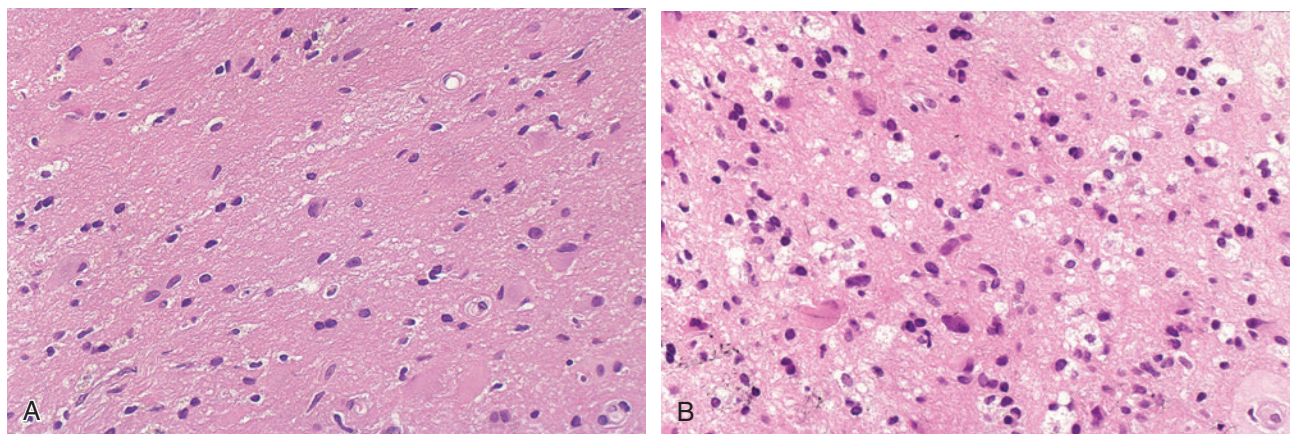


Fig. 23-4. Acquired encephalocele.

A, Acquired encephalocele, in which normal CNS tissue characterized by the presence of neuroglial tissue herniates into the middle ear space. This patient had a long-standing history of chronic otitis media and had undergone multiple operations. **B**, In some examples of acquired encephalocele, there may be changes of reactive gliosis characterized by astrocytic hypertrophy and hyperplasia.

- Associated symptoms may include unilateral conductive hearing loss, persistent otorrhea, leakage of CNS tissue, and/or recurrent episodes of meningitis.
- In patients suspected of having ectopic neuroglial tissue in this site, radiologic imaging (e.g., CT scans) may prove valuable in identifying a defect and/or connection to the CNS.

Pathology

Histology

- Includes a heterogeneous population of cells, including glial cells, histiocytes, and mature lymphocytes; reactive alterations of the neuroglial tissue (gliosis) may be present
- In addition, granulation tissue and keratinizing squamous epithelium (cholesteatoma) may be present
- Immunohistochemistry:
 - Confirmation of neuroglial tissues includes reactivity with glial fibrillary acidic protein (GFAP).

Differential Diagnosis

- Chronic otitis media:
 - Fibrillary appearing stroma that are often present may simulate the appearance of neurofibrillary matrix
 - GFAP will assist in confirming or excluding the presence of neuroglial tissues.
- Glial neoplasms

Treatment and Prognosis

- Management for acquired encephalocele is surgical:
 - For defects smaller than 1 cm in diameter, the transmastoid approach can be used.
 - For defects larger than 1 cm, the combined transmastoid-minicraniotomy approach provides good access.
- Potential complications include brain abscess.

ACQUIRED LESIONS OF THE EAR

EXTERNAL EAR

Keloid (Figs. 23-5 and 23-6)

Definition: Nonneoplastic dermal fibroproliferative process representing exaggerated tissue response to trauma representing one extreme of the spectrum of reparative reactions of the skin.

- “Keloid” derived from the Greek word *chele*, meaning “claw-like,” describing the tendency for these lesions to extend beyond the site of injury

Clinical

- Equal gender predilection; can occur at any age but is most common in young adults under 30 years of age



Fig. 23-5. Keloids.

A, Keloid appearing as polypoid mass covered by thin, glistening, hairless skin. **B**, Keloid with associated ulceration.

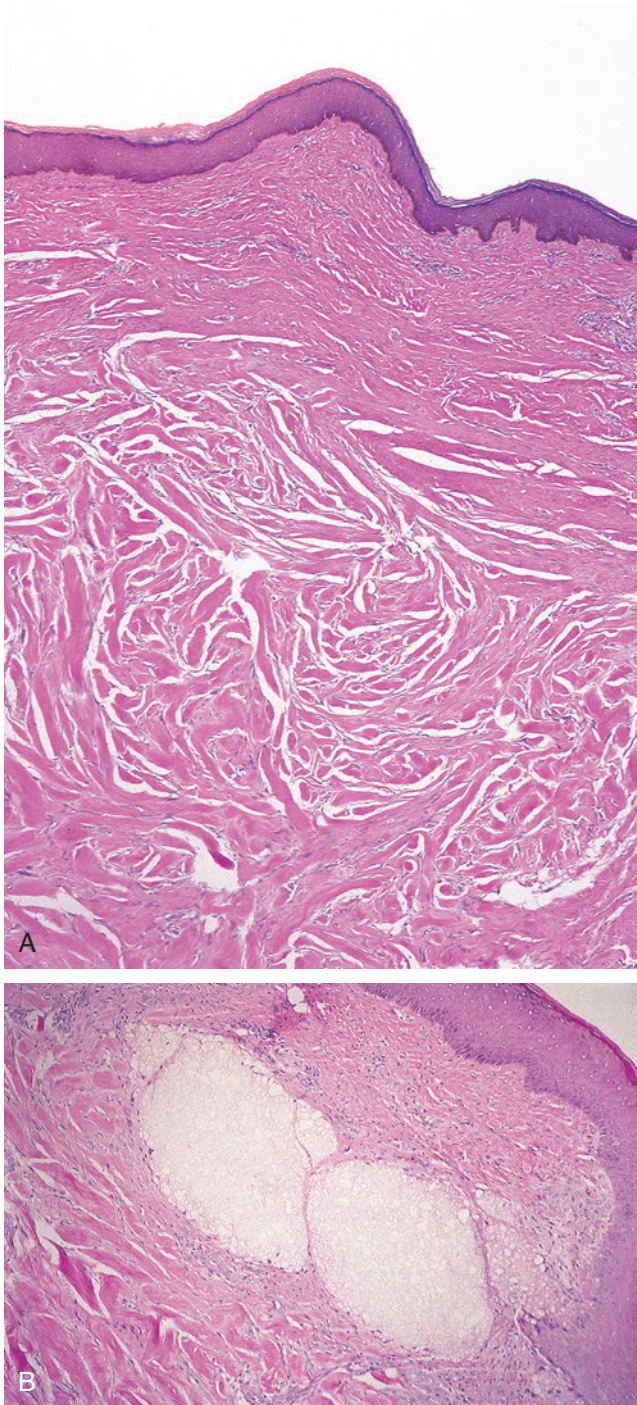


Fig. 23-6. Keloid.

A, Keloid composed of haphazard fascicles of hyalinized collagen that blend with surrounding dermal fibers; the overlying cutaneous squamous epithelium is thin and devoid of dermal adnexa. **B,** Keloid treated by steroid injection resulting in small subepithelial steroid lakes.

- Common in dark-skinned people, especially in young black women who have had their ears pierced
- Most common sites include presternum, limbs, neck, and face; the latter include the earlobes and pinna.
- Most often are asymptomatic but may be associated with pruritus, paresthesia, and pain
- Often associated with a variety of cutaneous injuries, including surgery, ear piercing, BCG vaccinations, injections, burns, lacerations, insect bites; the development following injury may occur anywhere from weeks up to a year.

Pathology

Gross

- Often polypoid in appearance covered by thin, glistening, hairless skin; size is variable, usually measuring less than 2 cm; however, they may attain a diameter of several centimeters.

Histology

- Haphazardly arranged fascicles of hyalinized collagenous fibers with scattered fibroblasts and myofibroblasts
- Proliferation is not encapsulated but blends subtly with the surrounding dermal fibrous tissue:
 - Collagen bundles are often separated by dermal mucosubstance, creating an “edematous” appearance.
- Poorly vascularized with widely scattered dilated blood vessels
- Overlying epidermis is thin and atrophic, without dermal adnexal structures.
- Foreign body giant cell reaction is uncommon, except in patients treated with corticosteroid injection.
- Pools of amorphous mucin-like material may also be seen following steroid injection.

Differential Diagnosis

- Hypertrophic scar:
 - Lack the dense hyalinized collagenous fibers, have more delicate fibrillar collagen, and have a more orderly arrangement of the collagen and fibroblastic cells often with a parallel orientation to the skin surface
 - Mature hypertrophic scars generally do not have an abundance of mucosubstances and therefore have a more compact microscopic appearance.
 - Hypertrophic scars usually do not recur following excision.
- Dermatofibroma (DF) and dermatofibrosarcoma protuberans (DFSP):
 - Extremely low cellularity of keloids distinguishes it from DF and DFSP.

- In contrast to keloids there is hyperplasia of the overlying epidermis in DF and DFSP.
- Unusual variant of dermatofibroma characterized by keloidal-type changes and termed keloidal dermatofibroma has been described:
 - Clinically appear similar to usual DF
 - Characterized by keloidal-like collagen admixed with elements typically present in DF
- DFSP shows immunoreactivity for CD34.

Treatment and Prognosis

- Surgical excision is the preferred treatment.
- Recurrence rates of 40% following simple surgical resection have been reported.
- Intralesional steroid (triamcinolone) injections alone provide response rates of 50% to 100% with recurrence rates of 5% to 50% at 5 years:
 - Intralesional triamcinolone injections considered gold standard in nonsurgical management
 - Intralesional verapamil, independent of or in conjunction with triamcinolone, has shown efficacy in treatment of keloids (and hypertrophic scars) with flattening of the raised scars and regaining normal pigmentation.
- When surgery is followed by steroid injection or radiation therapy (10 Gy), recurrence rates are consistently below 50%.
- Intralesional injection of interferon or bleomycin has shown 50% reduction in size, and response appears to be limited to the area treated.
- Intralesional cryosurgery has emerged as a safe and effective new treatment by destroying the hypertrophic scar tissue with minimal damage to the skin surface.
- TGF- β (transforming growth factor beta) and PDGF (platelet-derived growth factor) play an integral role in the formation of keloids, and future development of selective inhibitors of TGF- β might produce new therapeutic tools with enhanced efficacy and specificity for treatment of keloids.

Idiopathic Cystic Chondromalacia of the Auricular Cartilage

(Figs. 23-7 and 23-8)

Definition: Benign cystic degeneration of the auricular cartilage of unknown cause.

Synonyms: Pseudocyst of the auricle; auricular or endochondral pseudocyst

Clinical

- Typically affects men and rarely seen in women; generally affects young and middle-aged adults
- Can occur along any portion of the auricle with the most common site adjacent to the helix



Fig. 23-7. Idiopathic cystic chondromalacia.

Idiopathic cystic chondromalacia appearing as a subepithelial swelling along the anterior pinna.

- Symptoms include unilateral, painless swelling of the auricular cartilage without overlying ulceration or erythema; symptoms develop over a period of weeks to years; may occur anywhere on the auricle but the scaphoid fossa (80%) is the most common site; occasionally lesions may be bilateral.
- Markedly elevated lactate dehydrogenase (LDH) levels may be found in aspirated fluid.
- Although trauma has been implicated in causing these lesions, there is no definitive connection to a prior traumatic event and the cause(s) for this condition remains unknown:
 - Belief that repeated trauma stimulated by such phenomena as sleeping on hard pillows, the wearing of motorcycle helmets, stereo headphones, or the Italian birthday custom of having one's auricle pulled
 - Ischemic necrosis of the cartilage or the abnormal release of lysosomal enzymes by chondrocytes may also be cofactors.
- May arise within a potential plane left during embryonic fusion of the auricular hillocks

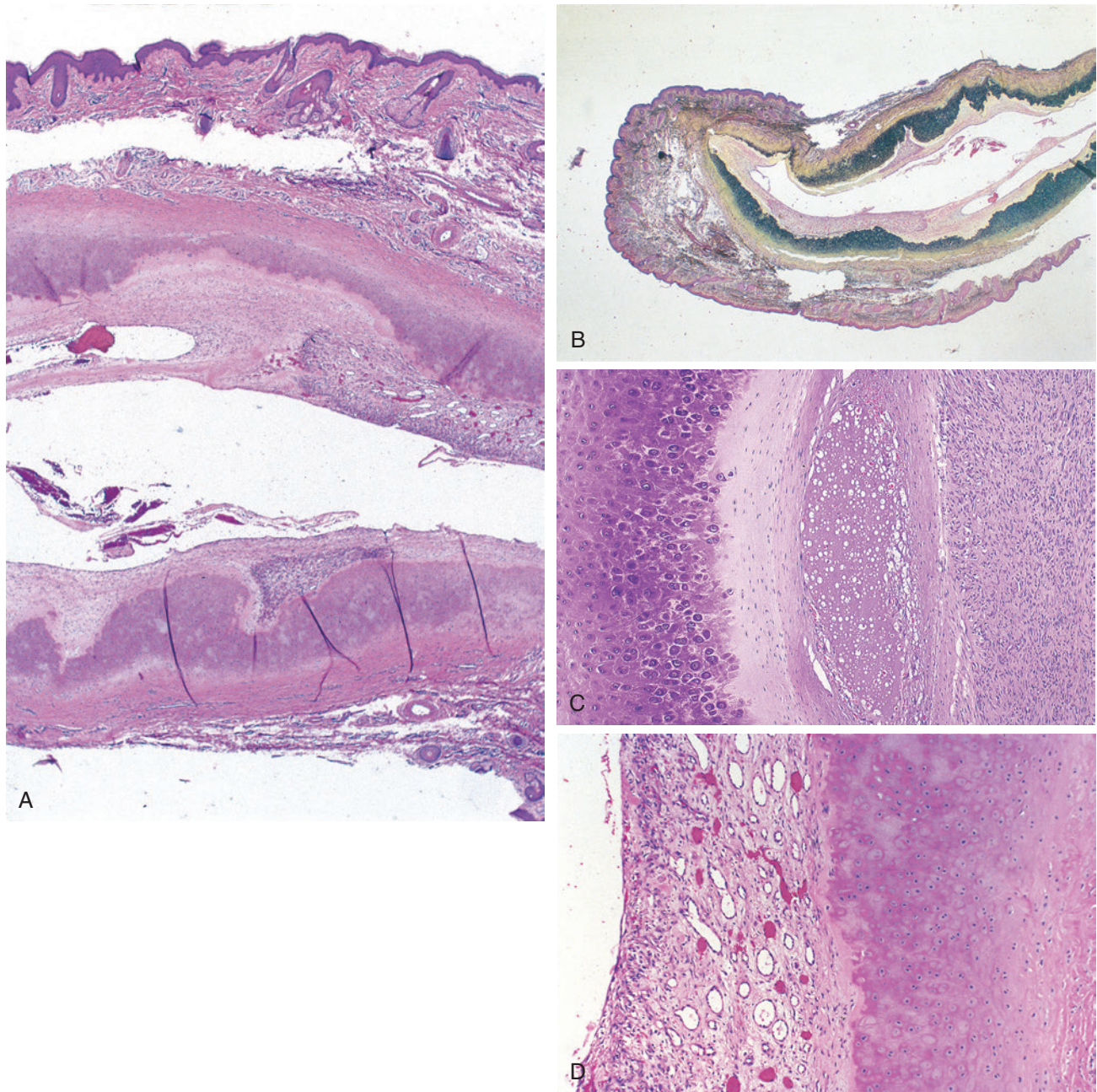


Fig. 23-8. Idiopathic cystic chondromalacia.

A and B, At low magnification idiopathic cystic chondromalacia appears with subepithelial intracartilaginous thin walled cysts. In **B**, the cartilage appears black in this elastic stain. **C**, The cysts lack an epithelial lining and **(D)** are in part lined by granulation tissue.

Pathology

Gross

- Fluid-filled distended mass
- Excised tissue may include only a fragment of the cyst wall or, less often, a full-thickness excision of the ear.

- Intact cyst usually contains fluid described as “olive-oil-like.”
- Cyst wall consists of a 1- to 2-mm rim of cartilage.
- Cyst lining may be a smooth and glistening cartilaginous surface or may include roughened rust-colored patches.

- Cyst is usually an elongated cleft, but multifocal cystic degeneration may be seen.

Histology

- Changes are restricted to the cartilage within which irregular-shaped cystic areas are seen; cyst is the result of loss of cartilage.
- Cysts lack an epithelial cell lining (pseudocyst) and generally are devoid of content.
- Cystic cleft is often centrally placed in the cartilaginous plate.
- Rim of fibrous tissue may be seen along the inner portion of the cyst or a granulation tissue reaction composed of fibrovascular tissue, and scattered chronic inflammatory cells can be seen in association with the cysts.
- In long-standing cases fibrous tissue may essentially obliterate the cystic space.
- Some examples are characterized by a distinctly proliferative cartilaginous response, developing a thickened cartilaginous wall.
- Surrounding cartilage is unremarkable.

Differential Diagnosis

- Relapsing polychondritis
- Subperichondrial hematoma
- Chondrodermatitis nodularis chronicus helices

Treatment and Prognosis

- Complete surgical excision without distortion of the underlying cartilaginous plate is the preferred treatment and is curative.
- Due to the potential for surgical-related deformity, full-thickness resection is not advocated.
- In addition to the obvious cosmetic concerns, long-standing lesions may result in deformity of the ear.
- Steroid injection alone has been unsuccessful and may result in cartilage deformity.
- Incision and drainage or curettage have shown variable success; needle aspiration alone results in rapid reaccumulation of fluid but, when combined with bolster suture compression, long-term follow-up has shown an absence of recurrences.

Chondrodermatitis Nodularis Chronicus Helicis (CNCH)

(Figs. 23-9 and 23-10)

Definition: Idiopathic nonneoplastic ulcerative lesion of the auricle.

Synonyms: Winkler disease or nodule

Clinical

- More common in men in late middle age and older age groups; considered uncommon in women



Fig. 23-9. Chondrodermatitis nodularis chronicus helices.

Chondrodermatitis nodularis chronicus helices (CNCH) of the auricular anterior pinna (antitragal) appearing as a raised, oval nodule with central ulceration.

- Most frequently occurs along the superior portion of the helix; lateral helical, antihelical, and antitragal involvement also seen
- Spontaneously occurring unilateral painful nodule is the most common clinical presentation; manipulation of the lesion results in intense pain; pain is thought to result from the perichondrial involvement.
- Clinically, the lesions appear as round, reddish areas usually measuring less than 1 cm in diameter; many cases are clinically considered to be carcinomas.
- Cause remains unknown; however, several theories have been suggested, including:
 - Cold exposure
 - Actinic damage
 - Local trauma
 - Degenerative change with pressure necrosis
 - The skin of the auricle is thin with little subcutaneous fat and therefore may be unusually sensitive to injury; further, the vascular supply to the area is somewhat deficient with the avascular cartilage depending on the dermal circulation for its sustenance; these anatomic features may predispose the auricle to the development of CNCH.
- Winkler considered the underlying pathologic event to be a cartilaginous-based process; however, the cause appears to be linked to a primary cutaneous alteration because the cutaneous changes are more significant and a more constant feature.
- Likely that the development of CNCH is multifactorial and includes actinic damage

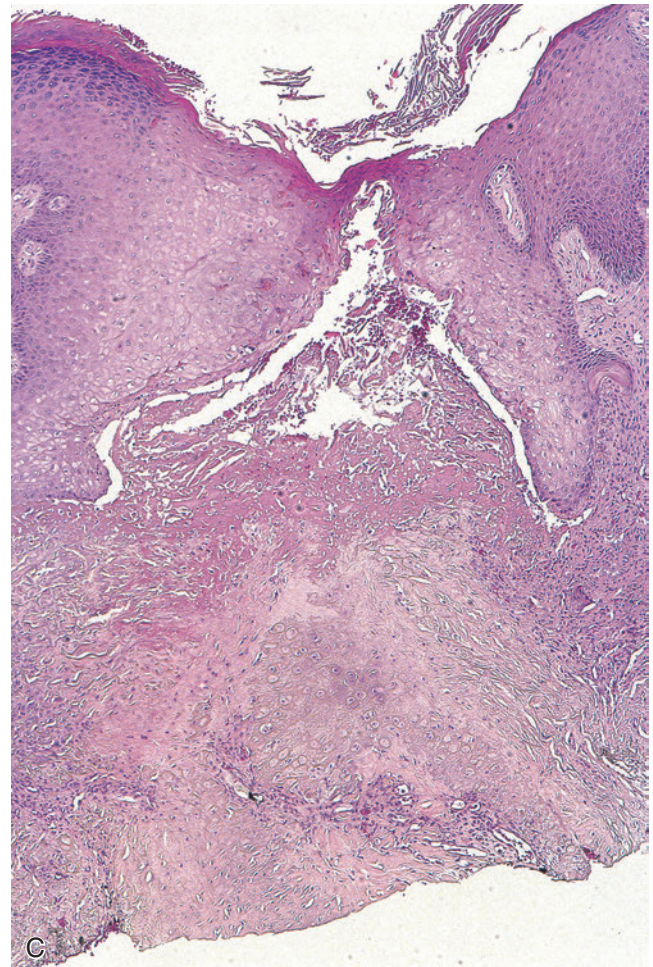
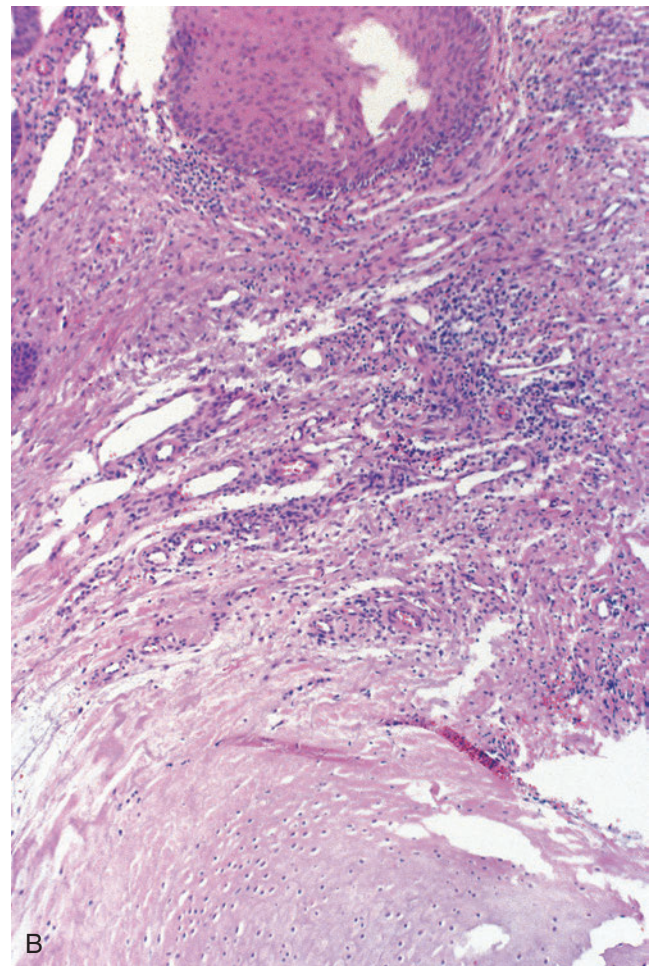
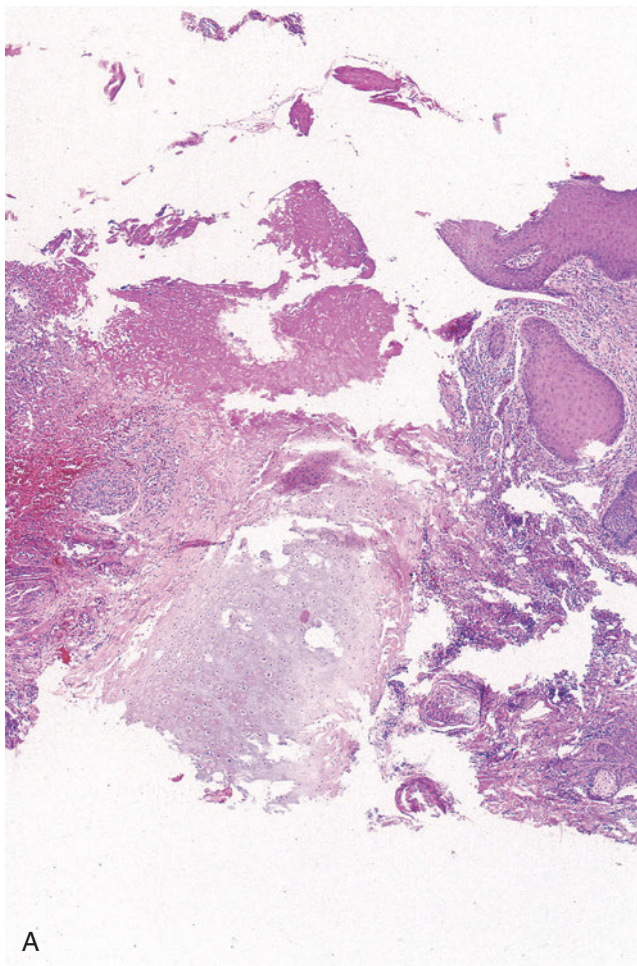


Fig. 23-10. CNCH.

A, Histologic features of CNCH include ulcerated epithelium with fibrinoid necrosis, associated granulation tissue, and an inflammatory cell infiltrate. **B,** The inflammatory cell infiltrate may extend into cartilage. **C,** Another example of CNHC in which inflammatory and granulation tissue process extend to subjacent cartilage with re-epithelialization of the surface ulceration.

Pathology

Gross

- Usually appears as a dome-shaped, discrete nodule with a scaly crust covering a central area of ulceration ranging in diameter from 3 to 18 mm, with an average of 7 mm:
 - Rarely, CNCH may achieve diameters of 2 to 3 cm.

Histology

- Central portion of the involved epidermis is ulcerated with adjacent epithelium showing acanthosis, hyper- and parakeratosis, and pseudoepitheliomatous hyperplasia.
- Base of the ulcer shows granulation tissue, edema, fibrinoid necrosis, and an acute and/or chronic inflammatory cell infiltrate.
- Granulation tissue and inflammatory process usually extend to and involve the perichondrium and cartilage.

Differential Diagnosis

- Basal cell carcinoma
- Squamous cell carcinoma
 - CNCH is frequently misdiagnosed as a cutaneous malignancy, particularly as basal cell carcinoma or squamous cell carcinoma.
 - Same mistake may be perpetuated by microscopic examination, particularly if the epidermal hyperplastic changes are misinterpreted as representing either squamous cell carcinoma or a hypertrophic actinic keratosis; careful attention to the extensive dermal changes and usually some degree of cartilaginous alterations, along with the well-demarcated nature of the epidermal proliferation and lack of cytologic atypia in the adjacent epidermis, should help in excluding a squamous neoplasm in cases of CNCH.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative:
 - Surgery includes wedge excision or cartilage excision alone.
- In a minority of patient trials with injection of glucocorticoids directly into the lesion have been shown to be effective in eradicating the lesion.
- No malignant potential

Exostosis of the External Auditory Canal (Figs. 23-11 and 23-12)

Definition: Localized overgrowth of bone classically described as a reactive lesion consisting of a compact proliferation of layers of bone of varied size and

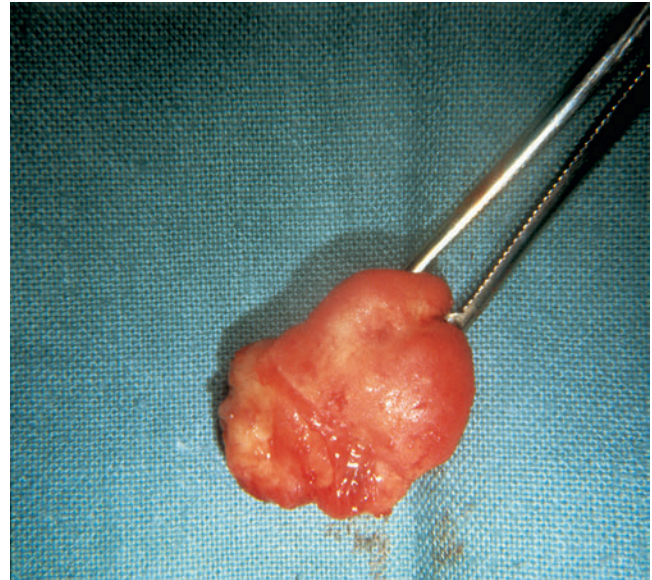


Fig. 23-11. Exostosis.

Excised external auditory canal (intact) exostosis appearing as a broad-based, mound-like bony proliferation.

appearance, including nodular, mound-like, pedunculated, or flat protuberances on the surface of a bone.

Synonym: Surfer's ear

NOTE: Broad-based lesions are referred to as exostosis; pedunculated lesions have been termed osteoma.

Clinical

- Broad-based outgrowths of bone arising from the wall of the external auditory canal
- Usually are multiple and bilateral
- Tend to remain asymptomatic until they reach a size sufficient to interfere with the normal egress of cerumen and exfoliated skin:
 - Obstruction of the external auditory canal may cause recurrent episodes of external otitis, conductive hearing loss, and tinnitus.
- Predilect to cold water swimmers and surfers, with the highest incidence being found in Australia and New Zealand:
 - White water kayakers are the first inland population to experience exostoses at the rates seen in coastal populations (e.g., surfers); earplugs may be protective.

Pathology

Gross

- Appearance of exostoses is usually better appreciated by the surgeon, as only fragments are available to the pathologist in most cases.
- The intact exostosis is a broad-based, mound-like bony proliferation that is similar in color and texture to normal cortical bone.

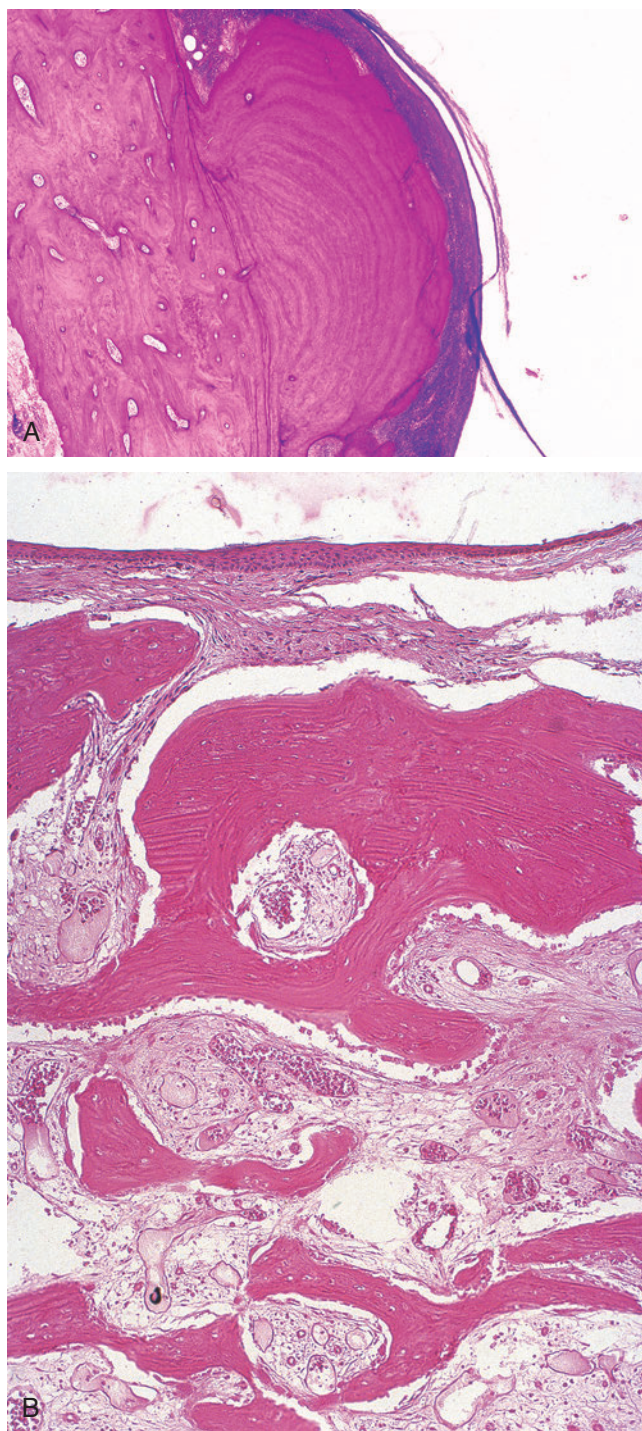


Fig. 23-12. Exostosis.

A, Exostosis composed of laminated compact bone creating an “onion skin–like” appearance on cross section lying beneath the intact but disrupted keratinizing squamous cells of the external auditory canal. **B**, Another external auditory canal benign osseous proliferation perhaps better designated as an osteoma composed of dense compact cancellous bone with intervening loose fibrovascular tissue lying beneath an intact keratinizing squamous epithelium.

Histology

- The bone is covered by a layer of periosteum with overlying thin skin.
- The periosteal layers are like the skin of an onion and usually lack trabecular architecture or marrow spaces.

Differential Diagnosis

- Osteoma:
 - Much less common lesion in relationship to the external auditory canal
 - Distinction between exostosis and osteoma is usually readily made on the basis of the clinical presentation; there has been some controversy regarding the ability to distinguish between the two lesions histologically; some authorities consider the lesions histologically different, whereas others do not find the microscopic features sufficiently distinctive to be separated.

Treatment and Prognosis

- Medical treatment resolves the symptomatic external otitis and related hearing loss.
- For patients who do not respond to medical treatment, transmeatal surgical excision is the preferred treatment.

Synovial Chondromatosis of the Temporomandibular Joint (TMJ)

(Figs. 23-13 and 23-14)

Definition: Reactive process of unknown pathogenesis characterized by the formation of multiple cartilaginous nodules in the synovium, with many becoming detached and floating within the joint space.

Synonyms: Synovial osteochondromatosis; synovial chondrometaplasia

Clinical

- Predilects to women and generally occurs in adults
- May present with preauricular swelling and limited motion of the joint with deviation of the mandible
- May involve the external auditory canal, resulting in an asymptomatic mass lesion
- Radiographic features include the presence of numerous radiopaque loose bodies within the region of the joint but destruction of bone is absent:
 - CT scan excellent to define bony surfaces of the articular joints but fails in detection of loose bodies when these are not yet calcified
 - MRI is gold standard when diagnosis is suspected because it can visualize loose bodies at early stage and also evaluate disk condition and eventual extra-articular tissue involvement

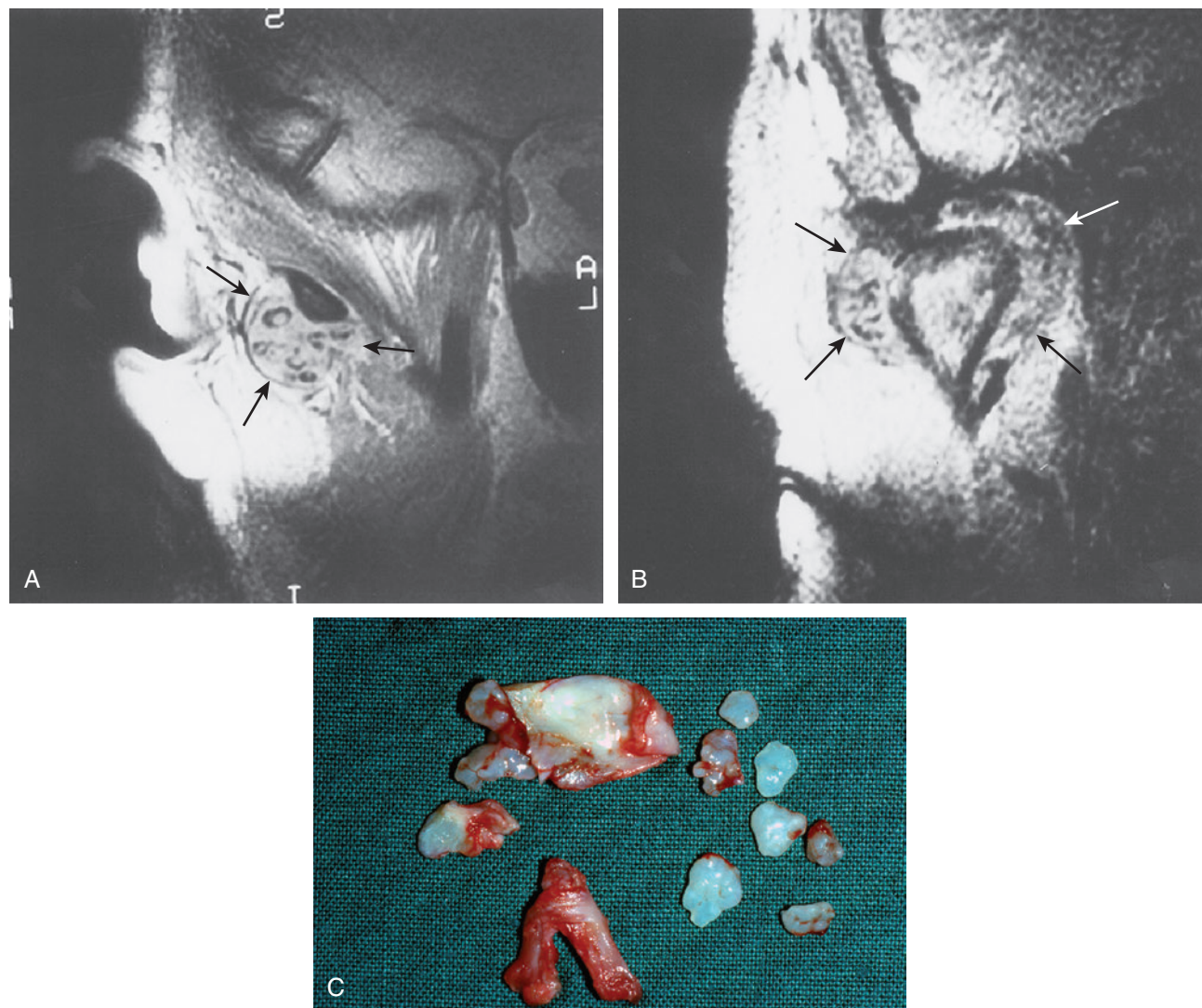


Fig. 23-13. Synovial chondromatosis with synovial bodies.

A, Sagittal image shows expansion of the joint capsule (*arrows*) with multiple low signal intensity rounded bodies in the joint. **B**, Coronal proton-density MR image showing expansion of the lateral and medial capsule walls (*arrows*), which indicates a neoplastic intraarticular process with multiple areas of low signal intensity consistent with synovial chondromatosis. **C**, Small bodies of cartilage material removed from this joint showing synovial chondromatosis. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 26-84, A-C, p 1589.)

- On T2-weighted imaging:
 - Signs of low signal nodules within amorphous iso-intensity signal tissues; signs of low and intermediate signal nodules within joint fluids used to detect loose cartilaginous nodules
- Intraoperatively, the lesion is usually confined to the joint space itself and is easily enucleated; on occasion the lesion may extend beyond the joint capsule into the parotid gland, auditory canal, temporal bone, or cranium.
- Rarely occurs in association with pseudogout (calcium pyrophosphate dihydrate deposition disease); see later.
- Pathogenesis:
 - Synovial chondromatosis is a condition in which foci of cartilage develop in the synovial membrane of a joint apparently through metaplasia of the sublining connective tissue of the synovial membrane.
 - Fibroblast growth factor 2 (FGF-2) found to be expressed in chondrocytes and fibroblast-like

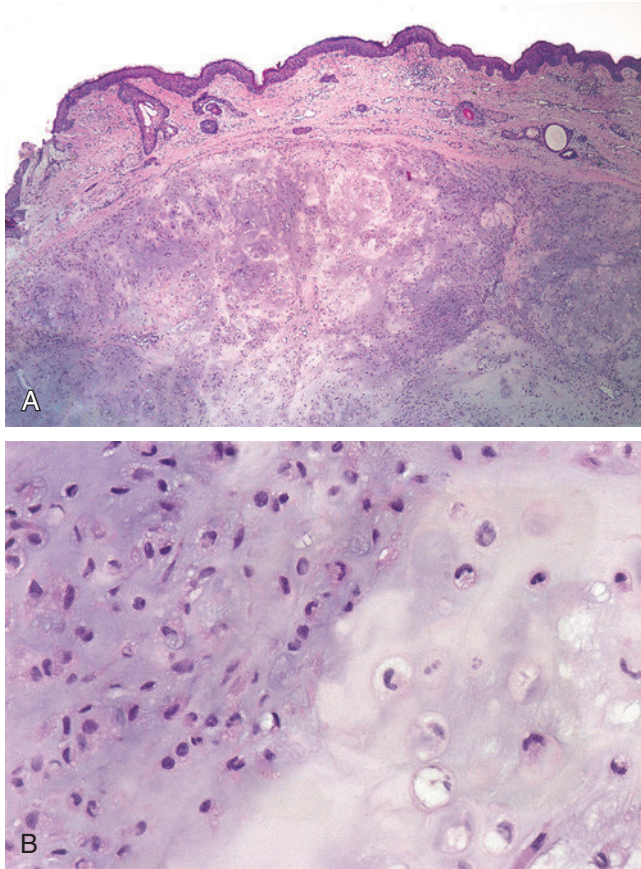


Fig. 23-14. Synovial chondromatosis.

The histologic features of synovial chondromatosis of the temporomandibular joint include (A) subcutaneous well-delineated nodular proliferation of mature cartilage showing variable cellularity and (B) rather typical appearing chondrocytes (*right*) juxtaposed to chondrocytes with increased cellularity, including pleomorphic and hyperchromatic nuclei and occasional, binucleated chondrocytes (*left*).

cells of loose bodies and believed to be involved in the pathogenesis

- Clonal chromosomal alterations (chromosome 6 abnormalities) in synovial chondromatosis suggest this is a neoplastic lesion rather than a metaplastic/reactive process.
- Cell proliferation studies have shown intermediate proliferative activity of the cellular composition of synovial chondromatosis between enchondromas and chondrosarcomas.

Pathology

Gross

- Synovium may be diffusely studded with innumerable nodules.

- Nodules are polypoid or pedunculated with a delicate stalk, and vary in size from as small as 1 mm up to 3 cm.
- External surface varies from smooth to convoluted and granular.

Histology

- Consists of nodules of mature cartilage of varying cellularity within the synovium and lying loosely in the joint space.
- Cartilage may appear atypical with hypercellularity, hyperchromasia, binucleated chondrocytes, and increased mitoses.
- Calcification and ossification may be present.
- Immunohistochemistry:
 - No increase in proliferation activity as determined by Ki67 (MIB1) staining

Differential Diagnosis

- Chondrosarcoma:
 - Presence of increased cellularity with atypical features, including binucleated chondrocytes, may suggest a diagnosis of chondrosarcoma. In such examples, correlation with the radiographic appearance would be essential to differentiate these lesions. The radiographic features of synovial chondromatosis include the presence of numerous radiopaque loose bodies within the region of the joint.

Treatment and Prognosis

- Conservative surgical management is the preferred treatment.
- May rarely extend into the cranial cavity and skull base
- Reported cases of synovial chondrosarcoma suggest the possibility of malignant transformation of synovial chondromatosis.

MIDDLE AND TEMPORAL BONE

Cholesteatoma (Keratoma)

(Figs. 23-15 through 23-20)

Definition: Pseudoneoplastic lesion of the middle ear characterized by presence of stratified squamous epithelium that forms a saclike accumulation of keratin within the middle ear space with invasive growth; despite their invasive growth, cholesteatomas are not considered to be true neoplasms.

Synonyms: The term cholesteatoma is a misnomer in that it is not a neoplasm nor does it contain cholesterol; the designation of keratoma would be more accurate but the term cholesteatoma is entrenched in the literature.

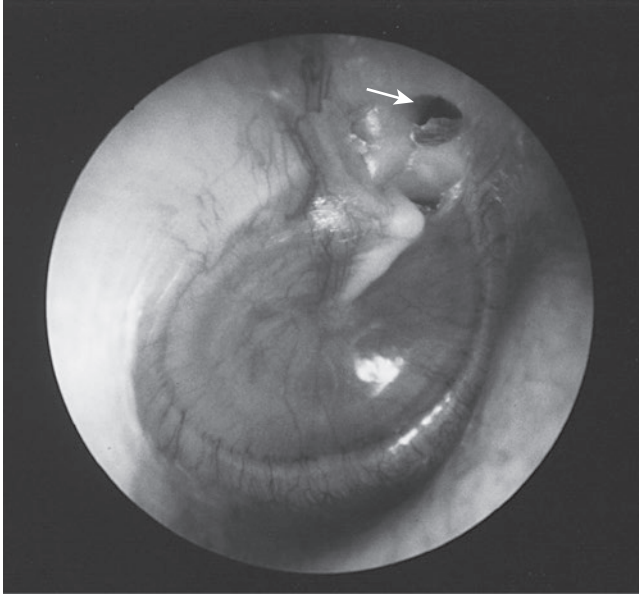


Fig. 23-15. Cholesteatoma.

Otoscopic view of the pars flaccida retraction pocket (arrow) in the right tympanic membrane. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 18-40, p 1204.)

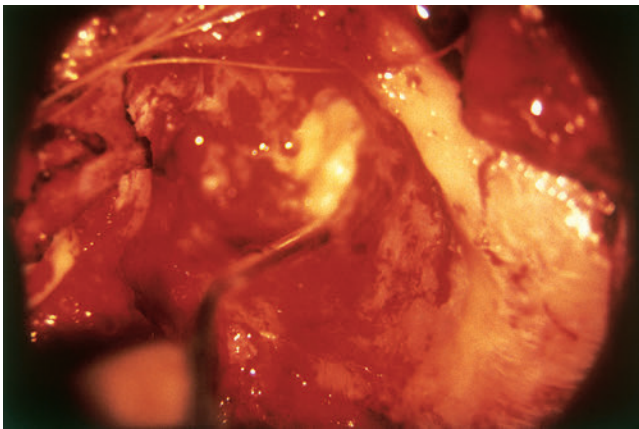


Fig. 23-16. Cholesteatoma.

Intraoperative appearance of cholesteatoma appearing as white mass/debris within the middle ear.

- Other designations include epidermal cyst or epidermal inclusion cyst of the middle ear.
- Cholesterol granuloma is not synonymous with cholesteatoma and these lesions are distinctly different pathologic entities and should not be confused with one another.
- Cholesteatomas may be divided into acquired and congenital types.

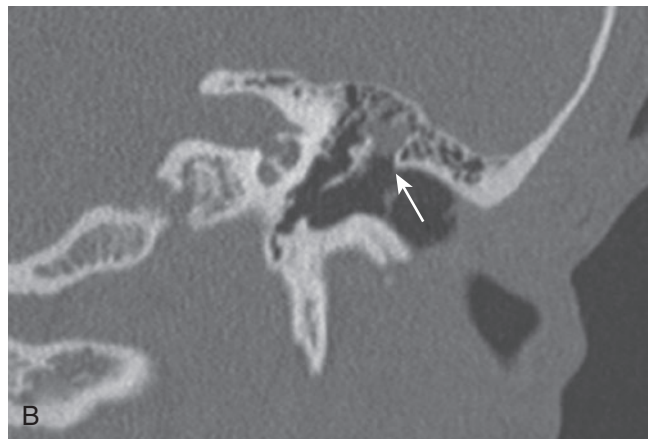
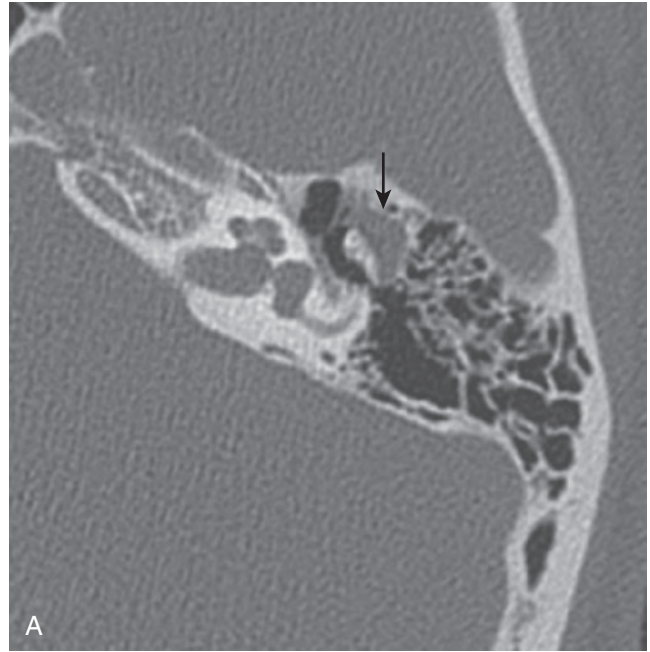


Fig. 23-17. Pars flaccida cholesteatoma.

A, Axial CT demonstrates a soft tissue mass with remodeling of the lateral attic wall (arrow). The ossicles are slightly medially displaced. **B**, Coronal CT image again demonstrates a soft tissue mass interposed between the lateral attic wall and malleus head. Note the blunted scutum (arrow). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 18-41, p 1204.)

Acquired Cholesteatoma

Clinical

- More common in men than in women and are most common in the third to fourth decades of life
- Middle ear space is the most common site of occurrence:

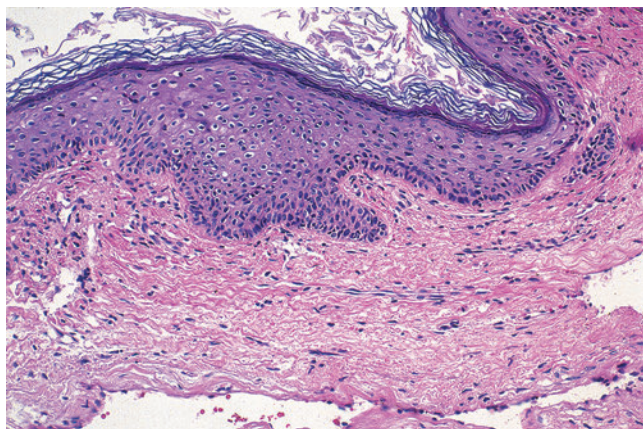


Fig. 23-18. Cholesteatoma.

The histologic features of a cholesteatoma include the presence of stratified keratinizing squamous epithelium and subepithelial fibroconnective tissue; this histologic picture of a specimen from the middle ear is diagnostic for cholesteatoma.



Fig. 23-19. Cholesteatoma.

Cholesteatomatous involvement of a middle ear ossicle in which a fragment of keratinizing squamous epithelium (*left*) is seen involving bone.

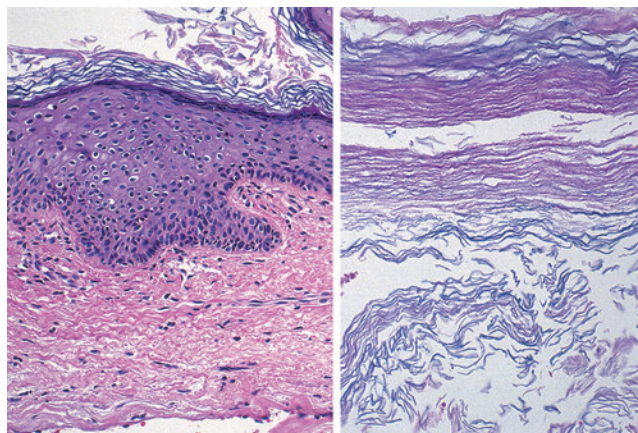


Fig. 23-20. Cholesteatoma.

Left, Diagnostic findings of a cholesteatoma characterized by the presence of keratinizing squamous epithelium, which was identified from within the middle ear space. *Right*, The presence of keratin debris only is not considered diagnostic for a cholesteatoma irrespective of a high index of clinical suspicion for a cholesteatoma and/or a prior diagnosis of cholesteatoma. In the absence of the epithelial component, a diagnosis of cholesteatoma should not be rendered.

- Most acquired cholesteatomas arise in the pars flaccida portion of the tympanic membrane and extend into Prussak space:
 - Prussak space is bordered laterally by the pars flaccida (Shrapnell membrane), medially by the neck of the malleus, superiorly by the attachment of the pars flaccida to the tympanic ring near the scutum, and inferiorly by the lateral or short process of the malleus.
- Initially, cholesteatomas may remain clinically silent until extensive invasion of the middle ear space and mastoid occurs.
- Symptoms include:
 - Hearing loss, malodorous discharge, and pain and may be associated with a polyp arising in the attic of the middle ear or perforation of the tympanic membrane
 - External ear canal cholesteatomas generally occur in older aged individuals, present with otorrhea and unilateral chronic pain, and do not produce a conductive hearing loss.
- Otoscopic examination may reveal the presence of white debris within the middle ear, which is considered diagnostic.
- Radiology:
 - Given the localization to Prussak space, most acquired cholesteatomas displace the malleus medially and erode the adjacent bony scutum; from there the mass may extend posteriorly via

the epitympanum in the superior incudal space to the posterolateral attic and then via the aditus ad antrum to the antrum and mastoid air spaces.

- Radiographic evidence of widening of the aditus is an important diagnostic finding.
- Acquired cholesteatomas may occur in the external auditory canal:
 - Generally occur in older aged individuals
 - Present with otorrhea and unilateral chronic pain, does not produce a conductive hearing loss
- Pathogenesis:
 - Majority of cholesteatomas are acquired and either arise de novo without a prior history of middle ear disease or arise following a middle ear infection
 - A small percentage of cases are congenital (see below).
 - Pathogenesis of acquired cholesteatoma is thought to occur via migration of squamous epithelium from the external auditory canal or from the external surface of the tympanic membrane into the middle ear
 - Mechanism by which the epithelium may enter the middle ear probably is by a combination of events, including perforation of the tympanic membrane (particularly in its superior aspect referred to as the pars flaccida or Shrapnell membrane following an infection) coupled with invagination or retraction of the tympanic membrane into the middle ear as a result of long-standing negative pressure on the membrane secondary to blockage or obstruction of the eustachian tube.
 - Other theories by which cholesteatomas are thought to occur include traumatic implantation, squamous metaplasia of the middle ear epithelium, and congenital derivation.

Congenital Cholesteatoma

Definition: Cholesteatoma of the middle ear that exists in the presence of an intact tympanic membrane, presumably occurring in the absence of chronic otitis media that may result in perforation or retraction of the tympanic membrane.

Clinical

- No gender predilection; found in infants and young children
- Majority of cases of congenital cholesteatomas are found in the anterosuperior part of the middle ear
- In early lesions no symptoms and lesions are discovered by otoscopic examination; in later lesions the signs and symptoms may be the same as acquired cholesteatoma.

- Pathogenesis:
 - Small colonies of epidermoid cells referred to as epidermoid formations are found on the lateral anterior superior surface of the middle ear in temporal bones after 15 weeks' gestation.
 - During the first postpartum year the epidermoid colonies disappear; however, if the epidermoid cells do not disappear but continue to grow, they will become congenital cholesteatomas.

Pathology

- Similar pathologic findings for acquired and congenital cholesteatomas

Gross

- Cholesteatomas appear as a cystic white to pearly-appearing mass of varying size containing creamy or waxy granular material.

Histology

- Histologic diagnosis is made in the presence of a stratified keratinizing squamous epithelium, sub-epithelial fibroconnective or granulation tissue, and keratin debris.
- Essential diagnostic feature is the keratinizing squamous epithelium; presence of keratin debris alone is not diagnostic of a cholesteatoma.
- Keratinizing squamous epithelium is cytologically bland and shows cellular maturation without evidence of dysplasia.
- In spite of its benign histology, cholesteatomas are “invasive” and have widespread destructive capabilities:
 - Destructive properties result from a combination of interrelated reasons, including mass effect with pressure erosion of surrounding structures from the cholesteatoma and production of collagenase, which has osteodestructive capabilities by its resorption of bony structures and bone resorption.
 - Collagenase is produced by the squamous epithelial and fibrous tissue components of the cholesteatoma.
- Keratosis obturans (see below) is composed of loosely packed, irregularly arranged keratin squames in the external auditory canal.
- Immunohistochemistry:
 - Cytokeratins and p63 positive
- Ploidy analysis performed to determine whether cholesteatomas were low-grade squamous carcinomas found cholesteatomas to be diploid; due to a lack of overt genetic instability, cholesteatomas could not be considered to be malignant neoplasms.
- Cytogenetics and molecular genetics:

- Identification of upregulation of human microRNA-21(hsa-miR-21) concurrent with downregulation of potent tumor suppressor proteins PTEN and programmed cell death 4:
 - These proteins control aspects of apoptosis, proliferation, invasion, and migration.
 - Model for cholesteatoma proliferation through microRNA dysregulation
- Genes found to be induced or upregulated in cholesteatoma include:
 - Genes involved in cell proliferation and differentiation (e.g., calgranulin A, calgranulin B, psoriasin, thymosin beta-10)
 - Genes involved in cell invasion (e.g., cathepsin C, cathepsin D, cathepsin H)
- Upregulation of proliferating cell nuclear antigen (PCNA) and osteoclast stimulating factor-1 (OSF-1):
 - Two candidate proteins in the pathogenesis of cholesteatoma relating to cellular proliferation and bone destruction
- EGFR/PI3K/Akt/cyclinD1 signaling pathway is active in cholesteatoma and may play a role in cholesteatoma epithelial hyperproliferation.
- Keratinocyte growth factor (KGF), a mesenchymal cell-derived paracrine growth factor that specifically stimulates epithelial cell proliferation, is present in cholesteatomas:
 - Keratinocyte growth factor protein (KGFR) and mRNA localized in the epithelium in 72% of cases
 - Significant correlation between KGF+/KGFR+ expression and recurrence
 - KGF and KGFR may play a role in enhanced epithelial cell proliferative activity and recurrence of cholesteatomas.
- Angiogenesis and angiogenic growth factors are present in cholesteatoma:
 - Close relationship is seen between the density of capillaries, degree of inflammation, and expression of the angiogenic factors.
 - Increased number of microvessels
 - Angiogenesis enables and supports the sustained migration of keratinocytes into the middle ear cavity.
 - Represent a pivotal factor in the destructive behavior of middle ear cholesteatoma

Differential Diagnosis

- Squamous cell carcinoma:
 - In contrast to cholesteatomas, squamous cell carcinoma shows dysplastic or overtly malignant cytologic features with a prominent desmoplastic stromal response to its infiltrative growth
 - Cholesteatomas do not transform into squamous cell carcinomas.
- Epidermoid of the petrous apex (Fig. 23-21):
 - Represents an epidermoid cyst of this location and bears no relation to cholesteatoma of the middle ear
 - It is likely of congenital origin possibly arising from sequestration of epidermal cells at the time of closure of the medullary groove between the third and fifth embryonic week.
 - Usually affects people 20 to 35 years old
 - Symptoms may include ipsilateral headaches, involvement of the third division of the fifth cranial nerve, signs of extrinsic compression of the eustachian tube with middle ear effusion and conductive hearing loss, and signs of compression of the internal carotid artery with ischemic effects (e.g., blurring of vision and faintness); as the lesion enlarges there may be involvement of the seventh and eighth cranial nerves in the cerebellopontine angle with progressive facial paresis preceded by progressive facial spasms (seventh cranial nerve involvement) and progressive sensorineural hearing loss, vertigo (eighth nerve involvement)
 - The tympanic membrane frequently remains intact.
 - Diagnosis established on the basis of prolonged clinical course, seventh and eighth cranial nerve involvement, and imaging findings
- Keratosis obturans (KO):
 - Results when the normal self-cleaning mechanism of keratin maturation and lateral extrusion from the external auditory canal is defective, causing accumulation of keratin debris deep within the bony aspect of the external auditory canal.
 - Cause of KO remains unclear.
 - KO occurs most commonly in the first two decades of life, and symptoms generally relate to conductive hearing loss due to the keratin plug.
 - Pain is not an uncommon finding.
 - Keratin debris may exert pressure effects on the bony canal wall, resulting in widening of the external auditory canal, bone remodeling, and inflamed epithelium.
 - Histologic appearance is that of tightly packed keratin squames in a lamellar pattern.
 - Treatment for KO is debridement of the keratin plug.
 - In contrast to KO, external ear canal cholesteatomas generally occur in older aged individuals, present with otorrhea and unilateral chronic pain, do not produce a conductive hearing loss, and are composed histologically of loosely packed, irregularly arranged keratin squames that may erode or invade bone (Fig. 23-22).

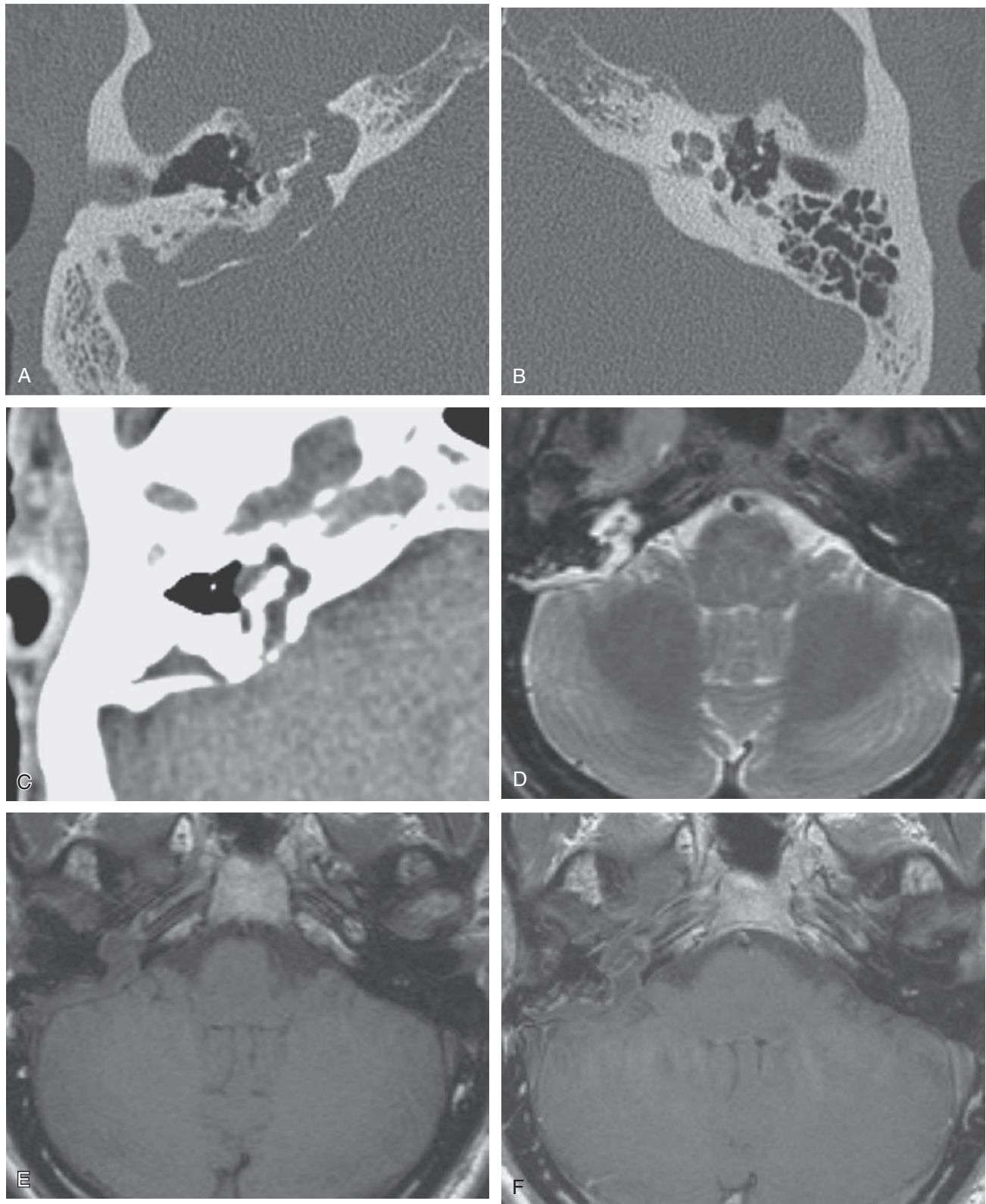


Fig. 23-21. Petrous apex epidermoid.

A and **B**, Axial CT images in bone algorithm. There is extensive erosion of the petrous apex, including much of the otic capsule (**A**). Compare with the normal left side at the same level (**B**). **C**, Axial CT image in soft tissue algorithm. The epidermoid is hypodense. **D** to **F**, Axial T2-weighted image and pre- and post-contrast-enhanced T1-weighted images. The mass is hyperintense on T2-weighted sequence, hypointense on T1-weighted sequence, and does not enhance. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 20-173, p 1367.)

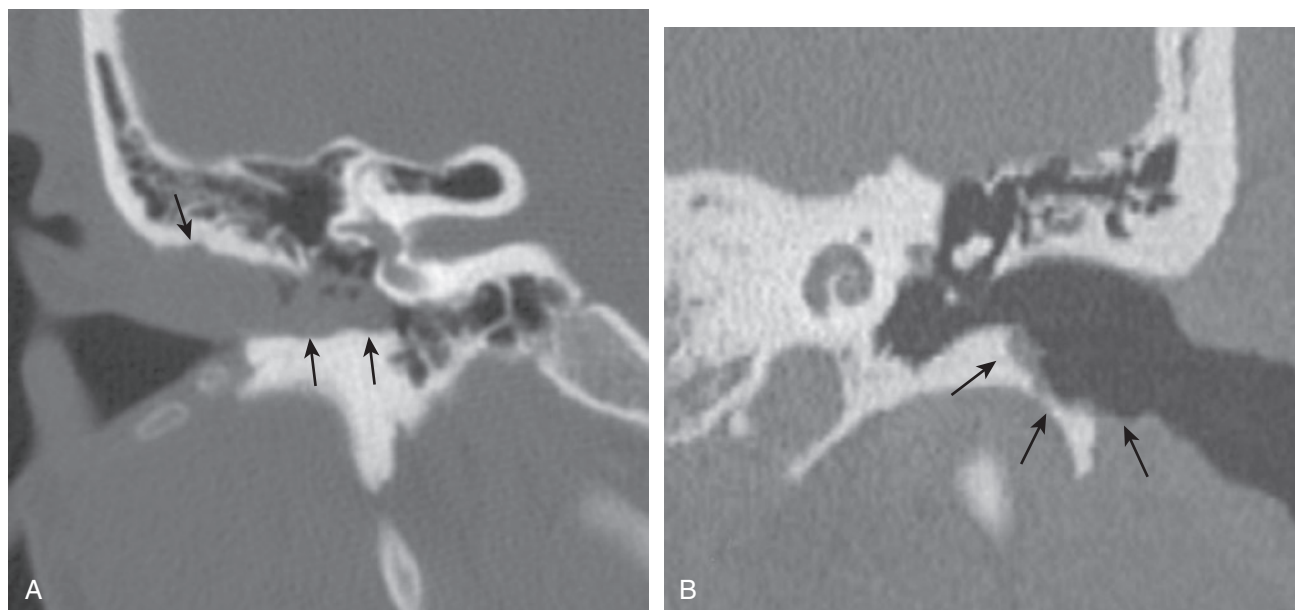


Fig. 23-22. External auditory canal cholesteatoma (EACC).

A, Coronal CT image shows soft tissue opacification of the EAC with erosions along the floor and roof (arrows). Soft tissue bulges into the middle ear cavity. At surgery, this was found to be an EACC with an intact but retracted tympanic membrane. **B**, Different patient. Coronal CT image demonstrates "punched-out" erosions (arrows) in the floor of the EAC with minimal associated soft tissue. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 18-8, p 1187.)

Treatment and Prognosis

- Complete surgical excision of all histologic components of the cholesteatoma is the preferred treatment.
- If not completely excised, cholesteatomas can have progressive and destructive growth, including widespread bone destruction, which may lead to hearing loss, facial nerve paralysis, labyrinthitis, meningitis, and epidural and/or brain abscess.

Langerhans Cell Histiocytosis (LCH) (Figs. 23-23 through 23-27)

Definition: Clonal proliferation of Langerhans cells, a cellular component of the dendritic cell system, occurring as an isolated lesion or part of a systemic (multifocal) proliferation.

Synonyms: Langerhans cell (eosinophilic) granulomatosis (LCG), eosinophilic granuloma

NOTE: The designation of Langerhans cell histiocytosis has been used to replace the previous nomenclature of the group of diseases termed histiocytosis X that included eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease.

Clinical

- Tends to occur in males; most commonly occurs in the second to third decades of life



Fig. 23-23. Langerhans cell histiocytosis.

Young girl with temporal bone involvement by Langerhans cell histiocytosis presenting with swelling and ulceration of skin.

- Lesions are most often osseous based:
 - Most frequent osseous sites involved occur in the skull (including the middle ear and temporal bone)
- In patients with middle ear and temporal bone involvement, symptoms include aural discharge, swelling of the temporal bone area, otitis media, bone pain, otalgia, loss of hearing, and vertigo.

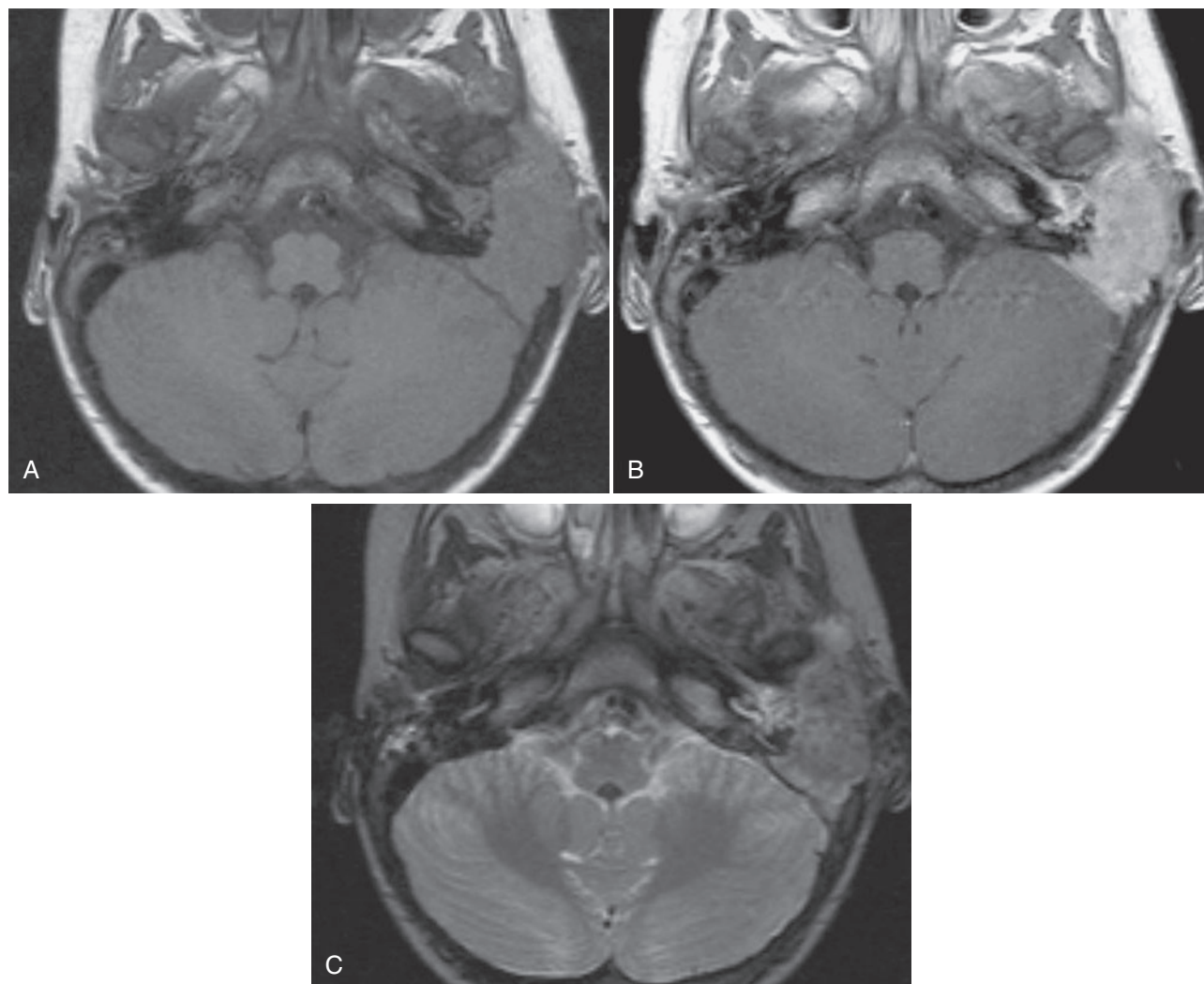


Fig. 23-24. Langerhans cell histiocytosis of the temporal bone.

The patient is a 2-year-old boy with a history of periauricular swelling and chronic otorrhea. **A** and **B**, Axial, pre- and post-contrast-enhanced, T1-weighted images. There is a large, avidly enhancing, soft tissue mass involving the left mastoid temporal bone and middle ear cavity, with invasion of the sigmoid sinus. **C**, T2-weighted image. The mass is heterogeneously hypointense, indicating hypercellularity. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 20-182, p 1374.)

- A single or multiple sharply circumscribed osteolytic lesion can be seen by radiographic studies.

Pathology

Histology

- Characterized by a proliferation of Langerhans cells (LC), which are arranged in sheets, nests, or clusters and composed of cells with reniform nuclei characterized by nuclear membrane lobations or indentations
- Nuclei have a vesicular chromatin with inconspicuous to small centrally located basophilic nucleoli and a moderate amount of eosinophilic cytoplasm.
- LCs may show mild pleomorphism and mitotic figures are uncommonly seen.
- An inflammatory cell infiltrate primarily consists of eosinophils and accompanies the LC proliferation; other inflammatory cells are present, including polymorphonuclear leukocytes, plasma cells, and lymphocytes.
- Foamy histiocytes and multinucleated giant cells may also be present:
 - These histiocytes may show phagocytosis of mononuclear cells.
- Immunohistochemistry:
 - LCs are diffusely immunoreactive with S100 protein and CD1a.

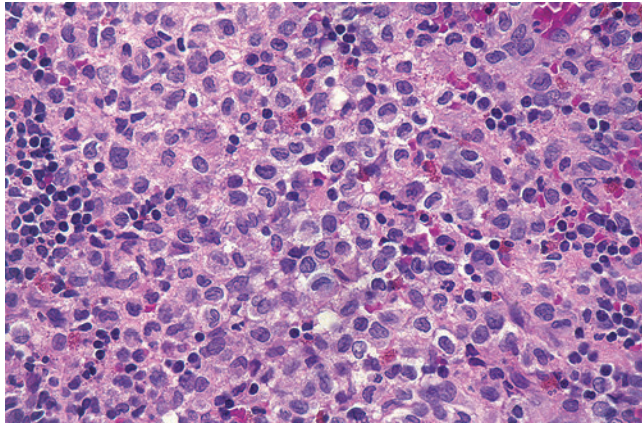


Fig. 23-25. Langerhan cell histiocytosis.

Langerhans cell histiocytosis characterized by the presence of sheet-like proliferation of Langerhans cells, which are the cells with round, vesicular nuclei showing lobation or indentation of the nuclear membrane and a moderate amount of eosinophilic cytoplasm; admixed inflammatory cells including eosinophils and mature lymphocytes are present.

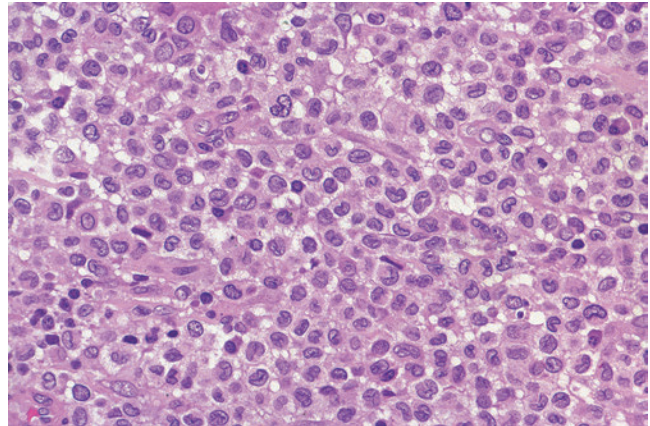


Fig. 23-26. Langerhan cell histiocytosis.

Langerhans cell histiocytosis composed almost exclusively of characteristic Langerhans cells with characteristic lobation or indentation of the nuclear membrane; in this example there is almost complete absence of an associated inflammatory cell infiltrate.

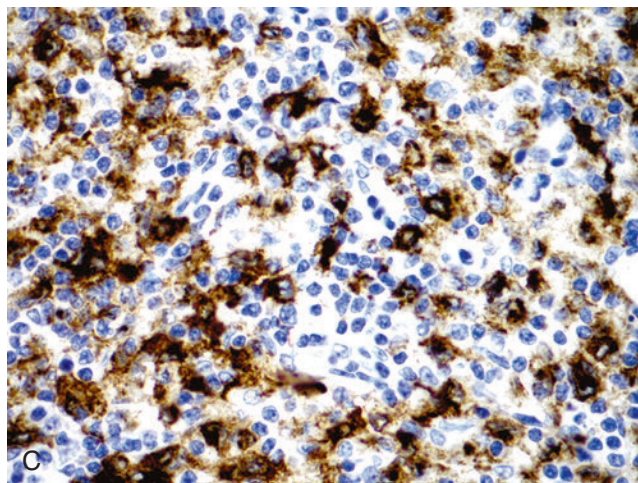
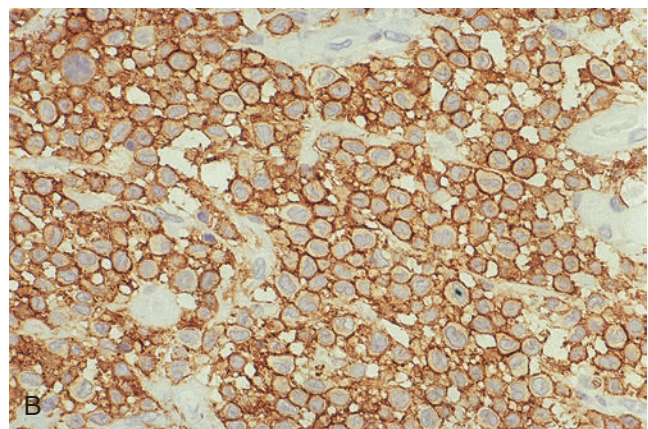
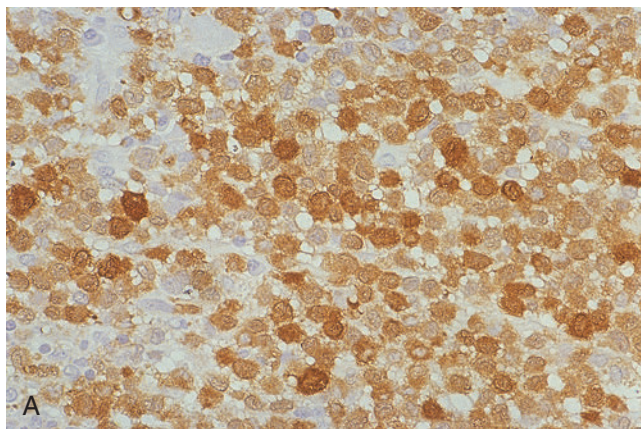


Fig. 23-27. Langerhan cell histiocytosis.

The diagnosis of Langerhans cell histiocytosis is confirmed by immunoreactivity of Langerhans cells for (A) S100 protein (nuclear and cytoplasmic reactivity); (B) CD1a (membranous reactivity); (C) Langerin (cytoplasmic and membranous reactivity).

- Langerin, a type II transmembrane C-type lectin associated with the formation of Birbeck granules in LC, represents a highly selective marker for LCs and the lesional cells of LCH.
- Langerin immunoreactivity shows a membranous and granular cytoplasmic pattern.
 - Assists in substantiating the diagnosis of LCH and in differentiating LCH from other non-Langerhans cell histiocytic proliferations
- Foamy histiocytes and multinucleated giant cells are S100 protein and CD1a negative but react with CD68 (KP1).
- Electron microscopy:
 - Elongated granules referred to as Langerhans or Birbeck granules can be seen within the cytoplasm of the LCs.
- Cytogenetics and molecular genetics:
 - Detection of BRAF (V600E) mutation found in LCH:
 - May provide new opportunities for devising targeted therapy
- Like LC, the cells of Rosai-Dorfman disease are S100 protein reactive but differ in that these cells are nonreactive with CD1a and/or Langerin.
- Non-Hodgkin malignant lymphoma:
 - Differentiating LCH from a malignant lymphoproliferative disease is usually not problematic by light microscopy; if necessary, immunohistochemical stains help differentiate LCH from a malignant lymphoma

Treatment and Prognosis

- Different therapeutic approaches can be considered depending on the affected organ, including surgery, radiotherapy, and chemotherapy:
 - Surgical excision (curettage) and low-dose radiotherapy for isolated temporal bone disease
 - Chemotherapy used for multifocal and systemic disease
- Prognosis for isolated disease considered very good
- Recurrence may be part of a systemic or multifocal process and generally occurs within 6 months of the diagnosis.
- Failure of a new bone lesion to occur within 1 year of diagnosis is considered a cure.
- In general, the younger the patient at onset of disease and the more extensive the involvement (multiple sites including bone and viscera), the worse the prognosis.

Differential Diagnosis

- Extranodal sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease):
 - May occasionally involve the ear and temporal bone region

INFECTIOUS AND INFLAMMATORY LESIONS

NECROTIZING EXTERNAL OTITIS (NEO)

(Figs. 23-28 through 23-30)

Definition: Virulent and potentially fatal form of external otitis related to *Pseudomonas aeruginosa* infection.

Synonyms: “Malignant” external otitis; necrotizing granulomatous otitis

Clinical

- No gender predilection; primarily affects older aged patients
- Typical clinical setting is that of a diabetic patient and/or a patient who is chronically debilitated or immunologically deficient although NEO may occur in nondebilitated patients.
- Originates in the external auditory canal with initial symptoms of an acute otitis externa and progression of disease pain, purulent otorrhea, and swelling.



Fig. 23-28. Necrotizing external otitis.

Necrotizing external otitis characterized by a swollen draining ear with a necrotic-appearing exudate.

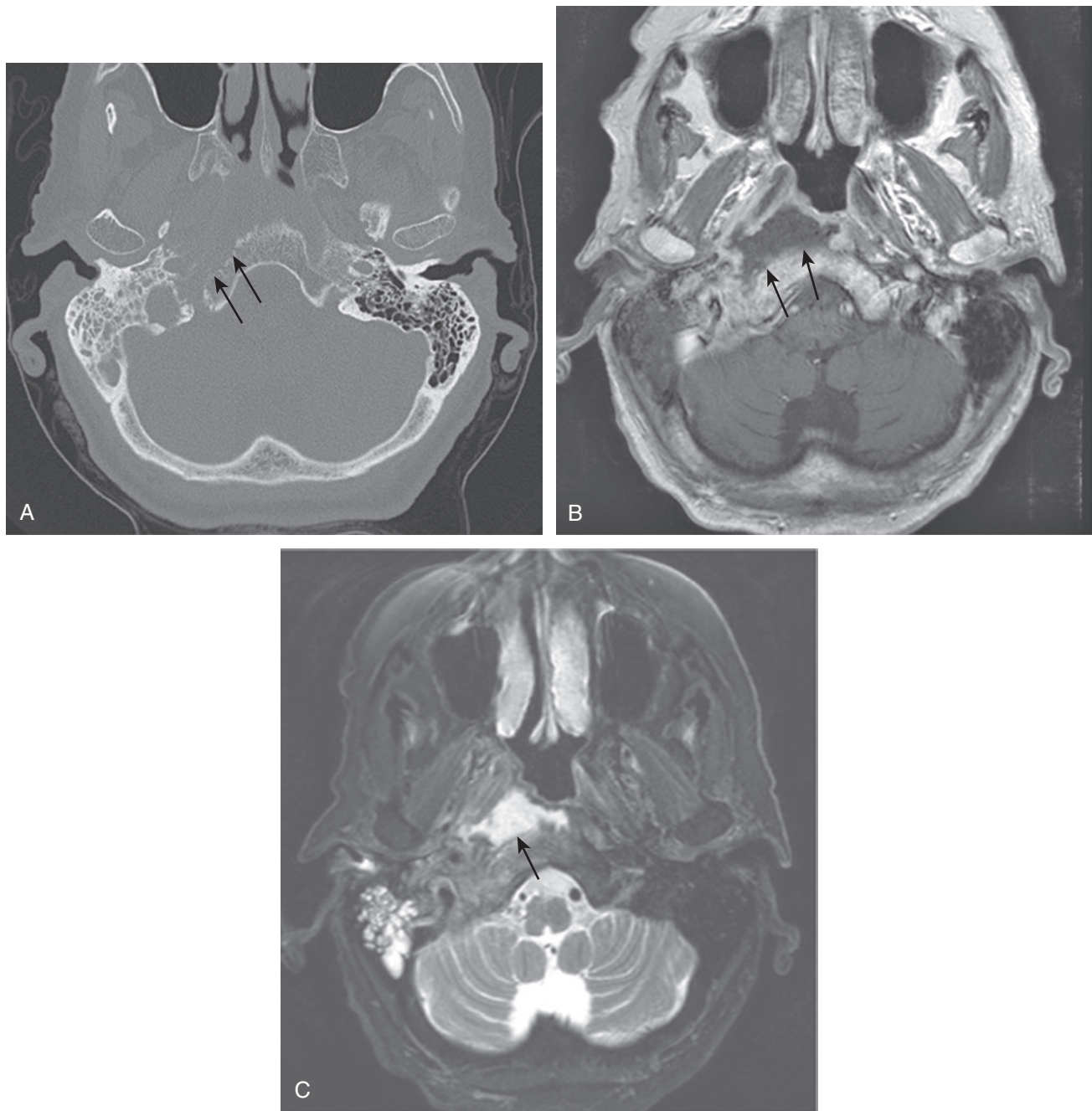


Fig. 23-29. Malignant otitis externa with osteomyelitis of the skull base.

A, Axial CT image in bone window in this patient with diabetes and otitis externa demonstrates extensive destruction of the right basiocciput (*arrows*). The right mastoid air cells are opacified. **B** and **C**, Axial contrast-enhanced T1-weighted image and axial T2-weighted image demonstrate a large fluid collection in the right basiocciput extending to the pharyngeal region with irregular peripheral enhancement (*arrows*). Fluid opacification of the right mastoid air cells is again seen. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 18-5, p 1185.)

- With time, the infectious process may extend into the surrounding soft tissue structures (cellulitis), cartilage (chondritis), bone (osteomyelitis), base of skull, and middle ear space, leading to cranial nerve palsies, meningitis, intracranial venous thrombosis, and brain abscess.
- Pathogenesis:
 - Felt to be caused by tissue ischemia secondary to an underlying predisposing pathologic state (diabetic angiopathy) and a migratory defect of polymorphonuclear leukocytes related to systemic disease

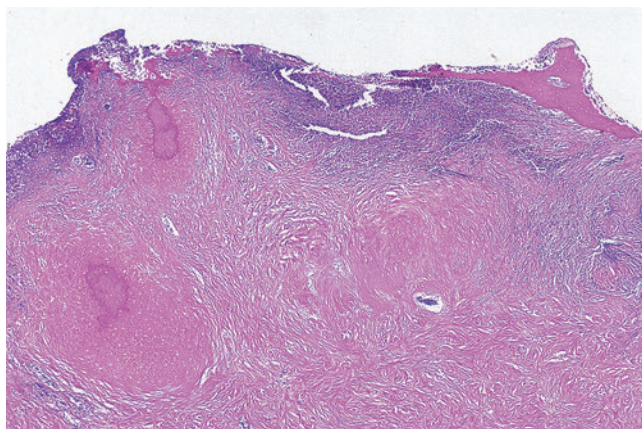


Fig. 23-30. Necrotizing external otitis.

The histology of necrotizing external otitis with epithelial ulceration, an acute and chronic inflammatory cell infiltrate extending to bone and thick, acellular collagenous bands replacing most of the subcutis tissues.

- These host factors impede the inflammatory response to infection, and combined with the destructive devices of *P. aeruginosa* are thought to be responsible for lethal potential of NEO
- The microorganism, by virtue of its endo- and exotoxins, neurotoxins, collagenases, and elastases, is capable of causing rapid extensive tissue necrosis and necrotizing vasculitis that compounds the destruction.

Pathology

Gross

- Changes most pronounced in the osseous portion of the external canal, where the destructive infection usually begins; in this area, the skin becomes ulcerated, leaving a layer of thick granulation tissue covering the exposed and irregularly eroded bone, usually along the anterior and inferior surfaces of the external auditory canal
- Necrotic tissue is abundant in fully developed NEO, and may, along with purulent exudate, obstruct the canal.

Histology

- Histologic appearance dominated by the presence of necrotic material and exuberant granulation tissue
- Squamous epithelium is commonly ulcerated; intact epithelium may show marked reactive and/or atypical changes, including pseudoepitheliomatous hyperplasia adjacent to denuded areas.
- Diffuse heavy acute and chronic inflammation is seen in the subcutis, and a necrotizing vasculitis is commonly present.

- Thick, acellular collagen is seen replacing most of the tissue extending from the cartilage to the overlying dermis.
- Bone and cartilage are necrotic, with acute and chronic inflammatory cells massively infiltrating adjacent viable bone; sequestra of nonviable bone or cartilage may be seen.
- Dermis is eventually replaced by acellular collagen.
- Histochemistry:
 - Gram-negative bacilli are easily demonstrated by tissue Gram stain.

Differential Diagnosis

- Squamous cell carcinoma:
 - Infectious nature of NEO is usually evident from the clinical course and the histologic findings.
 - Presence of squamous epithelial pseudoepitheliomatous hyperplasia may suggest a squamous cell carcinoma.
 - Conversely, squamous cell carcinoma, if associated with extensive necrosis, may elude diagnosis by biopsy, yielding only necroinflammatory material such as one finds in NEO.
 - Occasionally the clinical presentation of squamous cell carcinoma of the external auditory canal may closely mimic NEO or the two diseases may occur concurrently.

Treatment and Prognosis

- Antibiotics, surgical debridement, and control of diabetes in patients suffering from that disease are the preferred treatments.
- Cures can be achieved with early recognition and aggressive treatment:
 - Combination therapy with intravenous ceftazidime and oral fluoroquinolone remains relevant despite concerns of culture-negative cases and multidrug-resistant *Pseudomonas*.
 - Fungal (aspergillus, others) and polymicrobial temporal bone infections have been reported with increasing frequency, and in culture-negative and/or multidrug-resistant cases, considerations should be given to causes by organisms other than *P. aeruginosa*.
- Hyperbaric oxygen therapy may be used as an adjunctive modality.
- Despite advances in antibiotic treatment, a significant proportion of patients succumb to this disease.
- Mortality rates may exceed 75% if the diagnosis and treatment are delayed.
- Death may result from extensive spread of the infection to adjacent structures, including intracranial involvement:
 - Involvement of the clivus portends a poorer prognosis.

OTITIS MEDIA

(Figs. 23-31 through 23-34)

Definition: Acute or chronic infectious disease of the middle ear space.

Clinical

- No gender predilection; may occur at any age but is predominantly a childhood disease particularly common in children under 3 years of age.
- Symptoms include fever, otalgia, and decreased hearing typically preceded by several days of an upper respiratory tract infection.
- Most common organisms implicated in causing disease are *Streptococcus pneumoniae* and *Haemophilus influenzae*.

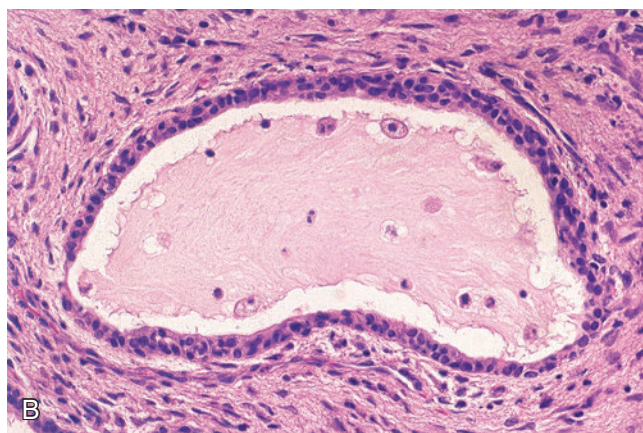
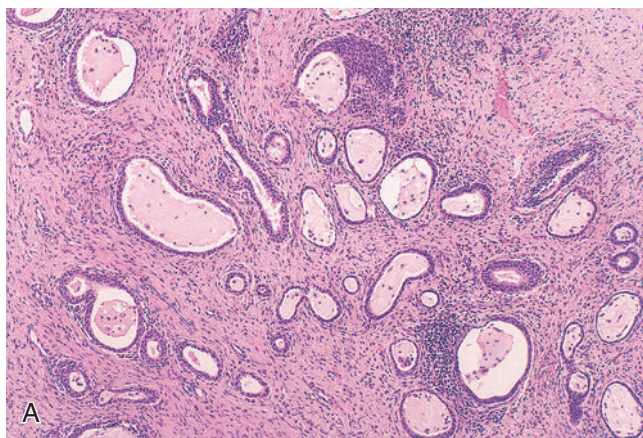


Fig. 23-31. Chronic otitis media.

A, Chronic otitis media with associated glandular metaplasia. The metaplastic glands are unevenly distributed and proliferate in the setting of fibrosis and chronic inflammation; the metaplastic glands are of variable size and shape and contain thin (serous) fluid. **B**, Metaplastic glands are lined by a low cuboidal epithelium and contain serous-appearing fluid; along the superior aspect hair-like (cilia) structures are present.

- Otoscopic examination reveals a hyperemic, opaque, bulging tympanic membrane with limited mobility; purulent otorrhea may be present.
- Bilateral involvement is not uncommon.
- Middle ear infection is thought to result from infection via the eustachian tube at the time of or following a pharyngitis (bacterial or viral).

Pathology

Gross

- No specific macroscopic features; the tissue specimens usually are received as multiple small fragments of soft to rubbery granulation-appearing tissue.

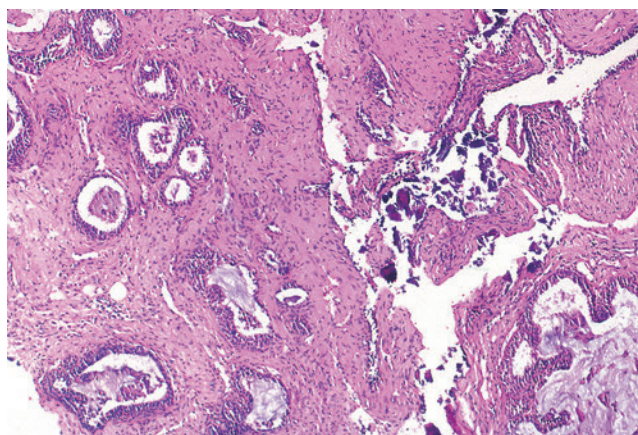


Fig. 23-32. Chronic otitis media.

Tympanosclerotic foci appearing as mineralized debris are seen in association with other alterations of chronic otitis media, including glandular metaplasia and fibrosis.

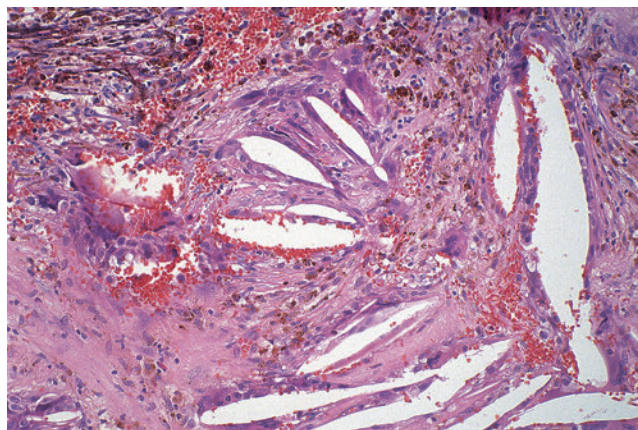


Fig. 23-33. Cholesterol granuloma.

Cholesterol granuloma appearing as empty, irregular-shaped clefts or as spaces surrounded by a foreign body giant cell reaction; fresh hemorrhage and hemosiderin pigment deposition are present.



Fig. 23-34. Complications of chronic otitis media.

Clinical findings that can be seen as complications of chronic otitis media may include (A) acute mastoiditis and (B) chronic mastoiditis.

- If tympanosclerosis is present, then the tissues may be firm to hard, consisting of calcific debris.

Histology

- In general, all of the tissue fragments should be processed for histologic examination.
- Histology of otitis media varies and depends on the disease state.

Acute Otitis Media

- Virtually never a surgical disease
- Middle ear mucosa, also referred to as the mucoperiosteum, responds to infection with inflammation, hyperemia, polypoid thickening, and edema.
- Inflammatory infiltrate in acute otitis media is composed predominantly of polymorphonuclear leukocytes with a variable admixture of chronic inflammatory cells.
- Secretory otitis media refers to an otitis media with associated effusion behind an intact tympanic

membrane; the exudate may be serous, hemorrhagic, fibrinous, mucoid, purulent, or an admixture of types.

- Acute otitis media usually heals by resorption by the mucoperiosteum.
- Localized destruction of the middle ear ossicles may occur, and granulation tissue may develop resulting in scar formation; fibrosing osteitis is seen in areas of bone destruction that may result in reactive sclerotic bone.
- Acute otitis media may be superimposed on chronic otitis media.

Chronic Otitis Media

- Histologic changes include a variable amount of chronic inflammatory cells consisting of lymphocytes, histiocytes, plasma cells, and eosinophils; multinucleated giant cells and foamy histiocytes may be present.
- Middle ear cuboidal epithelium may or may not be seen.

- Glandular metaplasia, a response of the middle ear epithelium to the infectious process, may be present:
 - Glands tend to be more common in nonsuppurative otitis media than in suppurative otitis media.
 - Metaplastic glands are unevenly distributed in tissue.
 - Glands are variably shaped and are separated by abundant stromal tissue.
 - Glands are lined by a columnar to cuboidal epithelium with or without cilia or goblet cell metaplasia.
 - Glandular secretions may or may not be present so that the glands may appear empty or contain varying secretions, including thin (serous) or thick (mucoid) fluid content.
- In addition to the inflammatory cell infiltrate and glandular metaplasia, other histopathologic findings that usually are seen in association with COM or represent sequelae of chronic otitis media include:
 - Fibrosis, granulation tissue, tympanosclerosis, cholesterol granulomas, and reactive bone formation
- Due to the presence of scar tissue, the middle ear ossicles may be destroyed (partial or total) or may become immobilized.
- Perforation of the tympanic membrane pars tensa may occur with resulting ingrowth of squamous epithelium, potentially leading to the development of cholesteatoma.

Tympanosclerosis (Fig. 23-32)

- Represents dystrophic mineralization (calcification or ossification) of the tympanic membrane or middle ear that is associated with recurrent episodes of otitis media.
- Incidence of tympanosclerosis in otitis media varies from 3% to 33%.
- Tympanosclerosis of the tympanic membrane can be seen in children following myringotomy and tube insertion; in this setting the tympanosclerotic foci may or may not be permanent.
- Tympanosclerosis of the middle ear typically affects older patients, represents irreversible accumulation of mineralized material, and is associated with conductive hearing loss.
- On gross examination, tympanosclerotic foci may be localized or diffuse and appear as white nodules or plaques.
- Histologically, dense “clumps” of mineralized calcified or ossified material or debris can be seen within the stromal tissues or in the middle (connective tissue) aspect of the tympanic membrane.
- Tympanosclerosis may cause scarring and ossicular fixation.
- Tympanosclerosis may occur independent of otitis media.

Cholesterol Granuloma (Fig. 23-33)

- Represents a foreign body granulomatous response to cholesterol crystals derived from the rupture of red blood cells with breakdown of the lipid layer of the erythrocyte cell membrane.
- Arises in the middle ear in any condition in which hemorrhage occurs (e.g., otitis media) combined with interference in drainage and ventilation of the middle ear space; otoscopic picture is referred to as “blue ear syndrome.”
- Cholesterol granuloma of the middle ear may present as idiopathic hemotympanum; patients may also complain of hearing loss and tinnitus.
- Involvement of the petrous apex is more likely to be associated with sensorineural hearing loss; headaches, cranial nerve deficits, and rarely bone erosion with involvement of the posterior or middle cranial fossa may occur.
- Histology includes the presence of irregular-shaped, clear-appearing spaces surrounded by histiocytes and/or multinucleated giant cells (foreign body granuloma).
- Cholesterol granulomas are not related to cholesteatomas but may occur in association with or independent of a cholesteatoma.
- Cholesteatomas may or may not be associated with otitis media.

Differential Diagnosis

- Middle ear adenoma:
 - Pathologic alterations are generally straightforward, but secondary changes such as glandular metaplasia of the surface epithelium, the result of chronic infection, may occur that might be confused with a true gland-forming neoplasm (e.g., middle ear adenoma).
 - In middle ear adenomas the histology is dominated by the presence of a diffuse glandular and/or solid cell proliferation rather than the haphazard arrangement of the (metaplastic) glands as occurs in chronic otitis media.
 - Identification of cilia is confirmatory of middle ear glandular metaplasia and is a feature not found in association with middle ear adenomas.
- Cholesteatoma
- Langerhans cell histiocytosis
- Rhabdomyosarcoma:
 - In view of the fact that the inflammatory cell infiltrate seen in cases of otitis media may be extremely dense, the pathologist must be vigilant in evaluating these specimens, especially in the pediatric age group so as not to overlook the presence of rhabdomyoblasts and a diagnosis of rhabdomyosarcoma.

- Similarly, the inflammatory cell infiltrate may overrun and obscure Langerhans cells and a diagnosis of Langerhans cell histiocytosis.

Treatment and Prognosis

- Antibiotic therapy directed at the specific pathogen is curative
- Recurrent infections of the middle ear are common, especially in the pediatric population.
- In adults, an unresolving otitis media should warrant detailed examination of the nasopharynx to rule out the presence of a (malignant) neoplasm (i.e., nasopharyngeal carcinoma).
- Squamous cell carcinomas of the middle ear typically arise in patients suffering from (long-standing) chronic otitis media.
- In the antibiotic era, complications associated with otitis media are not generally seen; however, if left unchecked, complications of otitis media occur, which can be divided into:
 - Intratemporal complications
 - Intracranial complication

Intratemporal Complications of Otitis Media

- Include mastoiditis, petrositis, labyrinthitis, and facial nerve paralysis

Mastoiditis

- Due to the continuity of the middle ear space with the mastoid cavity, some degree of mastoiditis can be expected to occur in patients with otitis media; infrequently, acute suppurative mastoiditis occurs.
- Pneumococci and group A streptococci represent the more frequent pathogens in mastoiditis, whereas *Streptococcus pneumoniae* and *Haemophilus influenzae* representing the more common bacteria implicated in otitis media are uncommonly associated with mastoiditis.
- Mastoiditis is the most frequent complication of otitis media (acute and chronic).
- In contrast with the mild form of mastoiditis that frequently occurs in otitis media, the clinically severe form of mastoiditis results in bone destruction.
- Inflammatory destruction of bone may result in necrosis and abscess formation; bone resorption and repair lead to new bone formation typified by the presence of immature woven bone and sclerosis.

Petrositis

- Petrositis or petrous apicitis represents extension of the inflammation of the middle ear or mastoid cavity into the pneumatized cells of the petrous apex, which can occur by direct extension via the pneumatized

air cells of the petrous pyramid or via thrombophlebitis through the small vascular channels of the temporal bone.

- Osteitis and osteomyelitis of the petrous apex require pneumatization of the petrous pyramid, but the extent of pneumatization is not a factor in the development of petrositis.
- Petrositis occurs in two clinical forms:
 - Apical:
 - Characterized by its tendency to extend into the sphenoid bone and skull base, formation of abscesses in the nasopharynx and neck, and its potential source for otogenic septicemia
 - Paralabyrinthine:
 - Involves the paralabyrinthine cells around the semicircular canals and the internal auditory canal
 - Empyema of the of the endolymphatic sac with extension into the posterior cranial fossa and involvement of cranial nerves may occur.
 - Hematogenous dissemination via the petrosal and cavernous sinuses may occur.

Labyrinthitis

- Inflammation of the inner ear and includes pathologic changes of the labyrinth that arise in response to a variety of injuries, including infectious, inflammatory, and traumatic
- Can occur due to complications of otitis media or meningitis or from seeding of microorganisms via the vascular system
- Based on the pathologic changes seen, labyrinthitis can be classified into serous, suppurative, chronic, viral, and ossifying.
- Clinical manifestations of labyrinthitis depend on the severity and extent of the pathologic changes, varying from transient mild vertigo that might accompany an upper aerodigestive tract infection to severe vertigo with nystagmus and profound sensorineural hearing loss caused by suppurative labyrinthitis.
- Serous labyrinthitis is the mildest form of labyrinthitis, representing reactive changes in response to an irritant to the region as might occur secondary to either acute or chronic otitis media but without direct bacterial invasion of the inner ear:
 - In serous labyrinthitis there is accumulation of granular eosinophilic material within the labyrinth and/or perilymphatic spaces; mild endolymphatic hydrops may be seen
- Suppurative labyrinthitis is the result of bacterial invasion of the inner ear originating in the middle ear/temporal bone region (tympanogenic labyrinthitis) or from the meninges (meningogenic labyrinthitis):

- In suppurative labyrinthitis, an acute inflammatory infiltrate, including polymorphonuclear leukocytes, is present in the perilymphatic spaces and surrounding tissues with identifiable bacterial colonies.
- Gram stain may be of assistance in the identification of bacteria.
- With time there is necrosis and destruction of the sensory end organs and the membranous labyrinth.
- Chronic labyrinthitis may be focal or diffuse and results from a local osteitis of the otic capsule as a consequence of a previous acute suppurative labyrinthitis or as a result of a chronic inflammatory process of the membranous labyrinth:
 - This type of labyrinthitis may be associated with sudden or gradual loss of hearing and balance.
- Ossifying labyrinthitis is the end stage of suppurative labyrinthitis and is characterized by the new bone formation in the labyrinth likely representing an osseous metaplasia:
 - Histologic changes in ossifying labyrinthitis include ossification of the labyrinthian structures in the absence of an inflammatory infiltrate.
 - Designation of labyrinthitis for this process is liberally applied.
- Viral labyrinthitis is the result of generalized viral infection such as mumps, measles, and cytomegalovirus (CMV) infection with involvement of the scala media and vestibular end organs resulting in sensorineural hearing loss:
 - Viral labyrinthitis produce viral cytopathic changes in the scala media (stria vascularis, tectorial membrane, and organ of Corti) with associated cellular swelling, degeneration, cyst formation, and destruction.
- Complications of labyrinthitis include extension and involvement of intracranial structures, including meningitis, venous thrombophlebitis, intracranial abscess, facial nerve paralysis, and otitic hydrocephalus.

Intracranial (Endocranial) Complications

- Intracranial complications of otitis media include meningitis, lateral sinus thrombophlebitis, and brain abscess.

Miscellaneous Infections of the Ear and Temporal Bone

- Uncommonly, otitis media may be caused by:
 - Tuberculosis
 - Syphilis
 - Fungi, including *Candida*, *Mucor*, *Cryptococcus*, and *Aspergillus* and actinomycosis

- Viruses including herpes, cytomegalovirus (CMV), rubella, rubeola, and mumps can infect this region and may result in labyrinthitis and sensorineural hearing deafness.
- The setting for some of these infections, particularly mycoses, is in patients who are diabetic, debilitated, and/or immunosuppressed.
- In patients infected with human immunodeficiency virus (HIV) infection or who suffer from acquired immune deficiency syndrome (AIDS), *Pneumocystis jiroveci* (previously *carinii*) may seed from pulmonary lesions to the middle ear and temporal bone; in this setting (Fig. 23-35):
 - Initial clinical presentation may occur as an aural polyp.

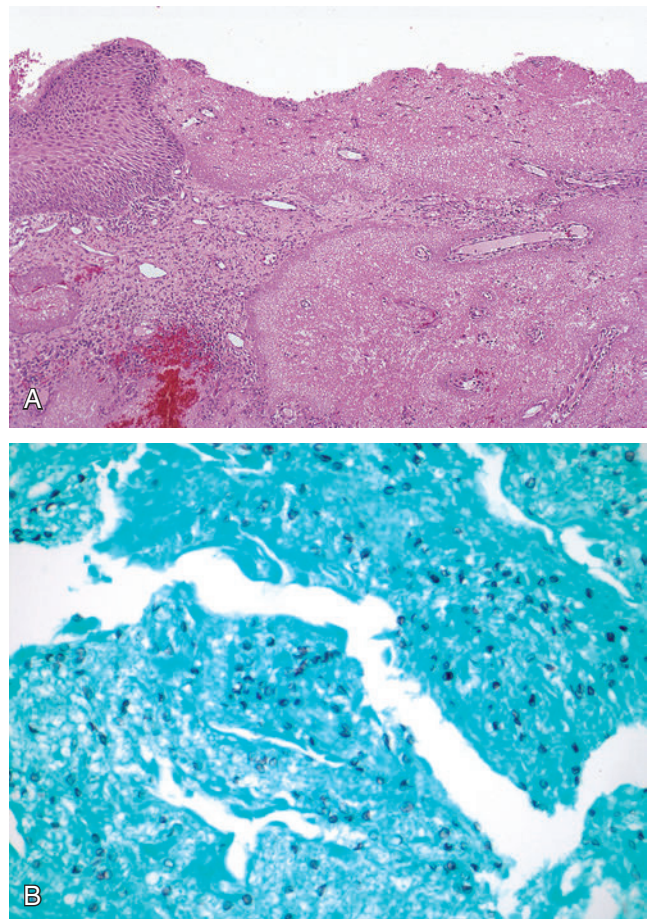


Fig. 23-35. HIV-infected patient who presented with an aural polyp.

The polyp was removed and histologically showed (A) ulceration of the squamous epithelium with a submucosal acellular, eosinophilic “foamy” appearing infiltrate; (B) Gomori methenamine stain revealed numerous clusters of *Pneumocystis jiroveci* (previously *carinii*) microorganisms in which the cysts are black appearing as round, ovoid, or collapsed cuplike structures within the foamy exudate.

- Histologic examination shows characteristic foamy exudate containing the causative microorganisms:
 - Organisms best visualized by GMS stain in which cysts appear as round, ovoid, or collapsed cuplike structures measuring 3.5 to 7 microns in diameter with a membrane of variable thickness.

Differential Diagnosis

- Myospherulosis (see Section 1 on the Sinonasal Tract for illustrations):
 - Iatrogenically induced pseudomycotic lesion resulting from the interaction of red blood cells and petrolatum-based ointments
 - Myospherules originate from red blood cells, which react with petrolatum or lanolin found in ointment used.
 - Common sites of occurrence in the head and neck region include the nasal cavity and paranasal sinuses and occasionally the middle ear.
 - Typically, prior to the development of a mass patients give a recent history of prior surgery followed by packing of the area with a petrolatum-based ointment.
 - Histologically, myospherulosis is characterized by the presence of cysts devoid of an epithelial lining (pseudocysts) embedded within fibrotic tissue with an associated chronic inflammatory infiltrate composed of lymphocytes, histiocytes, giant cells, and plasma cells; the pseudocysts contain round, saclike structures called parent bodies; these parent bodies in turn contain numerous spherules or endobodies.
 - Special stains for fungi are invariably negative and assist in differentiating myospherulosis from fungal infections (e.g., rhinosporidiosis, coccidioidomycosis).
 - Treatment is symptomatic.

OTIC (AURAL) POLYP

(Figs. 23-36 and 23-37)

Definition: Inflammatory polypoid proliferation originating from the middle ear mucosa secondary to chronic otitis media.

Synonyms: Inflammatory aural polyp; aural polyp

Clinical

- No gender predilection; may occur at any age
- Symptoms include a otorrhea, conductive hearing loss, and/or a mass protruding from the external auditory canal.
- Despite origin from the middle ear, otic polyps may perforate the tympanic membrane with extension into the external auditory canal:

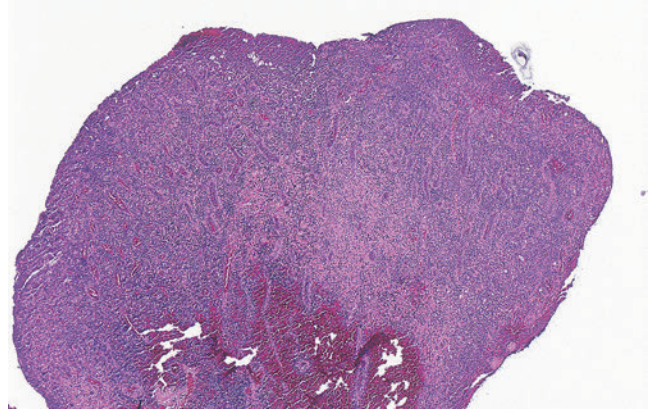


Fig. 23-36. Otic polyp.

Otic polyp appearing as a polypoid lesion that had perforated the tympanic membrane presenting as an external auditory canal mass.

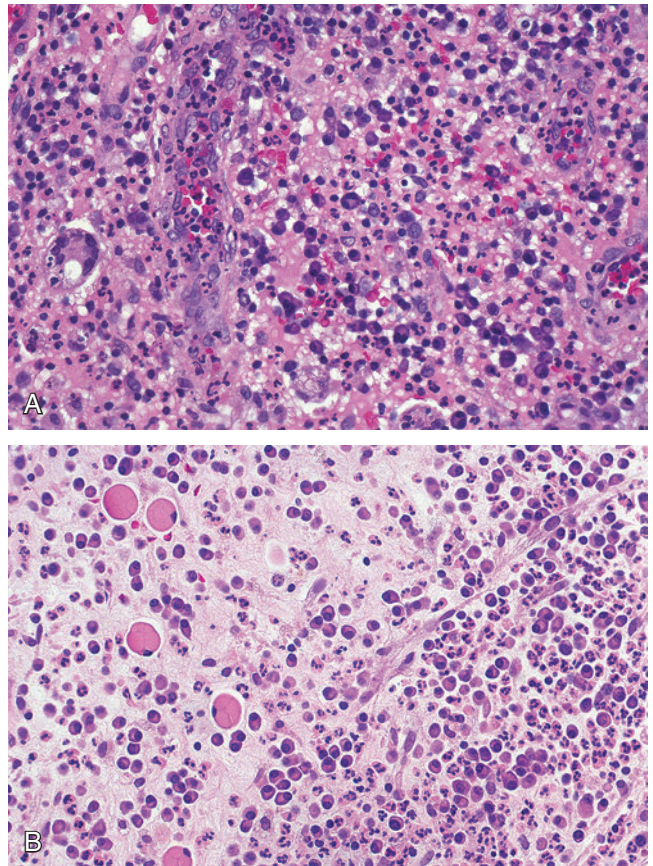


Fig. 23-37. Otic polyp.

A, Otic polyp composed of a heterogeneous inflammatory cell infiltrate including neutrophils, mature plasma cells, lymphocytes, and multinucleated giant cells. **B,** Admixture of neutrophils and mature plasma cells, the latter containing large eosinophilic immunoglobulins referred to as Russell bodies or Mott cells.

- In this situation, the polyp may appear to be originating from the external auditory canal.
- Results secondary to chronic otitis media with perforation of the tympanic membrane and extension from the middle ear into the external auditory canal
- In large polyps completely obstructing the external ear, radiographic studies are an invaluable aid in identifying the origin of the polyp.
- In long-standing cases destruction (partial or complete) of the ossicles may occur.
- May rarely occur in association with Samter triad:
 - Tend to be bilateral, associated with conductive hearing loss, persistent otorrhea, and aural fullness
 - May represent a secondary immunologic dysfunction and chronic otologic inflammation from Samter syndrome

Pathology

Gross

- Polypoid, soft to rubbery, tan-white to pink-red appearing tissue

Histology

- Cellular polypoid mass primarily consisting of a chronic inflammatory cell infiltrate, including mature lymphocytes, plasma cells, histiocytes, and eosinophils.
- Relative to the plasma cells, Russell bodies or Mott cells containing large eosinophilic immunoglobules can be seen and are indicative of a benign plasma cell proliferation.
- Polymorphonuclear leukocytes may be present.
- Stroma includes granulation tissue varying in appearance from edematous and richly vascularized to fibrous with a decreased vascular component.
- Multinucleated giant cells may be present.
- Cholesterol granulomas and calcific debris (tympanosclerosis) may be present.
- When the epithelium is present it appears as pseudostratified columnar or cuboidal cells with or without cilia and may demonstrate squamous metaplasia; a (metaplastic) glandular proliferation may be present
- Histochemistry:
 - Special stains for microorganisms (fungi, spirochetes, mycobacteriae, protozoa, and parasites) are negative but are indicated to rule out an infectious cause.

Differential Diagnosis

- Langerhans cell histiocytosis:
 - Inflammatory cell infiltrate may overrun and obscure Langerhans cells and a diagnosis of Langerhans cell histiocytosis:

- Langerhans cells immunoreactive for S100 protein, CD1a, and Langerin
- Middle ear adenoma
- Rhabdomyosarcoma:
 - In view of the fact that the inflammatory cell infiltrate may be extremely dense, the pathologist must be vigilant in evaluating these specimens, especially in the pediatric age group so as not to overlook the presence of rhabdomyoblasts and a diagnosis of rhabdomyosarcoma.
 - If rhabdomyosarcoma is suspected, immunohistochemical for desmin, myogenin (myf-4), and myoglobin will assist in diagnosis and differential diagnosis.
- Hematolymphoid neoplasms
 - In general, the presence of a mixed cell population of chronic inflammatory cells is benign so that a diagnosis of a malignant lymphoproliferative process is not an issue.
 - Rarely, lymphomatous or leukemic involvement of the middle ear and temporal bone occur secondary to systemic disease.
 - The dense plasma cell component may lead to consideration of a plasmacytoma; although plasma cell dyscrasia may rarely occur in this site, the presence of mature plasma cells, Russell bodies, and polyclonality by immunohistochemistry should preclude a diagnosis of plasmacytoma.
- Other neoplasms that may present as aural polyps include:
 - Meningioma
 - Malignant melanoma
 - Metastatic renal cell carcinoma
 - Adenoid cystic carcinoma

Treatment and Prognosis

- In the absence of an infectious cause, local surgical excision is curative.

MALAKOPLAKIA (Fig. 23-38)

Definition: Malakoplakia is an inflammatory disease that usually involves the genitourinary tract and may rarely occur in the middle ear. Malakoplakia is derived from Greek and means “soft plaque.”

Clinical

- Extremely uncommon lesion in the head and neck; the middle ear is one of the reported sites of occurrence.
- No specific demographics
- Symptoms relate to chronic otitis media and conductive hearing loss.

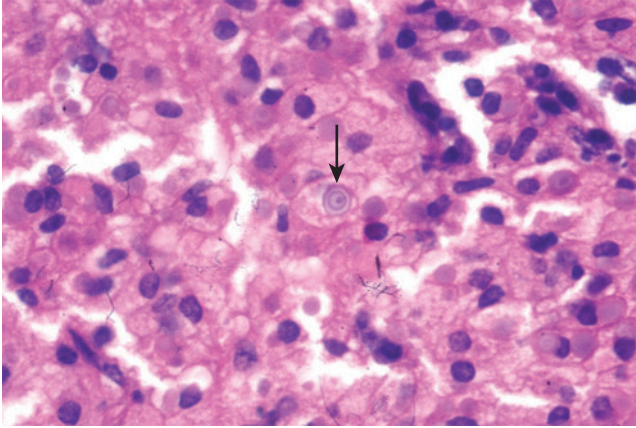


Fig. 23-38. Malakoplakia.

Malakoplakia of the middle ear composed of solid sheets of histiocytes with granular to vacuolated cytoplasm (so-called Hanseman cells) and the presence of a single intracytoplasmic targetoid basophilic inclusion referred to as Michaelis-Gutman body (arrow).

Pathology

Histology

- Light microscopic features include the presence of solid sheets of histiocytes with slightly granular to vacuolated cytoplasm (so-called Hanseman cells) admixed with inflammatory cells, including lymphocytes, plasma cells and neutrophils.
- Intracytoplasmic diastase-resistant PAS-positive targetoid basophilic inclusion bodies termed Michaelis-Gutmann bodies can be seen within occasional cells:
 - These inclusions or calcospherites, which can also be seen extracellularly, contain calcium and frequently iron salts, thereby showing reactivity with von Kossa stain for calcium and Prussian blue stain for iron.
- Malakoplakia is believed to represent an unusual host response to infection with a variety of organisms and ultrastructurally phagolysosomes that have ingested breakdown products of bacteria such as *E. coli* have been found.

Treatment and Prognosis

- Curettage is curative.

AUTOIMMUNE, SYSTEMIC, AND DEGENERATIVE DISEASES OF THE EAR

RELAPSING POLYCHONDritis (RP) (Figs. 23-39 and 23-40)

Definition: Uncommon systemic episodic or relapsing disease characterized by progressive degeneration of cartilaginous structures throughout the body.

Synonym: Polychondropathia

Clinical

- Equal gender predilection; may occur at any age with symptoms most frequently occurring in the fifth through seventh decades of life
- May affect any cartilage tissue in the body
- Auricular cartilage is involved, usually bilaterally, in nearly 90% of patients.
- Affected ear is erythematous, swollen, and very tender.
- In advanced cases there may be distortion of the pinna due to destruction of the cartilage.
- Overlying skin is not ulcerated.
- Disease manifestations relapse with severity and frequency of occurrence and are markedly variable.
- Progression of disease may result in “cauliflower” ears and “saddle” nose deformities.
- Involvement of the audiovestibular system may result in hearing loss (conductive, sensorineural, or mixed).
- Other cartilaginous sites, as well as noncartilaginous sites, of the body may be involved, including:
 - Arthropathy (large and small joints)
 - Laryngotracheal and bronchial chondritis
 - Nasal chondritis
 - Cardiovascular complications (valvular insufficiency, aneurysm)
 - Ocular manifestations (episcleritis, conjunctivitis, retinopathy)
 - Cutaneous involvement (oral and genital ulcers)
- Arthritic involvement of costochondral, sternoclavicular, and sternomanubrial joints is common.
- Clinical diagnostic criteria for RP are defined by three or more of the following:
 - Recurrent chondritis of both auricles
 - Nonerosive inflammatory arthritis; chondritis of nasal cartilages
 - Ocular inflammation including conjunctivitis, keratitis, scleritis/episcleritis, and/or uveitis
 - Chondritis of the upper respiratory tract involving the larynx and/or tracheal cartilages
 - Cochlear and/or vestibular damage manifested by sensorineural hearing loss, tinnitus, and/or vertigo
- Diagnosis can be confirmed when one or more of the above criteria occur in association with histologic

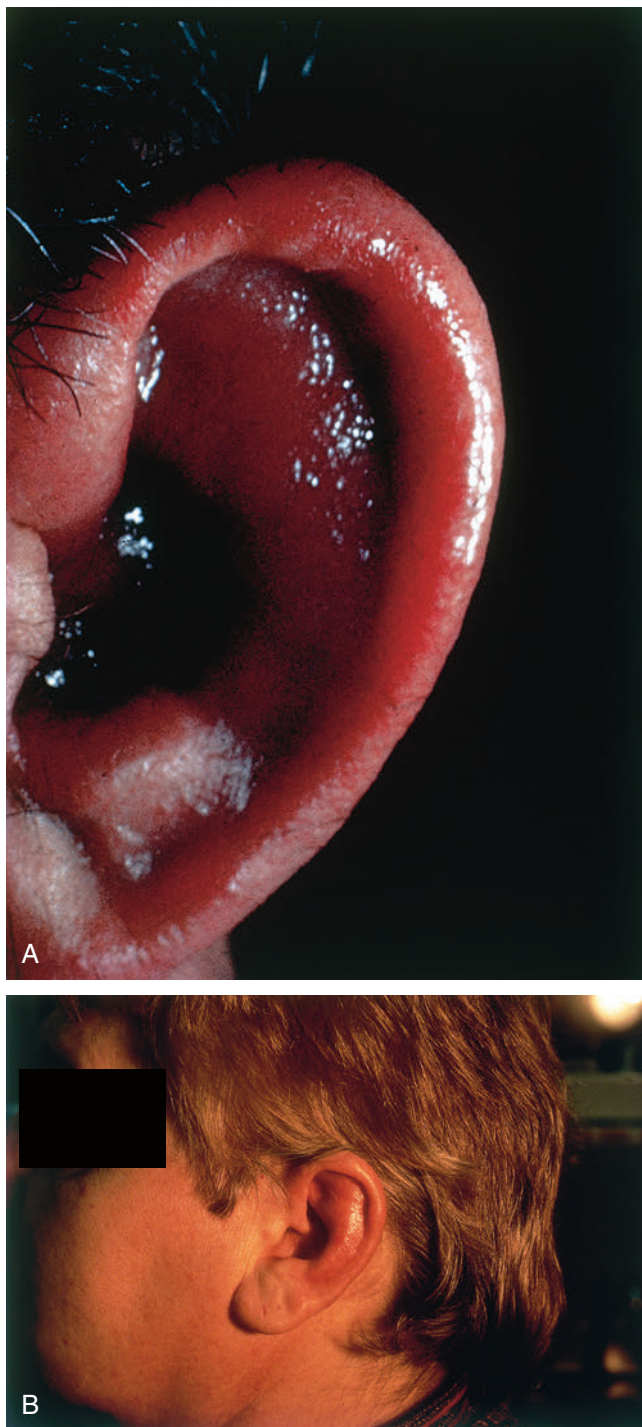


Fig. 23-39. Relapsing polychondritis.

Relapsing polychondritis presenting with (A) diffuse and (B) near total redness and swelling of the ear. In this condition, the ear is warm to touch and is painful.

confirmation or by the presence of chondritis in two or more separate anatomic locations with response to steroids and/or dapsone.

- Laboratory findings are nonspecific and include elevated erythrocyte sedimentation rate, mild

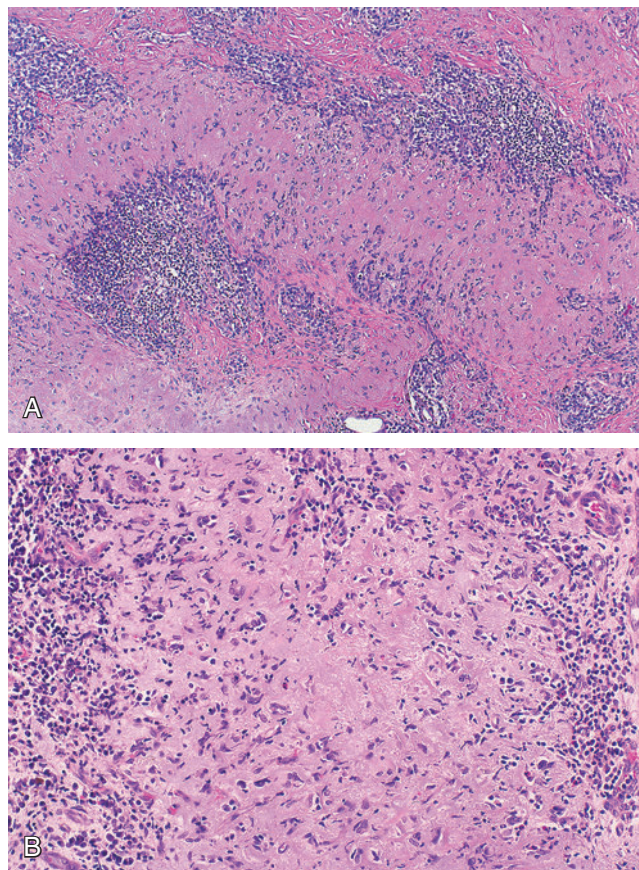


Fig. 23-40. Relapsing polychondritis.

A, A mixed inflammatory cell infiltrate is present in relapsing polychondritis, blurring the interface between the cartilaginous plate and dermal collagen; the cartilage has a ragged appearance. **B**, The mixed inflammatory infiltrate is composed of lymphocytes, plasma cells, polymorphonuclear leukocytes, and occasional eosinophils, completely obscuring the interface between the perichondrium and the auricular cartilage, and permeating throughout the cartilage. In both images the cartilage has an eosinophilic appearance with loss of its usual basophilia.

leukocytosis, and normochromic, normocytic anemia; the presence of elevated antineutrophil cytoplasmic antibodies (ANCA) titers has been reported.

- Etiology has not been clearly elucidated; however, there is evidence for an autoimmune process:
 - In association with RP, some patients suffer from other autoimmune disorders (Box 23-2).
- RP is likely a T helper 1 (Th1)-mediated disease as serum levels of interferon (IFN)- γ , interleukin [IL]-12, and IL-2 parallel changes in disease activity, while the levels of Th2 cytokines do not.
- Patients have been known to have factors in their serum that react with cartilage:

BOX 23-2 Autoimmune Diseases Associated with Relapsing Polychondritis

- Systemic lupus erythematosus
 - Rheumatoid arthritis
 - Scleroderma
 - Sjögren syndrome
 - Reiter syndrome
 - Glomerulonephritis
 - Autoimmune thyroid disease
 - Ulcerative colitis
 - Pernicious anemia
 - Raynaud syndrome
- Circulating antibodies to type II collagen found only in cartilage with titers reflecting severity of disease
 - Documentation of immunofluorescent localization of immune complex components at the perichondral-cartilaginous interface have been reported in patients with RP.
 - Patients have immune complexes of immunoglobulins and complement detected in the biopsy specimens taken from inflamed cartilage of involved ears; these findings coupled with the association of RP with an array of known autoimmune systemic diseases lend support to an autoimmune cause.
 - No evidence to support either hereditary or familial predisposition

Pathology**Histology**

- Histologic findings include perichondrial inflammation with a mixed infiltrate of lymphocytes, plasma cells, polymorphonuclear leukocytes, and occasional eosinophils, which blurs the interface between the perichondrium and the auricular cartilage.
- Loss of the usual basophilia in the cartilage, which assumes an eosinophilic appearance with hematoxylin-and-eosin staining.
- At advancing edge of the inflammation there is loss of chondrocytes and destruction of lacunar architecture.
- As cartilage is destroyed, it is replaced by tissue and eventually by fibrous tissue.
- Immunomicroscopic findings, including diffuse granular deposition of IgG and C3 in the perichondrial fibrous tissue, may be demonstrated.

Differential Diagnosis

- External otitis
- Acute (infectious) polychondritis
- Tophaceous gout
- Systemic vasculitides (e.g., granulomatosis with polyangiitis, formerly Wegener granulomatosis)
- Rheumatoid arthritis

Treatment and Prognosis

- Treatment of RP depends on the stage:
 - In the acute stages of disease, corticosteroids are used.
 - In more advanced stages, immunosuppressive agents may be used.
- Prognosis is variable and unpredictable, with some patients having a prolonged course and others suffering from a more aggressive and fulminant disease.
- Death may occur and is most often the result of respiratory tract or cardiovascular system involvement.
- Tocilizumab, a highly effective therapeutic agent for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis, has been reported to be potentially effective therapy not only for rheumatoid arthritis but also for nonrheumatoid arthritis, inflammatory rheumatic diseases, including relapsing polychondritis.
- Cytokine modulation using TNF α blockers, rituximab, anakinra, tocilizumab, and abatacept recently has shown effectiveness in some RP cases, but further substantiation is needed.

TOPHACEOUS GOUT

(Figs. 23-41 and 23-42)

Definition: Disorder of purine metabolism or renal excretion of uric acid, in which there is a precipitation of monosodium urate as deposits (tophi) throughout the body.

Clinical

- One of the more common sites of gouty tophi is the helix of the ear.
- In relationship to the ear, tophi may present as painful skin-covered firm nodules; auricular gouty tophi may be nonpainful.
- Laboratory findings include:
 - Presence of elevated urinary uric acid (hyperuricemia):
 - Measurement of 24-hour urinary uric acid excretion helps in determining whether uric acid overproduction is a cause of the hyperuricemia.
 - Additionally, there is often leukocytosis and increased erythrocyte sedimentation rate.
- In normal body tissues sodium urate is deposited (tophi), but in urine with a lower pH, uric acid is precipitated.
- Gout may occur as an inherited or acquired disease:
 - Primary gout (90% of cases) is an inherited error of metabolism that results from either an



Fig. 23-41. Gouty tophus.

Gouty tophus identified along the helix of the ear appearing as a discrete white nodule that is typically firm to the touch and painful.

enzymatic defect in purine synthesis or a defect in the renal excretion of uric acid.

- Secondary or acquired gout (10% of cases) occurs secondary to disorders that increase the production of uric acid (e.g., leukemias) or decrease excretion of uric acid (e.g., chronic renal failure).

Pathology

Histology

- Gouty tophi are composed of needle-shaped aggregates of urate crystals with a surrounding foreign body giant cell reaction.
- If a diagnosis of gout is suspected, the resected tissue should be fixed in absolute alcohol or any nonaqueous fixative as the urate crystals are water soluble.
- Crystals demonstrate negative birefringence:
 - When a primary color compensator is used in between two polarizing lenses, the crystals will change color from yellow to blue when

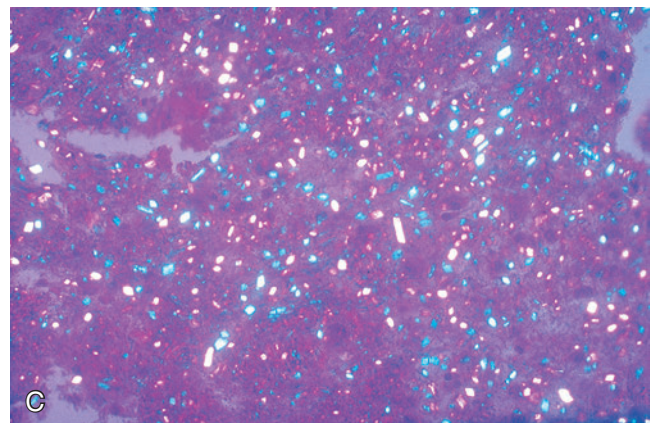
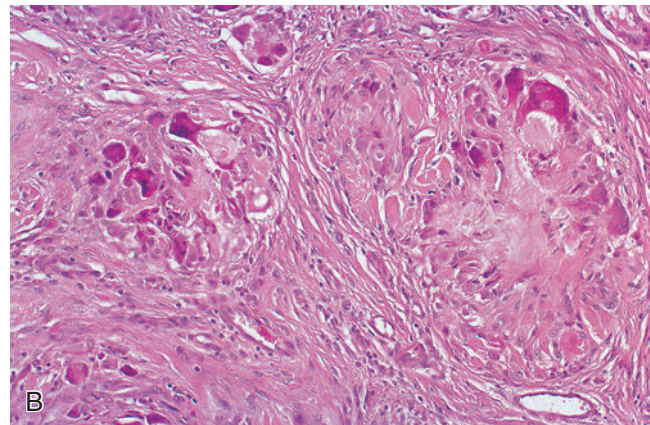
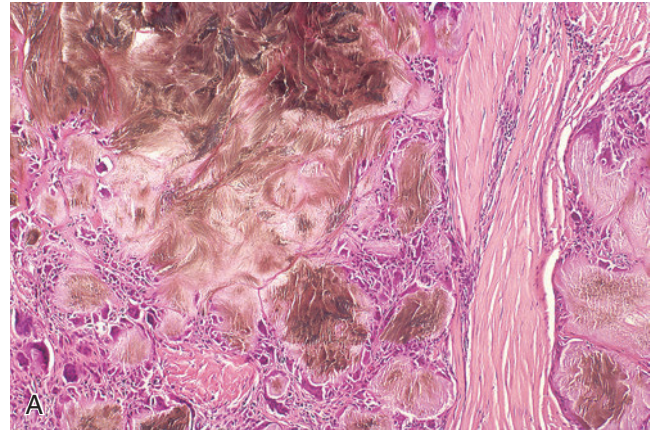


Fig. 23-42. Gout.

A, The histology of gout includes the presence of foreign body giant cell reaction typically surrounding needle-shaped crystals. **B,** In this example, a foreign body giant cell reaction is present but the crystals are not readily identifiable as the tissue was not fixed in absolute alcohol or a nonaqueous fixative. **C,** The crystals change color from yellow to blue when polarizing lenses were rotated from parallel to perpendicular.

rotating the polarizing lenses from parallel to perpendicular.

Differential Diagnosis

- Tophaceous pseudogout (Figs. 23-43 and 23-44):
 - Designation of pseudogout is used to describe the presence of calcium pyrophosphate dihydrate crystal deposition in synovial fluid in patients with gout-like symptoms but without sodium urate crystals.
 - Other designations include tumoral calcium pyrophosphate dihydrate deposition disease, chondrocalcinosis, pyrophosphate arthropathy.
 - More recently, this disease has been designated as calcium pyrophosphate dihydrate deposition disease (CPPD).
 - Mutations in the progressive ankylosis homolog human (*ANKH*) gene have been shown to cause familial CPPD.
 - Histologically, tophaceous pseudogout is characterized by:
 - Presence of a variably cellular chondroid-appearing tissue within which is crystalline material
 - Crystalline material appears rhomboid or needle shaped and under polarized light microscopy the crystals showed weak positive birefringence.
- In decalcified material the crystals may be lost.
- A foreign body granulomatous reaction can be seen in association with the crystal deposition.
- Chondroid metaplasia is often present in and around the areas of CPPD deposition.
- There is some evidence to indicate that metaplastic chondrocytes may play a role in the initial precipitation of CPPD crystals.
- Synovial chondrometaplasia may be seen in patients with pyrophosphate arthropathy.
- Metaplastic chondrocytes may show cytologic atypia that could lead to a diagnosis of chondrosarcoma; this is particularly true in decalcified sections from which CPPD crystals are lost.
- In contrast to pseudogout, radiographic calcification in gouty tophi is relatively uncommon.
- In addition, the identification of the specific positive birefringence of the calcium pyrophosphate crystals as seen in tophaceous pseudogout is not a feature seen in gouty tophi.

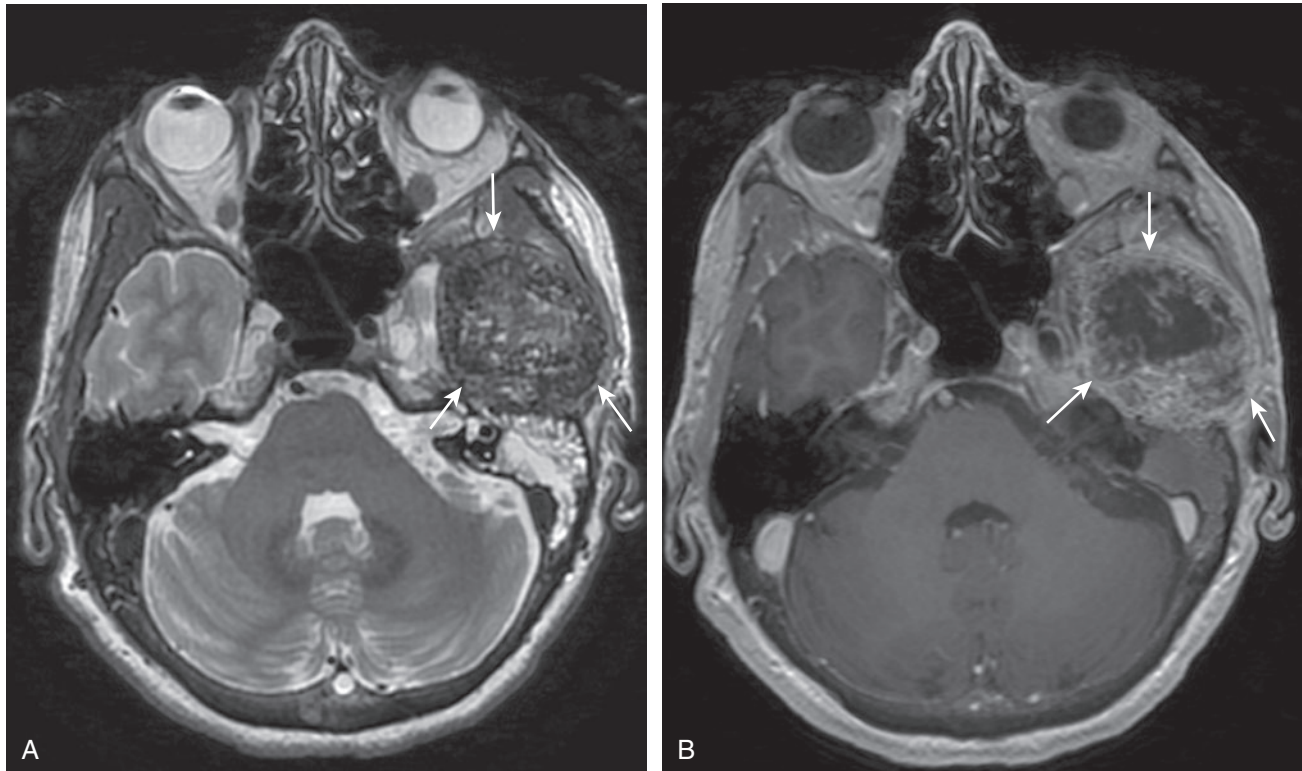
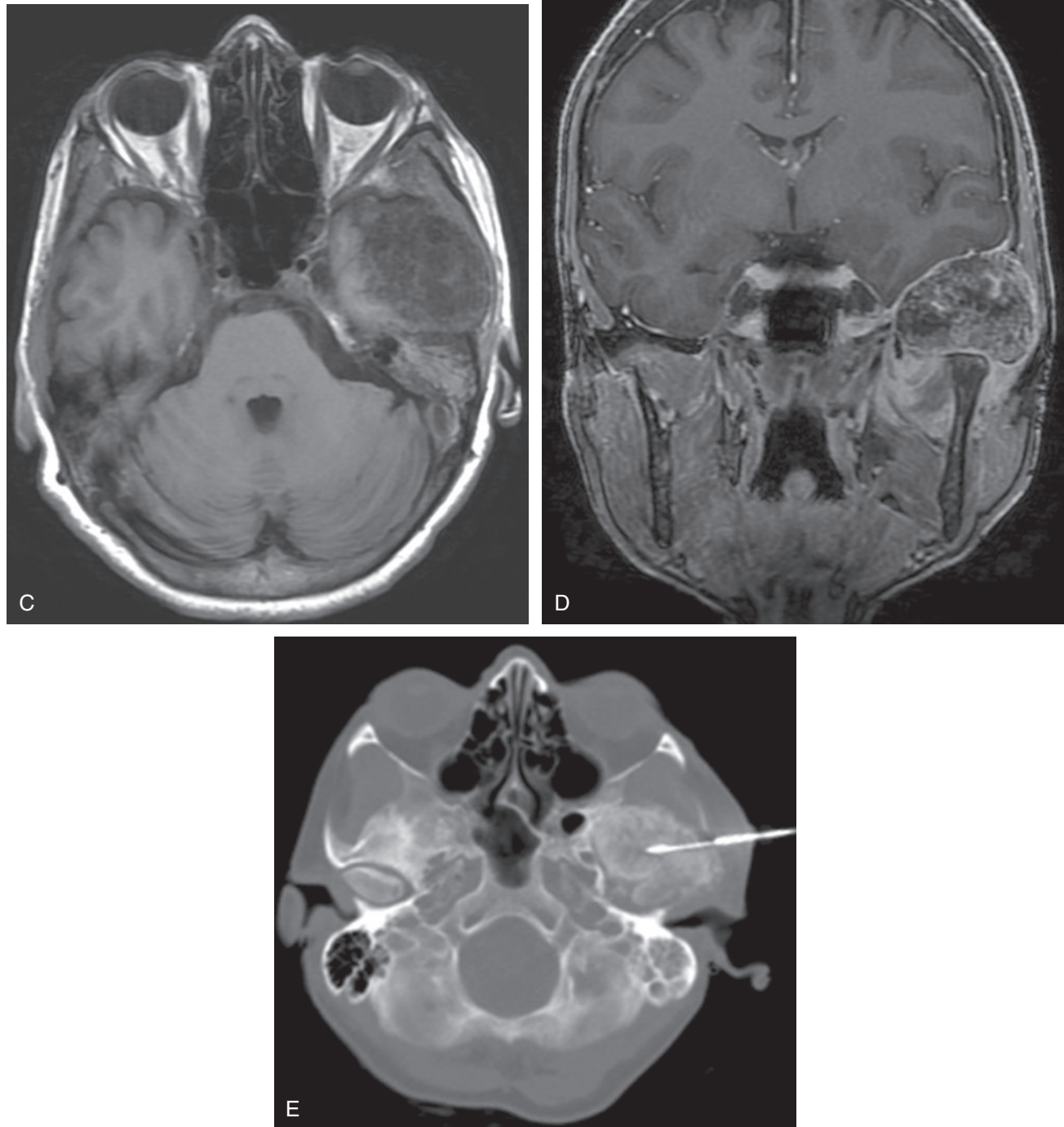


Fig. 23-43. Calcium pyrophosphate dihydrate deposition disease.

A, Axial T2-weighted image shows a large low signal intensity mass (arrows) in the left infratemporal fossa/TMJ region.
B, On contrast-enhanced T1-weighted image the lesion is partially enhancing.

**Fig. 23-43, cont'd**

C, On precontrast T1-weighted image the lesion has a heterogeneous low to intermediate signal. **D**, Coronal T1 postcontrast shows the heterogeneous mass in the left TMJ infratemporal fossa and middle cranial fossa region. There are erosions of the skull base and expansion in and mass effect on the temporal lobe in the middle cranial fossa. **E**, The lesion was biopsied under CT guidance using a 16-gauge core biopsy needle, and pathologic analysis confirmed calcium pyrophosphate dihydrate. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 26-90, p 1592.)

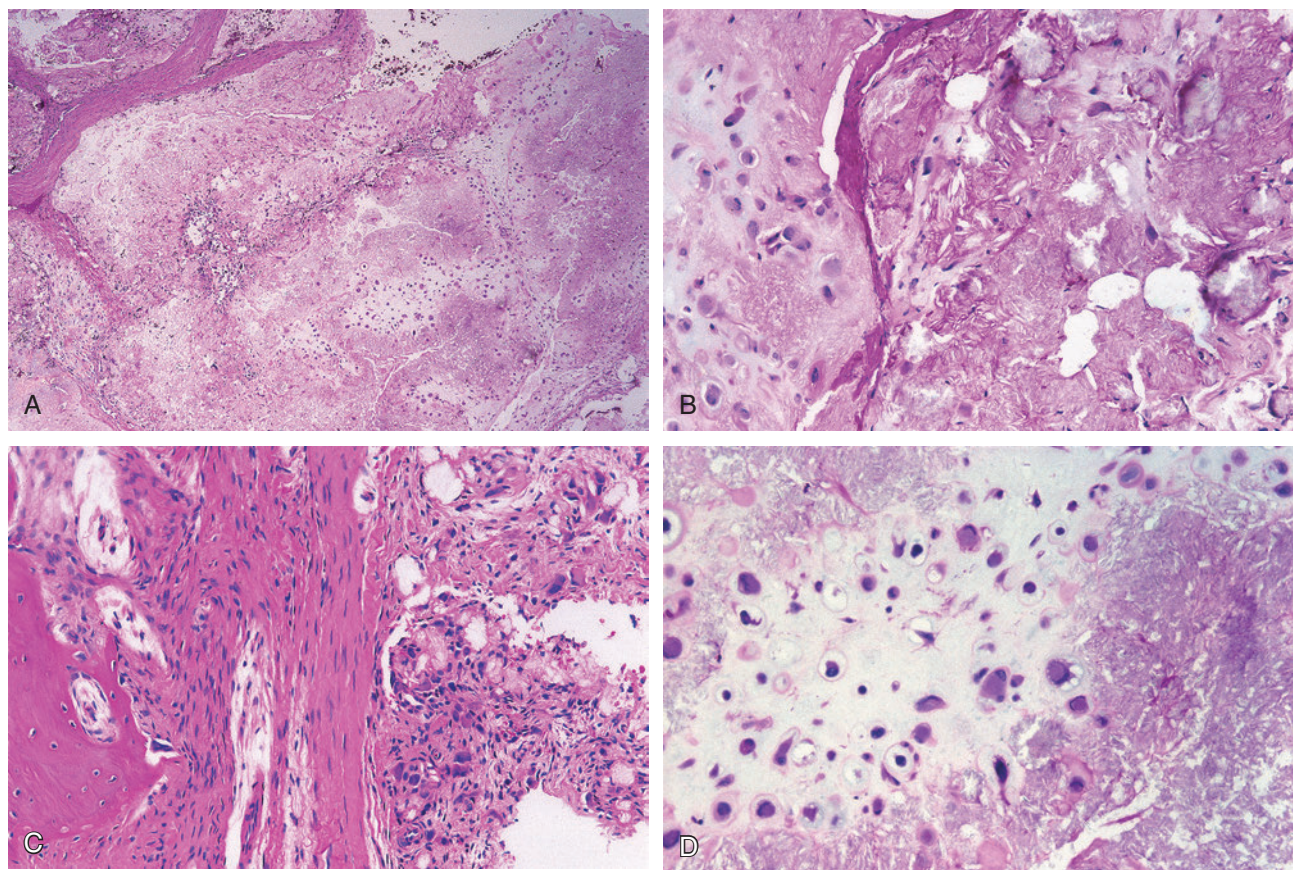


Fig. 23-44. Tophaceous pseudogout.

The histologic features of tophaceous pseudogout include (A) a variably cellular and vaguely lobular chondroid-appearing tissue; (B) crystalline-appearing material with a rhomboid or needle shape within the chondroid tissue (under polarized light microscopy the crystals showed weak positive birefringence, not shown); (C) a foreign body granulomatous reaction (*right*) can be seen in association with the crystal deposition; (D) chondroid metaplasia in and around the areas of CPPD deposition; the chondrocytes may show cytologic atypia.

Treatment and Prognosis

- In acute gout pharmacologic intervention is usually necessary and includes:
 - Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Oral colchicines
 - Corticosteroids
- Anti-interleukin 1 (IL-1) therapies may also be beneficial in treating acute gout symptoms.
- Resting the painful joint and applying topical ice are helpful in relieving the pain and terminating the attack as quickly as possible.
- In patients with multiple recurrent gout flares or advanced gout the goal of therapy is to prevent disease progression achieved by:
 - Lowering serum urate levels (less than 6.0 mg/dl resulting in mobilization and depletion of crystals to prevent recurrent flares and joint destruction)
 - Allopurinol and febuxostat (uricostatic drugs) are the most widely used approach.
 - Probenecid (uricosuric agent) increases renal excretion of uric acid but is not appropriate for patients who are urate overproducers because of the risk of nephrolithiasis.
 - Pegloticase (uricolytic agent) degrades uric acid into soluble end product, is given intravenously, and is being evaluated in patients for whom conventional therapy is either ineffective or inadequate.

GRANULOMATOSIS WITH POLYANGIITIS (GPA)

(See Section 1, Sinonasal Tract for images.)

Definition: Systemic necrotizing vasculitis that typically involves the kidneys, lung, and upper aerodigestive tract.

- Nomenclature: formerly referred to as Wegener granulomatosis
- Systemic GPA by definition includes kidney involvement.
- Localized GPA involves the sinonasal tract (or other head and neck sites) and/or the lungs.

Clinical

- Otologic involvement by GPA occurs in 20% to 60% of patients with disease of more usual sites.
- Most common otologic manifestations include unilateral or bilateral otitis media (serous or suppurative), perforation of the tympanic membrane, and sensorineural hearing loss; cutaneous involvement of the external ear with perforation of the earlobes and external otitis; facial palsy may occur as the initial manifestation of disease.
- Involvement of the middle ear may occur secondary to nasopharyngeal and sinonasal disease via the eustachian tube or may be due to direct involvement by disease.
- Antineutrophil cytoplasmic autoantibodies (ANCA) should be elevated in the active phase of GPA:
 - Two distinct staining patterns are found: cytoplasmic (c-ANCA) and perinuclear (p-ANCA)
 - GPA is associated with c-ANCA and infrequently with p-ANCA.
 - p-ANCA is more often associated with rheumatic diseases.
 - Patients with generalized GPA have a 60% to 100% c-ANCA positivity; patients with limited GPA have a 50% to 67% c-ANCA positivity.
 - c-ANCA results can be used in establishing a diagnosis of GPA in clinically suspect lesions in which the biopsies are not entirely diagnostic; false positive results are uncommon.
 - c-ANCA titers correlate with disease activity and recurrent disease.
- Proteinase 3:
 - Proteinase-3 (PR3) is a neutral serine proteinase present in azurophil granules of human polymorphonuclear leukocytes and monocyte lysosomal granules.
 - PR3 is the major target antigen of antineutrophil cytoplasmic antibodies with a cytoplasmic staining pattern (c-ANCA) in GPA.
 - ANCA with specificity for PR3 are characteristic for patients with GPA.
 - Patients with GPA demonstrate a significantly higher percentage of mPR3+ neutrophils than healthy controls and patients with other inflammatory diseases.
 - The detection of ANCA directed against proteinase 3 (PR3-ANCA) is highly specific for GPA.
 - ANCA positivity is found only in about 50% of the patients with localized GPA, whereas

PR3-ANCA positivity is seen in 95% of the patients with generalized GPA.

- Pathogenesis of vascular injury in GPA is ascribed to antineutrophil cytoplasmic antibodies directed mainly against PR3.
- Interaction of ANCA with neutrophilic ANCA antigens is necessary for the development of ANCA-associated diseases; ANCA bind to membrane-expressed PR3 and induce full-blown activation in primed neutrophils.
- In patients with GPA, high expression of PR3 on the surface of nonprimed neutrophils is associated with an increased incidence and rate of relapse.
- ANCA-associated vasculitis (AAV) includes GPA, microscopic polyangiitis (MPA), and allergic granulomatous angiitis (AGA):
 - Major target antigens of ANCA associated with vasculitis are PR3 and myeloperoxidase (MPO).
 - PR3-ANCA is the marker for GPA.
 - MPO-ANCA is related to MPA and AGA.
 - ANCA appears to induce vasculitis by directly activating neutrophils.
 - No immunoglobulins or complement components are detected in vasculitis lesions; as such, AAV is called pauci-immune vasculitis.

Pathology

Histologic features are similar to those described in the lungs, kidney, or upper aerodigestive tract (see Section 1, Sinonasal Tract for complete pathologic description and images).

NOTE: Elevation of serum levels of antineutrophil cytoplasmic autoantibodies (ANCA) are of great assistance in those cases in which the diagnosis is suspected but the histology is not definitively diagnostic.

- Special stains for microorganisms, including GMS and AFB, are negative.
- Inflammatory infiltrate shows immunoreactivity for leukocyte common antigen, B-cell markers, and T-cell markers.

Differential Diagnosis

- Other autoimmune or systemic diseases that may involve the middle or inner ear include polyarteritis nodosa and rheumatoid arthritis, which may also involve the middle and inner ear.
- Polyarteritis nodosa is a necrotizing vasculitis of small and medium-sized muscular arteries:
 - Aural-related symptoms include otitis media with effusion.
 - Sensorineural hearing loss may be the initial presentation or after the diagnosis has already be established.

- The histologic diagnosis is dependent on the presence of necrotizing vasculitis.
- Treatment includes corticosteroids and immunosuppressant agents.
- Manifestations of rheumatoid arthritis of the audio-vestibular system includes conductive hearing loss due to involvement of the incudomalleal and incudostapedial articulations; high-dose salicylates in combination with steroids and nonsteroidal anti-inflammatory agents are the preferred treatment.

Treatment and Prognosis

- Combined corticosteroid and immunosuppressive therapy may result in long-term remissions and is

capable of reversing the hearing loss and facial palsy if the diagnosis of GPA can be established and treatment initiated early in the disease course.

- Prognosis for hearing is poor when appropriate treatment is not given in the early stages of the disease.
- Early diagnosis and appropriate treatment are important to prevent irreversible changes in the middle ear and inner ear.

OTOSCLEROSIS (Fig. 23-45)

Definition: Disorder of the bony labyrinth and stapedial footplate that occurs exclusively in humans and is of

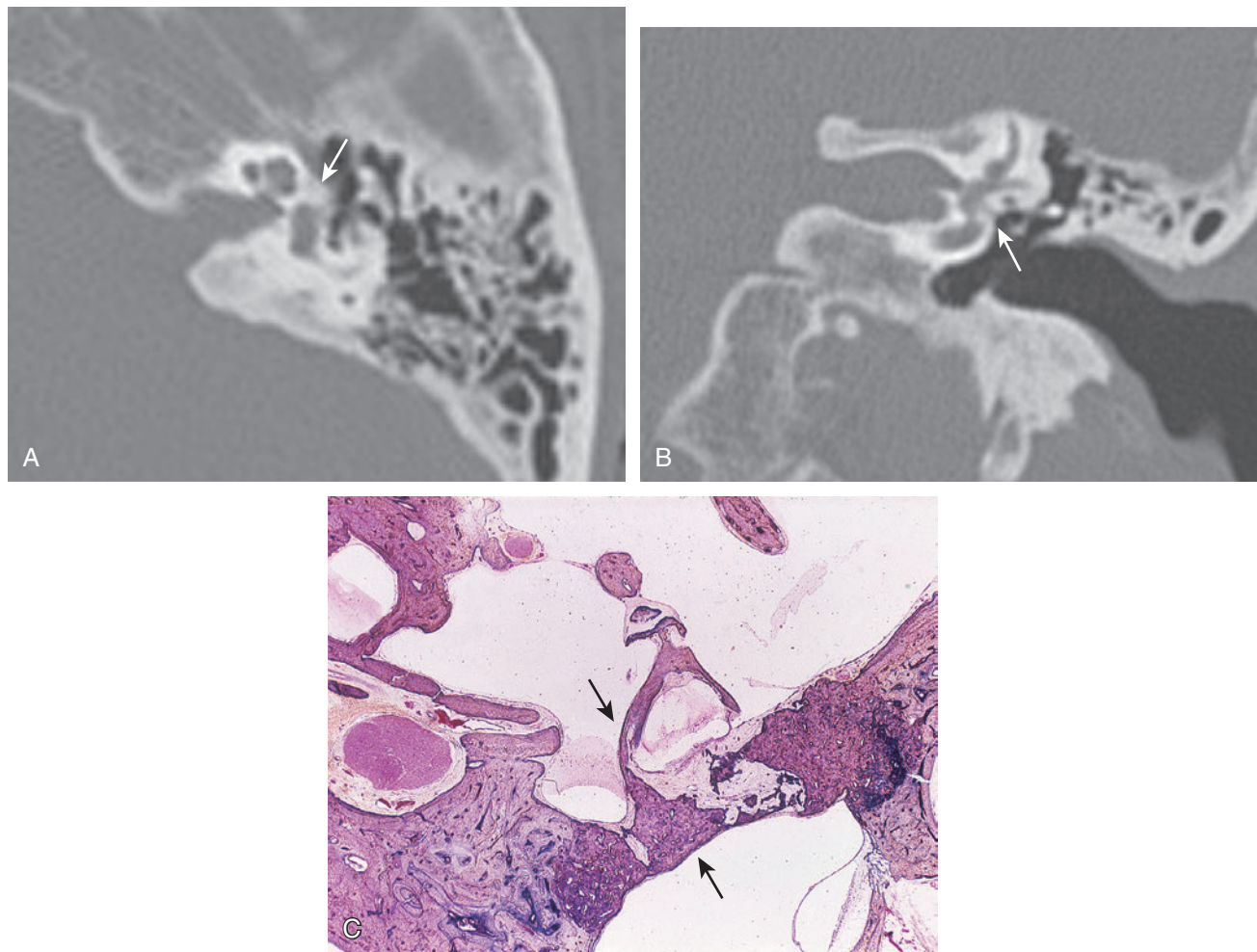


Fig. 23-45. Sclerotic phase of otosclerosis.

A, Axial CT image shows a focus of abnormal bone (*arrow*) just anterior to the footplate of the stapes. Note that the bone has almost the same density as the otic capsule. It is also enlarged in size. **B**, Coronal CT image shows the overgrowth of bone impinges on the oval window (*arrow*), causing significant narrowing. The bone has approximately the same density as the otic capsule. **C**, The histologic correlate of the CT findings shows the presence of densely sclerotic bone that resulted in fixation of the stapedial footplate (*arrows*). (*A and B*, From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 19-4, p 1233.)

unknown etiology. Otosclerosis means hardening of the ear and is derived from Greek (*ous*, ear; *skleros*, hard; *osis*, condition); osseous ankylosis (Greek: *ankoulon*, to stiffen).

Synonyms: Chronic metaplastic otitis; progressive otospongiosis

Clinical

- More often affects women than men; usually begins in the second and third decades of life and is slowly progressive
- Prevalence of otosclerosis varies with race and is more common in whites than in blacks, Asians, and Native Americans.
- Otosclerosis primarily causes conductive hearing loss; the extent of the hearing loss directly correlates with the degree of stapedial footplate fixation.
- Otosclerosis usually involves both ears; however, unilateral disease can occur in up to 15% of cases.
- It is not uncommon for patients with otosclerosis also to have vestibular disturbances.
- Radiology:
 - Imaging studies can confirm the clinical consideration of otosclerosis.
 - High-resolution CT is the preferred modality for evaluating middle and inner ear structures, including labyrinth in windows, stapes footplate, cochlear capsule.
- Although many theories regarding the etiology of otosclerosis appear in the literature, the etiology of otosclerosis is unclear:
 - Hereditary factors are often cited as among the causes of otosclerosis, although the mode of inheritance is still uncertain.
 - Family history occurs in more than 50% of cases.
 - The majority of epidemiologic studies on families with otosclerosis suggest an autosomal-dominant mode of inheritance with reduced penetrance of approximately 40%.
 - Genetic linkage studies have demonstrated the presence of six loci (OTSC1, OTSC2, OTSC3, OTSC4, OTSC5, and OTSC7) located on chromosomes 15q, 7q, 6p, 16q, 3q, and 6q, respectively:
 - Although these loci have been mapped, no causative genes have been identified.
 - Disturbed bone metabolism, persistent measles virus infection, autoimmunity, and hormonal and environmental factors also may play contributing roles in the pathogenesis of otosclerosis.
 - Evidence that otosclerosis is derived from the periosteum of the external canal:
 - External layer of the otic capsule arises from periosteal osteoblasts, which produce large numbers of Volkmann canals as well as lamellar bone.

- Main plaque of otosclerosis is a histologic replica of the external layer and seems to arise from similar cells in the periosteum and to follow a defined invasive course into the footplate of the stapes, the basal coil of the cochlea, and the saccule.
- Based on the invasiveness of the plaques apparently derived from the periosteum of the external layer of the otic capsule, some authorities have suggested that otosclerosis is a neoplasm of bone forming a replica of external layer otic capsule tissue (i.e., Volkmann canals and lamellar bone):
 - This suggestion is supported by the marked proliferation of osteoblasts and concomitant production of minicanals seen in the advancing edge of the plaques.

Pathology

Histology

- Initial alterations include resorption of bone around blood vessels.
- Cellular fibrovascular tissue replaces the resorbed bone, resulting in softening of the bone (otospongiosis).
- Immature bone is laid down with continuous active resorption and remodeling.
- New bone is rich in ground substance and deficient in collagen, but, over time, more mature bone with increased collagen and less ground substance is produced, resulting in densely sclerotic bone.
- Process most often begins anterior to the oval window, eventually involving the footplate of the stapes.
- Stapedial involvement causes fixation of the stapes and the inability to transmit sound waves, resulting in conductive hearing loss.
- Similar pathologic involvement of the inner ear may produce sensorineural hearing loss.

Differential Diagnosis

- Paget disease (see below)

Treatment and Prognosis

- Surgical management of the conductive hearing loss caused by stapes fixation (stapedectomy) is the preferred treatment.

PAGET DISEASE OF BONE

(Figs. 23-46 and 23-47)

Definition: Chronic progressive osseous disorder of unknown etiology.

Synonym: Osteitis deformans

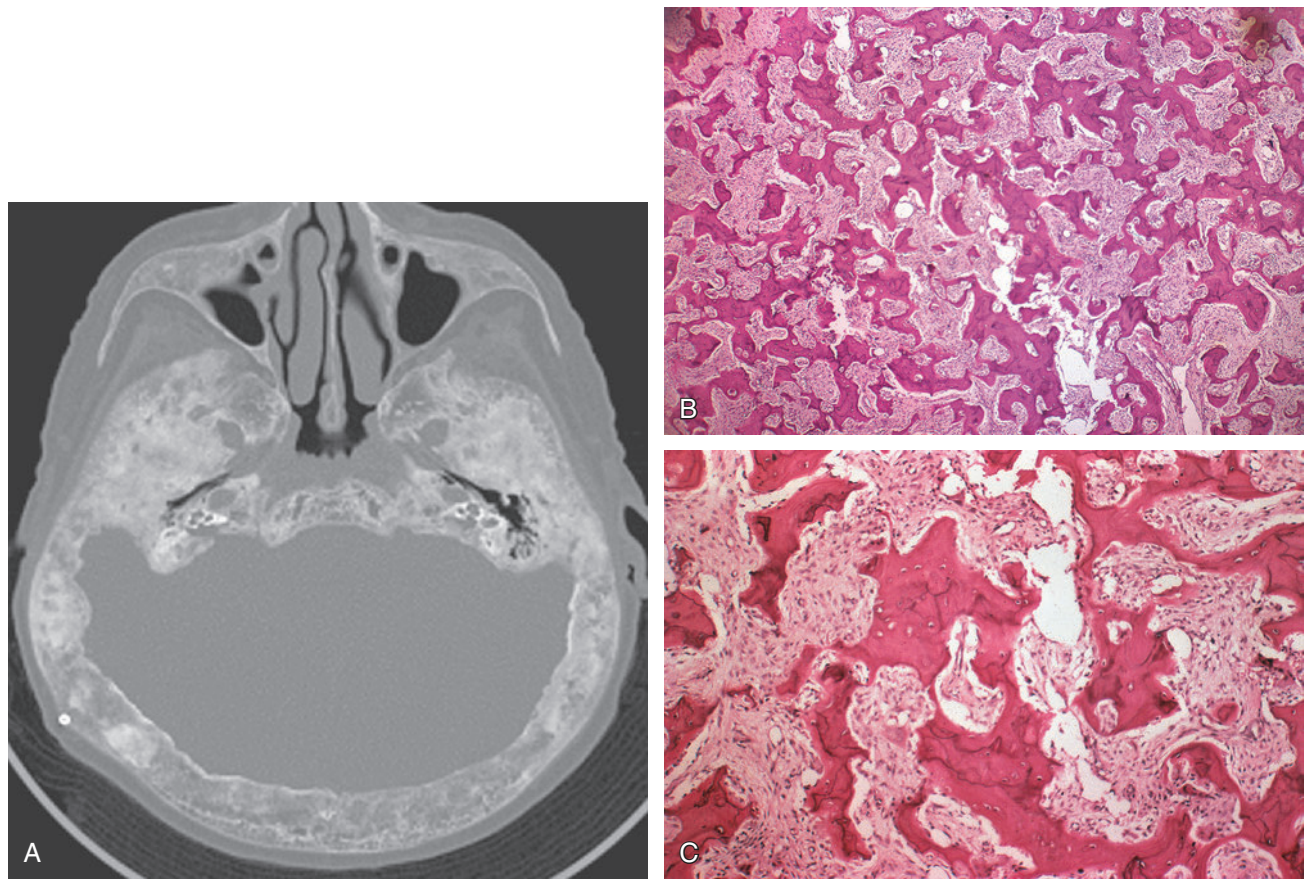


Fig. 23-46. Paget disease of the skull and temporal bone.

A, Axial CT image of Paget disease demonstrating thickening of the bony structures with mixed densities of otosclerosis and osteolysis. The changes are symmetric. Thinning of the cochlear capsule is noted bilaterally. The odontoid process protrudes above the foramen magnum to the level of the clivus. **B**, Histologic features include increased new bone characterized by dense irregular masses showing a mosaic pattern. **C**, Higher magnification shows the cement lines of Paget bone as well as scattered osteoclastic giant cells.

Clinical

- Skull and temporal bone involved in approximately 70% of cases:
 - Other sites of involvement include the external auditory canal, tympanic membrane, eustachian tube, ossicles, oval window, round window, internal auditory canal, cochlea, and endolymphatic sac.
- Slightly more common in men than in women; affects about 3% of the population over 40 years of age and as many as 11% of the population over 80 years of age
- Symptoms include hearing loss, tinnitus, and vertigo; the facial nerve is spared.
- Hearing loss is sensorineural, mixed sensorineural, and conductive, and less often only conductive:
 - Hearing losses are progressive and are due to involvement of the osseous portion of the external auditory canal, involvement of the ossicles, and/or involvement of the cochlea and labyrinth.
- Radiology:
 - High-resolution CT of the temporal bone may show mixed appearance of bone thickening and sclerosis.
 - In the temporal bone the disease begins at the petrous apex and progresses inferolaterally; with progression demineralization of the otic capsule may occur.
 - Stapedial footplate may become involved (i.e., thickened), contributing to the (conductive) hearing loss.
 - Frequently, the central skull is also involved.
- Etiology is unknown but consideration has been given for an infectious (viral) cause in genetically predisposed individuals:
 - Measles virus has been reported as playing an important role as an environmental factor in the pathogenesis of Paget disease.

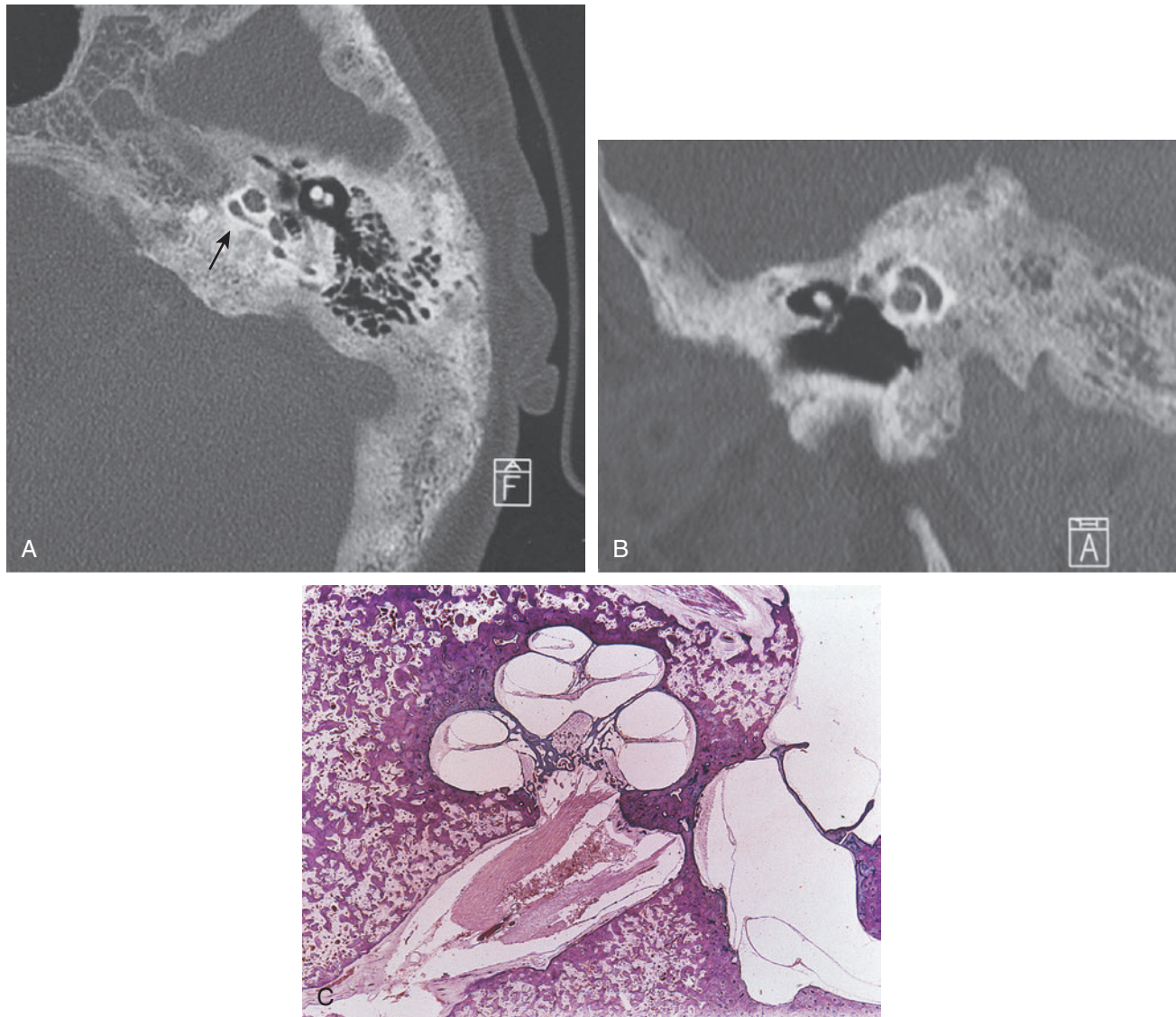


Fig. 23-47. Paget disease of petrous part of the temporal bone around the bony labyrinth.

A, CT scan in Paget disease shows the presence of bone with increase in size. There are demineralization and thinning of the otic capsule (*arrow*). **B**, Coronal image showing thinning of the otic capsule. **C**, The histology includes involvement of the otic capsule characterized by dense, irregular-appearing bone showing a mosaic pattern.

- Interleukin-6 (IL6) is increased in the bone marrow of patients with Paget disease, and measles virus nucleocapsid protein (MVNP) induces IL-6 secretion by pagetic osteoclasts.
- IL-6 plays a critical role in the development of pagetic osteoclasts and bone lesions induced by Paget disease, but the mechanisms regulating IL-6 production by MVNP remain unclear.
- MVNP decreases FoxO3/Sirt1 signaling to enhance the levels of IL-6, which in part mediate MVNP's contribution to the development of Paget disease.

Pathology Histology

- Paget disease is characterized by three histologic phases:
 - First (osteolytic phase): excessive osteoclastic activity resulting in bone resorption
 - Second (mixed or combined phase): new bone formation (osteoblastic activity) predominates over bone resorption (osteoclastic activity) with deposition of new bone next to areas of bone resorption

- Third (osteoblastic phase): increased new bone characterized by dense irregular masses showing a mosaic pattern referred to as cement lines

Differential Diagnosis

- Otosclerosis:
 - Features in Paget disease that assist in separating it from otosclerosis include:
 - Later age of onset
 - Greater sensorineural hearing loss
 - Enlarging calvaria
 - Enlargement and tortuosity of the superficial temporal artery and its anterior branches

Treatment and Prognosis

- Treatment is directed at slowing or preventing progression of disease by suppressing increased bone turnover using oral administration of biphosphonates, which act by decreasing the number of osteoclasts with deposition of structurally normal bone as opposed to deposition of less disordered bone deposition.
- Anti-inflammatory medications are used in relieving bone and joint pain.
- Hearing loss is permanent and cannot be reversed by medical therapy.
- Sarcomatous transformation occurs in approximately 1% of cases and usually transforms to an osteosarcoma:
 - Osteosarcomas arising in Paget disease are highly malignant, with less than 10% 5-year survival rates.

MÉNIÈRE DISEASE

Definition: Idiopathic disorder of the inner ear associated with a symptom complex of spontaneous, episodic attacks of vertigo, sensorineural hearing loss, tinnitus, and a sensation of aural fullness.

Synonyms: Endolymphatic hydrops; idiopathic endolymphatic hydrops; Lermoyez syndrome

Clinical

- Incidence of Ménière disease varies in the literature to include 157 per 100,000 people in England to 46 per 100,000 in Sweden to 7.5 per 100,000 in France.
- Occurs slightly more frequently in women than in men (1.6:1); the peak incidence is in the fifth to seventh decades of life but may occur in children as well as in older individuals (ninth and tenth decades)
- Characterized by a set of symptoms, including fluctuating sensorineural hearing loss, episodes of vertigo, tinnitus, and pressure sensation in the ear:
 - Onset of vertigo is frequently sudden, reaching maximum intensity within a few minutes lasting from an hour or more and either subsiding com-

pletely or continuing as a sensation of unsteadiness for hours to days.

- Etiology is uncertain, although the incidence of Ménière disease is noted to be increased in patients with certain genetically acquired major histocompatibility complexes (MHCs), including HLA B8/DR3 and Cw7, suggesting a possible autoimmune cause.
- Familial occurrence of Ménière disease has been reported, although the role genetic inheritance plays in the mode of transmission is variable.
- Pathogenesis of Ménière disease is distortion of the membranous labyrinth defined as changes in the anatomy of the membranous labyrinth as a consequence of the overaccumulation of endolymph (endolymphatic hydrops) and at the expense of the perilymphatic space:
 - Endolymph, which is produced by the stria vascularis in the cochlea and by cells in the vestibular labyrinth, circulates in a radial and longitudinal fashion.
 - In patients with Ménière disease it is believed that there is inadequate absorption of endolymph by the endolymphatic sac.

Pathology

Histology

- In the early stages of the disease endolymphatic hydrops primarily involves the cochlear duct and saccule but in the later stages the entire endolymphatic system is involved.
- Alterations of the membranous labyrinth include dilatation, outpouching, rupture, and collapse.
- Fistulae (unhealed ruptures) may occur.
- Severe cytoarchitectural and atrophic changes may occur in the sense organs with loss of neurons in the cochlea.

Treatment and Prognosis

- Medical management is the mainstay of therapy; therapy is aimed at reduction of symptoms and is therefore empiric and supportive.
- Optimally, management should resolve the vertigo, tinnitus, and hearing loss.
- Vertigo represents the most debilitating of symptoms, and current management is directed at relieving vertigo.
- Therapy includes prophylaxis via reduction of endolymph accumulation by dietary modification, intermittent dehydration, diuretics, enhancement of the microcirculation of the ear using vasodilators (e.g., betahistidine, adenosine triphosphate, isosorbide, others) and reduction in immune reactivity using steroids, immunoglobulin, and allergy therapy.
- Symptomatic therapies include antivertiginous medications, antiemetics, sedatives, antidepressants, and psychiatric management.

- Improvement in 60% to 80% of patients has been reported.
- Surgical treatment is reserved for those patients who have failed medical management (approximately 10% of patients) and includes shunting or decompression of the endolymphatic sac, labyrinthectomy, or sectioning of the vestibular nerve.
- Combined corticosteroid and immunosuppressive therapy may result in long-term remissions and is

capable of reversing the hearing loss and facial palsy if the diagnosis can be established and treatment initiated early in the disease course.

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Neoplasms of the Ear and Temporal Bone

CLASSIFICATION OF NEOPLASMS OF THE EAR AND TEMPORAL BONE

BOX 24-1 Classification of Neoplasms of the Ear and Temporal Bone

I. External Ear

A. Benign

- Epithelial/neuroectodermal/mesenchymal
 - Keratoacanthoma
 - Ceruminous gland neoplasms
 - Seborrheic keratoses
 - Squamous papilloma
 - Melanocytic nevi
 - Dermal adnexal neoplasms
 - Pilomatrixoma (calcifying epithelioma of Malherbe)
 - Neurilemmoma/neurofibroma
 - Osteoma; chondroma
 - Hemangioma
 - Others

B. Malignant

- Epithelial/neuroectodermal/mesenchymal
 - Basal cell carcinoma
 - Squamous cell carcinoma and variants (Verrucous carcinoma, spindle cell squamous carcinoma, adenoid squamous cell carcinoma, others)
 - Ceruminous gland adenocarcinomas
 - Malignant melanoma
 - Merkel cell carcinoma
 - Atypical fibroxanthoma
- Others

II. Middle and Inner Ear

A. Benign

- Epithelial
 - Middle ear adenoma
 - Middle ear papilloma
 - Others
- Neuroectodermal/mesenchymal
 - Jugulotympanic paraganglioma
 - Meningioma
 - Acoustic neuroma
 - Others

B. Malignant

- Epithelial
 - Middle ear adenocarcinoma
 - Primary squamous cell carcinoma
- Neuroectodermal/mesenchymal
 - Endolymphatic sac papillary tumor
 - Rhabdomyosarcoma
 - Vascular (angiosarcoma; Kaposi sarcoma)
 - Lymphoproliferative (malignant lymphoma; plasmacytoma)
- Secondary tumors

BENIGN NEOPLASMS OF THE EXTERNAL EAR

KERATOACANTHOMA (KA) (Fig. 24-1)

Definition: Solitary squamous epithelial neoplasm believed to arise from hair follicles, frequently occurring on sun-exposed areas of the skin and characterized by rapid development followed by involution and spontaneous regression.

NOTE: Some experts believe that solitary keratoacanthomas represent squamous cell carcinoma with a real but limited ability to metastasize.

Clinical

- No gender predilection; most frequently seen in the sixth to seventh decades of life
- Frequently develop on sun-exposed skin:
 - Majority occur on the face (most commonly on the cheek and nose)
 - Approximately 10% occur on the external ear (pinna); occasionally may occur on the lips
- Usually a solitary lesion but multiple KAs occur
- Initially the lesion appears as an erythematous papule or may resemble a wart but over a 1- to 2-month period undergoes rapid enlargement to appear as an exophytic or dome-shaped nodule with a central keratin crater measuring from 1 to 3 cm in diameter.
- Typically arise rapidly (6 to 8 weeks) followed by a stationary period lasting up to several months which in turn is followed by involution with spontaneous regression ultimately leading to (crateriform) scar.
- Whole growth process may be seen over periods of several months up to a year.
- Etiology is unknown but is probably the result of actinic damage.

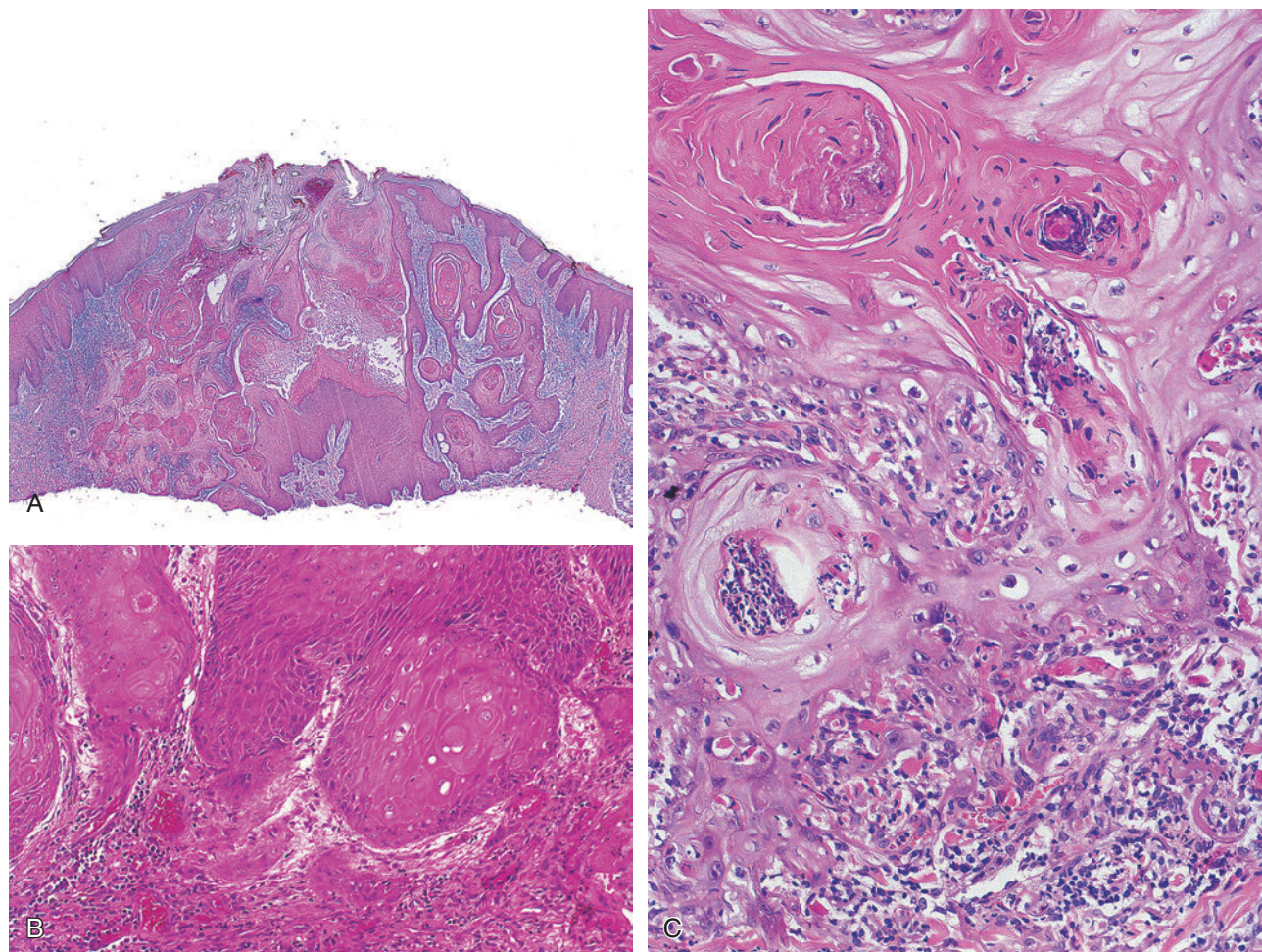


Fig. 24-1. Keratoacanthoma.

A, Keratoacanthoma characterized by the presence of a well-differentiated squamous epithelial proliferation with characteristic cup-shape and with a central keratin plug. **B**, In the depth of the lesion the epithelial proliferation is composed of nests of large keratinocytes with a “glassy”-appearing or eosinophilic cytoplasm and prominent intercellular bridges. **C**, A variable chronic inflammatory infiltrate may be seen composed of mature lymphocytes, histiocytes, eosinophils, and polymorphonuclear leukocytes with neutrophilic intraepithelial “microabscesses.”

- Multiple and syndromic keratoacanthomas exist and may occur in patients with genetic predisposition.
- Less common variants include:
 - Giant keratoacanthoma:
 - Grows rapidly and reaches a size of 5 cm or more
 - May cause destruction of underlying tissues
 - Spontaneous involution occurs after several months.
 - Most common sites are the nose and eyelids.
 - Keratoacanthoma centrifugum marginatum:
 - May reach 20 cm in diameter
 - No tendency to spontaneous involution
 - Peripheral extension with raised, rolled border and central atrophy
 - Most common sites are dorsa of hands and legs
- Subungual keratoacanthoma:
 - Aggressive behavior that fails to regress spontaneously
 - Destructive growth in distal portion under a fingernail
- Described as part of Muir-Torre syndrome, which is characterized by:
 - Multiple neoplasms of the skin, including those with sebaceous differentiation and internal (visceral) neoplasms, the most common of which are of colonic origin (adenocarcinoma, adenoma)
 - In Muir-Torre syndrome, KAs may be one of multiple cutaneous lesions or represent the only type of cutaneous tumor present in this syndrome.

Pathology

Gross

- Early lesions appear as an erythematous papule or a wart-like growth.
- Mature lesions are elevated and firm with an exophytic or dome-shaped appearance characterized by skin-colored edges and a central cavity or crater filled with keratin debris.
- Measures from 1 to 3 cm and occasionally may reach sizes measuring up to 5 cm

Histology

- Cup-shaped symmetric lesion with deep bulbous lobules of squamous cells
- Early lesion shows hyperkeratosis, parakeratosis, acanthosis with hypergranulosis, and papillomatosis with strands of atypical and dyskeratotic keratinocytes forming a central crater extending into the epidermis.
- Mature lesions form a crater filled with hyper- and orthokeratotic material, below which is the epithelial proliferation composed of nests of large keratinocytes with a “glassy”-appearing or eosinophilic cytoplasm and prominent intercellular bridges.
- Dyskeratosis and squamous pearl formation are commonly seen.
- Transition area between the adjacent squamous epithelium and the hyperplastic epithelium forming the crater is noted by the formation of “shoulders,” a characteristic low-power finding.
- A variable chronic inflammatory infiltrate may be seen in the dermis surrounding the lesion composed of mature lymphocytes, histiocytes, eosinophils, and polymorphonuclear leukocytes; neutrophilic intraepithelial “microabscesses” are often seen.
- Vascular and perineural invasion may be seen.
- With time the lesion involutes and is characterized by regression of the epithelial proliferation, a shallower central crater, granulation tissue proliferation, and fibrosis of the dermis.

Differential Diagnosis

- Benign keratosis
- Seborrheic keratosis, including inverted follicular keratoma
- Squamous cell carcinoma:
 - Differentiation from squamous cell carcinoma is made on the basis of the overall architecture because cytologic atypia is not a reliable criterion for differentiating KA from squamous cell carcinoma.
 - Differentiation can be extremely difficult especially if less than adequate biopsy material is provided (e.g., from the central aspects of the tumor).

- No reliable immunohistochemical staining and/or molecular biologic analyses allowing for differentiating KA from squamous cell carcinoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Despite the result of involution and regression, keratoacanthomas should be treated surgically for the following reasons:
 - Cosmetic considerations
 - Allow for the best overall architectural evaluation to confirm the diagnosis and help differentiate from a squamous cell carcinoma
 - Treatment would be the same for a well-differentiated squamous cell carcinoma in this location.
 - A small percentage of cases may recur.
- Keratoacanthomas have been reported to metastasize; however, the metastases have been squamous cell carcinomas, suggesting that the primary tumors may have also been squamous cell carcinomas.
- Presence of vascular and/or perineural invasion are not findings indicative of malignancy.
- Diagnosis of KA as opposed to squamous cell carcinoma can be made if certain conditions are met, including:
 - Clear-cut clinical description of the lesion is provided.
 - Clinical history of rapid evolving lesion with KA as the primary clinical diagnosis
 - No history of immunosuppression
 - Adequate biopsy provided allowing for complete visualization of the lesion
 - Classic histologic findings are identified.
 - In the absence of these conditions a diagnosis of squamous cell carcinoma is likely.

BENIGN CERUMINAL GLAND NEOPLASMS

Definition: Benign tumor of cerumen-secreting modified apocrine glands (ceruminal glands) located in the external auditory canal.

General Comments

- Ceruminal gland tumors arise from the cerumen-secreting modified apocrine glands (ceruminal glands) in the external auditory canal:
 - Ceruminal glands are located in the dermis of the cartilaginous (inner) portion (outer third) of the external auditory canal.

BOX 24-2 Classification of Ceruminal Gland Neoplasms**Benign Ceruminal Gland Tumors**

- Ceruminal gland adenoma (ceruminoma)
- Pleomorphic adenoma
- Syringocystadenoma papilliferum

Malignant Ceruminal Gland Tumors

- Ceruminal gland adenocarcinoma
- Adenoid cystic carcinoma
- Mucoepidermoid carcinoma

- In general, ceruminal gland neoplasms are uncommon but represent one of the more common tumors of the external auditory canal.
- The generic designation of ceruminoma should be avoided; ceruminal gland neoplasms should be specifically diagnosed according to tumor type.
- The classification of ceruminal gland neoplasms includes benign and malignant tumors ([Box 24-2](#)):
 - Benign ceruminal gland tumors include:
 - Ceruminal gland adenoma
 - Pleomorphic adenoma
 - Syringocystadenoma papilliferum
 - Malignant ceruminal gland tumors include:
 - Ceruminal gland adenocarcinoma
 - Adenoid cystic carcinoma
 - Mucoepidermoid carcinoma

Ceruminal Gland Adenoma

(Figs. 24-2 through 24-4)

Synonym: Ceruminoma**Clinical**

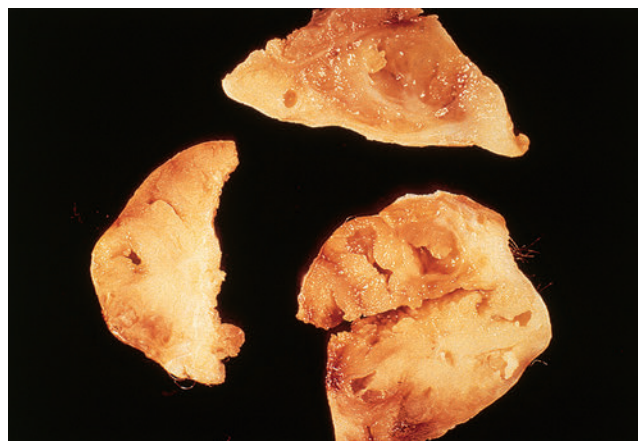
- Affect men more often than women; over a wide age range but is most frequently seen in the fifth to sixth decades of life
- Symptoms include a slow-growing external auditory canal mass or blockage, hearing difficulty, and infrequently, otic discharge.

Pathology**Gross**

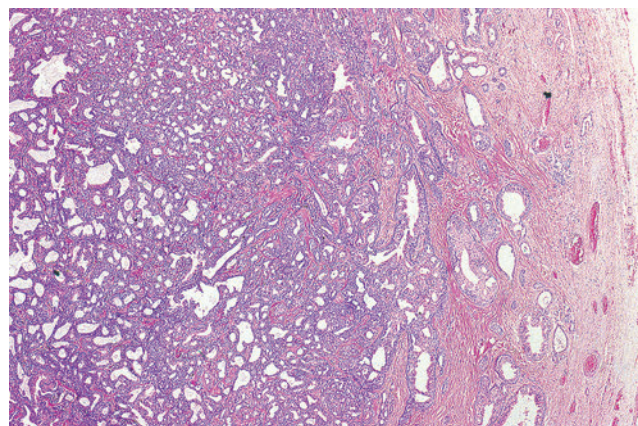
- Skin-covered, circumscribed, polypoid, or rounded mass ranging in size from 1 to 4 cm in diameter
- Ulceration is uncommon and may suggest a malignant neoplasm.

Histology

- Unencapsulated but well-demarcated glandular proliferation
- Glands vary in size and may have various combinations of growth patterns including solid, cystic, and

**Fig. 24-2. Ceruminal gland adenoma.**

Ceruminal gland adenoma resection specimen appearing as a skin-covered lesion with a glistening, golden yellow appearance.

**Fig. 24-3. Ceruminal gland adenoma.**

At low magnification ceruminal gland adenoma is circumscribed but unencapsulated in its depth (*right*).

papillary; a back-to-back glandular pattern is commonly seen.

- Glands are composed of two cell layers:
 - Inner or luminal epithelial cell is cuboidal or columnar appearing with an eosinophilic cytoplasm and a decapitation-type secretion (apical “snouts”) characteristic for apocrine-derived cells.
 - Outer cellular layer is a spindle cell with a hyperchromatic nucleus and represents myoepithelial or basal cells.
- Intracytoplasmic golden yellow-brown granular-appearing pigment can be seen in the inner lining (luminal) cells representing cerumen.
- Cellular pleomorphism and mitoses can be seen but are not prominent.

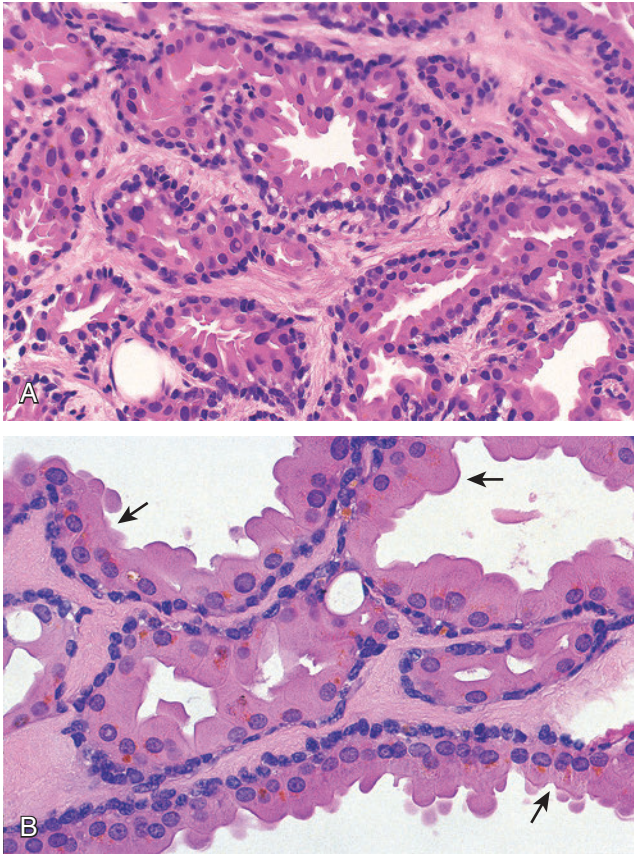


Fig. 24-4. Ceruminal gland adenoma.

A, The glands in ceruminal gland adenoma are composed of two cell layers, including inner or luminal epithelial cells with a cuboidal to columnar appearance and an eosinophilic cytoplasm with a decapitation-type secretion (apical "snouts") characteristic for apocrine-derived cells and the outer cellular (myoepithelial or basal cell) layer composed of cells with hyperchromatic nuclei. **B**, Intracytoplasmic golden yellow-brown granular-appearing pigment can be focally seen in the inner lining cells indicative of cerumen production. Immunohistochemical staining (not shown) includes strong and diffuse CK7 staining in luminal cells and CK5/6, S100 protein, and p63 in the basal cells.

- Intervening stroma shows a variable admixture of fibromyxomatous tissue.
- Histochemistry:
 - Diastase-resistant, PAS-positive, and/or mucicarmine-positive intracytoplasmic and/or intraluminal material may be seen.
- Immunohistochemistry:
 - Luminal cells:
 - Strongly and diffusely immunoreactive with CK7; CD117 positive
 - Myoepithelial or basal cells:
 - CK5/6, S100 protein, and p63 positive

- Ultrastructure:
 - Epithelial (apocrine cell) and myoepithelial cell differentiation including:
 - Epithelial cells show features of apocrine cells, including apocrine caps, microvilli, cell junctions, secretory granules, vacuoles, lipid droplets, and siderosomes.
 - Concentric membranous bodies of the endoplasmic reticulum, phagocytic activity of the tumor cells, intracytoplasmic lumina, ciliated cells, and also spiny collagen in the tumor stroma can be seen.

Differential Diagnosis

- Pleomorphic adenoma of ceruminal or parotid gland origin
- Middle ear adenoma:
 - May perforate the tympanic membrane and appear to present as an external auditory canal mass, creating potential difficulty in differentiation from a ceruminal gland adenoma
 - Histologic features of both tumor types should allow for relatively easy differentiation from one another.
- Ceruminal gland adenocarcinoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Recurrence of the tumor can occur and relates to inadequate surgical excision.

OTHER CERUMINAL GLAND BENIGN NEOPLASMS

Pleomorphic Adenoma of Ceruminal Gland Origin (Fig. 24-5)

- Uncommon tumor
- Histology is similar to pleomorphic adenomas of salivary gland origin, including a variable admixture of epithelial and myoepithelial components set in a myxoid to chondromyxoid stroma.

Syringocystadenoma Papilliferum of Ceruminal Gland Origin

(Figs. 24-6 and 24-7)

- Benign tumor of apocrine gland origin that usually occurs on the scalp and face area
- May originate in the external auditory canal from ceruminal glands
- Histology is similar to tumors of the more common cutaneous sites and to the salivary gland tumor termed sialadenoma papilliferum (see Section 6).

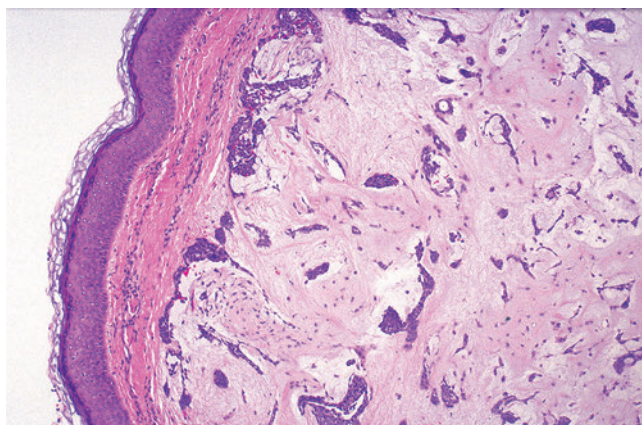


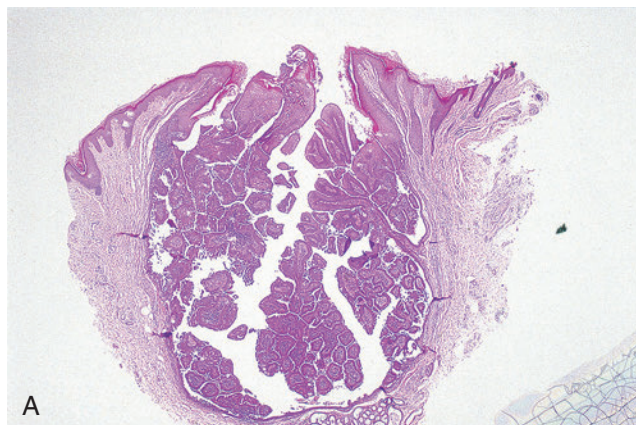
Fig. 24-5. Ceruminous gland pleomorphic adenoma.

Pleomorphic adenoma of ceruminous gland origin presenting as an external auditory canal mass and characterized by the presence of a subepithelial proliferation of glandular/tubular structures with myoepithelial cells in a chondromyxoid stroma.

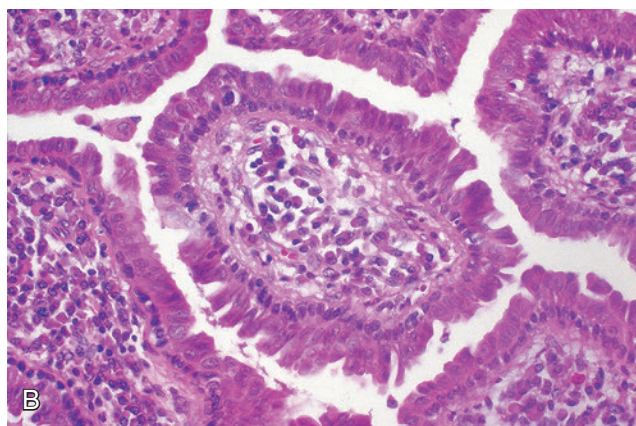


Fig. 24-6. Syringocystadenoma papilliferum.

Syringocystadenoma papilliferum appearing as a small discrete skin-covered nodule on the concha.



A



B

Fig. 24-7. Syringocystadenoma papilliferum.

A, The histology of syringocystadenoma papilliferum includes the presence of a cup-shaped cystic lesion filled by papillary proliferation and communicating with the skin surface. **B**, The papillary fronds are covered by a dual cell layer, including luminal columnar cells with eosinophilic cytoplasm showing apical snouting and inner layer of flattened cuboidal cells; the core of the papillary fronds is composed of lymphoplasmacytic inflammatory cell infiltrate.

BENIGN MESENCHYMAL TUMORS OF THE EXTERNAL EAR

Epithelioid Hemangioma (EH)

(Figs. 24-8 to 24-9)

- Epithelioid hemangioma (EH), also known as angiolymphoid hyperplasia with eosinophilia (ALHE), has been a controversial lesion with regard to its classification (reactive proliferation or neoplastic process) and its relationship to Kimura disease:
 - A reactive cause especially secondary to trauma has been proposed but a neoplastic origin is favored.
 - Considered to represent the benign end of the spectrum of vascular tumors characterized by

epithelioid endothelial cells, many of which are rich in lymphocytes and eosinophils

- Malignant end of the spectrum includes epithelioid hemangioendothelioma and epithelioid angiosarcoma.
- Shares features with Kimura disease, but the clinical and histologic differences allow these entities to be separated and considered as distinct clinicopathologic entities (Table 24-1)

Clinical

- No gender predilection; most frequently occurs in the third through fifth decades of life
- Subcutaneous proliferation with a predilection for the external ear (auricle and external canal), as well as other head and neck sites, including the scalp and forehead (Fig. 24-8)
- Symptoms include pruritus and bleeding following scratching; regional lymphadenopathy and peripheral eosinophilia are uncommon but may be present.

- History of trauma elicited in a number of cases, as well as the microscopic impression of vascular damage, and the demonstration of immunoglobulin deposits in the vessels have led several observers to favor a reactive or reparative etiology.
- Hormonal influences may play a role in some cases, as suggested by the association with pregnancy in some patients and by the age and gender distribution of the disease.
- Human herpesvirus 8 (HHV-8) has not been identified in association with EH.

Pathologic Features

Gross

- Characterized by single or multiple, pink to red-brown indurated cutaneous papules or subcutaneous nodules
- Measure from a few millimeters to 1 cm in diameter
- Clusters of papules may coalesce to form large plaque-like lesions.

TABLE 24-1 Epithelioid Hemangioma (EH) versus Kimura Disease

	EH	Kimura Disease
Gender	M = F or F > M	M > F
Peak incidence	3rd to 5th decades	2nd to 3rd decades
Head and neck site	Periauricular, forehead	Postauricular, scalp
Lymphadenopathy	Absent to rare	Common
Peripheral eosinophilia	<25%	>50%
Location	More superficial situated in subcutaneous, dermis	More deeply situated extending to the subcutaneous fat, fascia, and skeletal muscle
Histology	Nodular vascular proliferation lined by plump-appearing (epithelioid) endothelial cells with pleomorphic changes and hyperchromatic nuclei, and accompanied by a prominent inflammatory cell infiltrate with variable admixture of lymphocytes, histiocytes, plasma cells, and eosinophils	Vascular component is sparse with minimal epithelioid endothelial changes; lymphoid proliferation predominates, but prominent eosinophilic cell infiltrate, including eosinophilic microabscesses can be seen; associated fibrosis is present



Fig. 24-8. Epithelioid hemangioma.

Epithelioid hemangioma appearing as multiple superficial dull red-appearing papules; some of the papules appear to coalesce into plaque-like lesion.

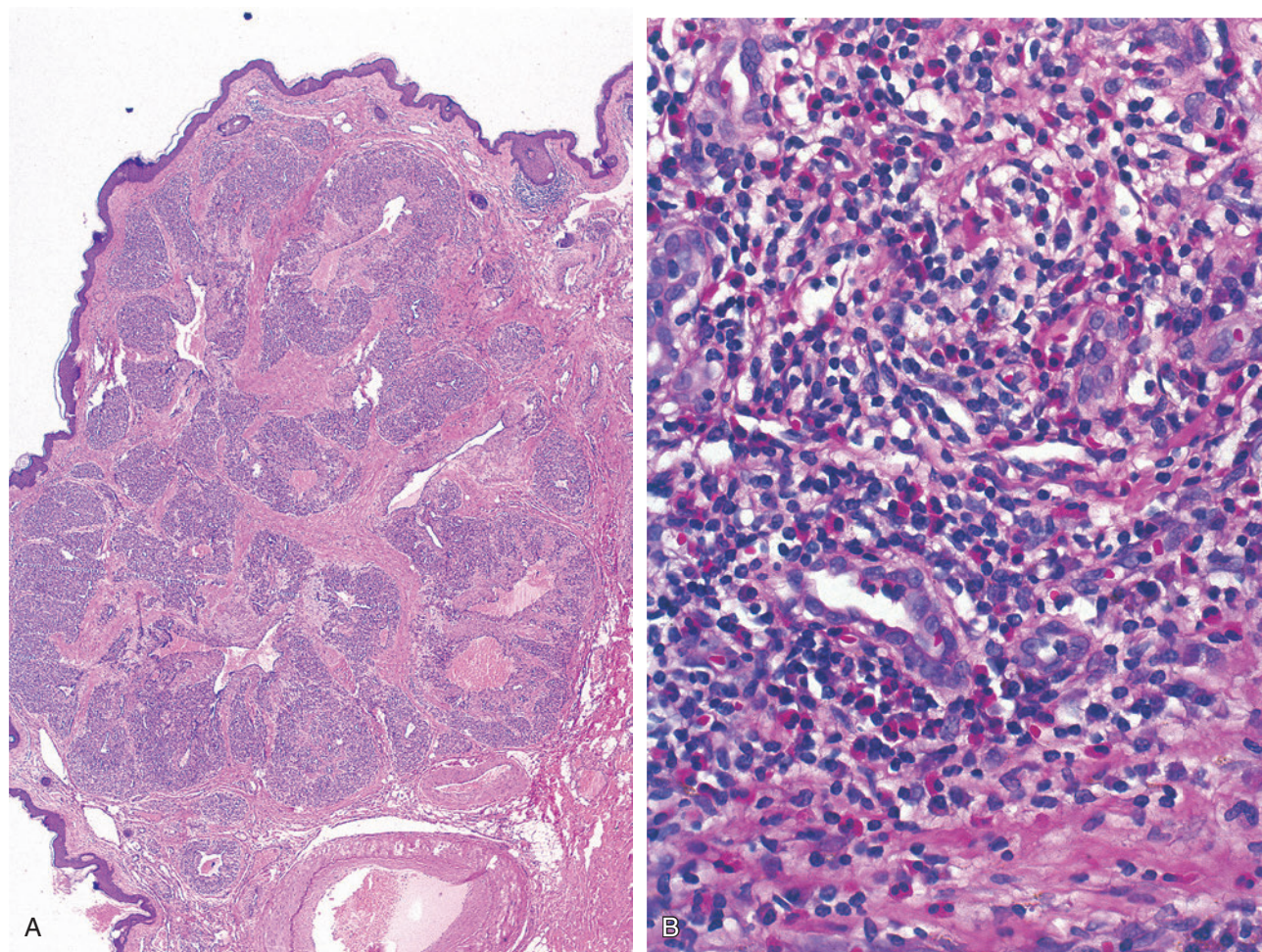


Fig. 24-9. Epithelioid hemangioma.

A, Epithelioid hemangioma of the ear characterized by the presence of subcutaneous nodular (lobular) growth composed of a proliferation of vascular spaces, varying in size from the dimensions of a capillary to medium-sized arteries and veins, and a mixed chronic inflammatory cell infiltrate. **B**, The vascular spaces are lined by plump-appearing (epithelioid) endothelial cells and surrounding inflammatory cells composed of mature lymphocytes, eosinophils, and histiocytes.

Histology (Fig. 24-9)

- Characterized by a nodular vascular proliferation accompanied by a variably dense lymphoid infiltrate rich in eosinophils
- Process is circumscribed but not encapsulated and may involve the subcutis or dermis, or both.
- Vascular component:
 - Varies in size from capillary to medium-sized arteries and veins
 - Vascular spaces are lined by plump-appearing (epithelioid) endothelial cells with pleomorphism, hyperchromatic nuclei, copious eosinophilic cytoplasm, and inconspicuous nucleoli.
 - Frequently, the endothelial cells protrude into the vessel lumen in a “hobnail” fashion, creating a cobblestone-like appearance.
 - Increased mitotic activity and moderate to marked nuclear pleomorphism not identified
- Lobular arrangement of the proliferating vessels may be evident; however, the distribution of vessels is more haphazard in some lesions:
 - Vessels vary from irregular, poorly canalized thin-walled spaces to rounded well-formed vessels with thickened walls.
 - In some cases there is evidence of disruption or damage to some of the involved vessels.
 - Origin from a small artery or vein is common but may depend on adequate sampling.
 - Common for the entire lesion to be intravascular (intravascular EH):
 - Differ from “conventional” EH by virtue of predominant spindle cell (pericytic) component
 - Predominantly occurs in young to middle-aged adults
 - Solitary nodule most often in head and neck or upper limb

- Inflammatory component surrounds the vascular proliferation and is characterized by an admixture of lymphocytes, histiocytes, and eosinophils; on occasion, eosinophils may be few in number or absent.
- Immunohistochemistry:
 - Endothelial cells are:
 - CD31, ERG, and to a lesser extent CD34 positive
 - Glucose transporter protein 1 (GLUT1) negative
 - Rarely cytokeratin positive

Differential Diagnosis

- Lobular capillary hemangioma:
 - Prominence of epithelioid endothelial features and associated lymphoplasmacytic and eosinophilic infiltrate contrast with findings in hemangiomas.
- Infantile hemangioma:
 - GLUT1 positive
- Angiosarcoma:
 - Shows a diffusely infiltrative lesion composed of anastomosing vascular channels lined by pleomorphic cells with increased mitotic activity
 - Presence of the characteristic inflammatory infiltrate in EH typically not found in angiosarcoma

Treatment and Prognosis

- Local surgical excision or desiccation are the preferred treatments and are curative:
 - Rarely, lesions may regress.
- Recurrence reported in up to one-third of cases
- Metastasis virtually never occurs.
- Superficial radiotherapy results in at least partial response in the majority of patients.
- Intralesional or systemic steroids, cryotherapy, and intralesional vincristine, bleomycin, and fluorouracil not proven to be curative

Kimura Disease (Fig. 24-10)

Clinical

- Not considered synonymous with EH
- Occurs in subcutis of the head and neck; other less common sites of involvement include groin, extremities, and chest wall
- In contrast to EH:
 - Occurs primarily in Asians and tends to affect males
 - Often associated with regional lymphadenopathy and peripheral eosinophilia
 - Increased serum immunoglobulin E (IgE), proteinuria, and nephrotic syndrome may occur as part of the disease.

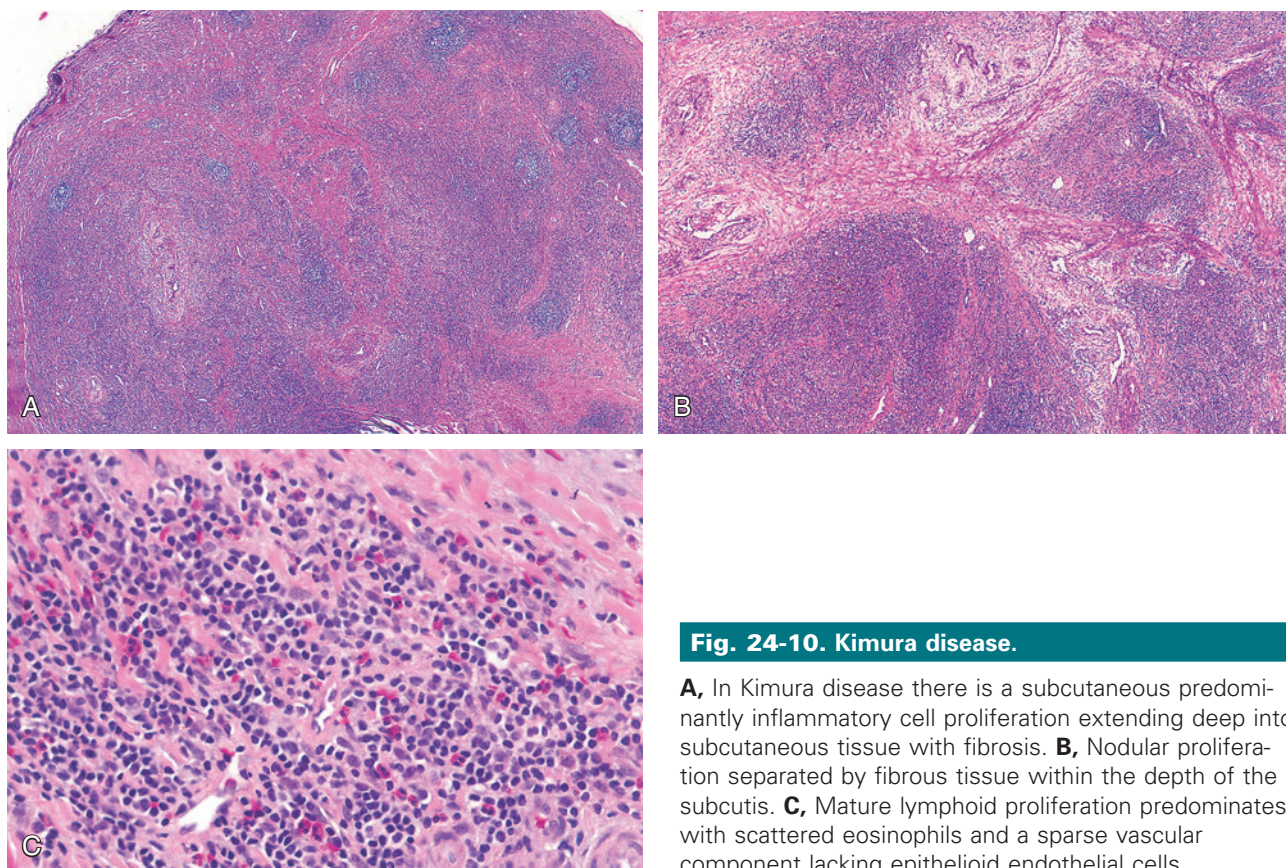


Fig. 24-10. Kimura disease.

A, In Kimura disease there is a subcutaneous predominantly inflammatory cell proliferation extending deep into subcutaneous tissue with fibrosis. **B**, Nodular proliferation separated by fibrous tissue within the depth of the subcutis. **C**, Mature lymphoid proliferation predominates with scattered eosinophils and a sparse vascular component lacking epithelioid endothelial cells.

- Tend to be larger lesions that are predominantly subcutaneous nodules with a tendency to occur in locations other than in the head and neck
- Etiology is unknown:
 - Presence of peripheral eosinophilic and elevated serum IgE suggests immunologic reaction to an unknown stimulus.

Pathology

Histology

- Shares histologic features with EH but differences are seen, including:
 - Lymphoid proliferation, including germinal centers, predominates; the vascular component is sparse and exhibits minimal epithelioid endothelial changes.
 - Lesion is usually located much deeper than EH, often extending to the fascia and to skeletal muscle, and the subcutaneous fat is usually fibrotic.
 - Eosinophils are always numerous in Kimura disease but may be sparse or even absent in EH.
 - Eosinophilic epithelioid granulomatous reaction and/or eosinophilic microabscess formation may be identified.

Differential Diagnosis

- Lobular capillary hemangioma
- Angiosarcoma

Treatment and Prognosis

- Local surgical excision or desiccation are the preferred treatments and are curative.
- Recurrence occasionally occurs.
- Malignant transformation or association with malignancy not reported

OTHER BENIGN MESENCHYMAL NEOPLASMS OF THE EXTERNAL EAR AND AUDITORY CANAL

- Mesenchymal tumors of the external auditory canal are rare and include osteoma, chondroma, leiomyoma, schwannoma, and myxomas.

Osteoma

- In contrast to exostosis, osteomas are true neoplasms of bone capable of unlimited growth.
- Occurs in the external auditory canal presenting as an asymptomatic solitary mass
- Histologically is composed of mature bone with associated intraosseous fibrovascular tissue

Treatment and Prognosis

- Surgery is curative.

Myxomas of the External Ear and External Auditory Canal (Fig. 24-11)

- Described in Carney complex as an autosomal-dominant syndrome complex that includes:
 - Cardiac myxomas:
 - May be associated with peripheral tumor emboli
 - Approximately one-quarter of all patients with cardiac myxomas die of its complications.
 - Cutaneous myxomas:
 - Tend to appear in early adulthood
 - Predilection for eyelids
 - Range from small sessile papules to large pedunculated, finger-like lesions
 - In most cases are multiple
 - Found in dermis or subcutis
 - Usually circumscribed
 - Significant percentage of patients may have myxoma of external ear:
 - 85% of patients with myxoma of external ear have Carney complex
 - Spotty pigmentation:
 - Lentigines on face and vermilion border of lips
 - Blue nevi including epithelioid blue nevi
 - Endocrine disease/tumors:
 - Primary pigmented nodular adrenocortical disease causing Cushing syndrome
 - Pituitary adenoma causing acromegaly

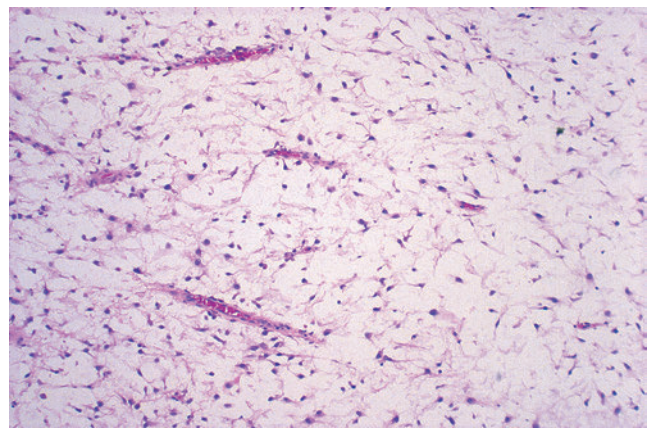


Fig. 24-11. External auditory canal myxoma.

Myxoma of the external auditory canal chiefly consisting of a myxoid/mucoid matrix and the presence of a relatively hypocellular proliferation of spindled to stellate cells with tiny, uniform nuclei. Slit-like capillary vessels are present but there is an absence of a delicate plexiform capillary vascular network.

- Sexual precocity associated with testicular lesions (e.g., Sertoli cell tumor)
- Thyroid diseases (hyperplasia)
- Increase risk of pancreatic ductal and acinar cell neoplasms
- Psammomatous melanotic schwannoma
- Occasionally associated with breast lesions including multifocal myxoid fibroadenomas and myomatosis
- Most patients with Carney complex harbor mutation of *PRKARIA* gene located at 17q22-24 encoding regulatory R1 alpha subunit of protein kinase A.
- Histology characterized by the presence of sparse cytologically bland spindle- and stellate-shaped cells in abundant myxoid stroma and prominent capillary vasculature:
 - Lesion consists chiefly of muroid material in which are suspended a loose framework of reticulin fibers.
 - Cellular component consists of a population of spindled to stellate cells with tiny pyknotic nuclei and delicate cytoplasmic process.
 - Cellular pleomorphism is not seen.
 - Periphery of the tumor is surrounded by a pseudocapsule of condensed reticulin fibers and compressed host tissue, particularly skeletal muscle.
 - Often associated with basaloid proliferation of overlying epithelium:
 - May result in misdiagnosis of basal cell carcinoma or trichofolliculoma
 - Myxoid matrix in myxoma stains with alcian blue and is hyaluronidase sensitive
 - Mucicarmine and colloidal iron stain the myxoid material.
 - Immunohistochemistry of cellular component includes:
 - CD34 and vimentin positive

- Cells may stain for actins and/or desmin, suggesting myofibroblastic differentiation.
- Typically negative for S100 protein, MUC4, cytokeratins

Differential Diagnosis

- Myxoid neoplasms:
 - Myxoid change occurs in a variety of benign neoplasms, including neurofibroma, neurilemmoma, and lipoma, may mimic myxoma, especially in limited biopsy material.
 - Of greater concern is that the histologic pattern in myxomas may mimic myxoid soft tissue malignancies, which are much more common in this location, particularly embryonal rhabdomyosarcoma, and less commonly undifferentiated pleomorphic sarcoma, low-grade fibromyxoid sarcoma, myxoid liposarcoma, and myxoid chondrosarcoma.
 - In contrast to myxoma, sarcomas display:
 - Much greater cellularity
 - A richer vascular pattern often with delicate plexiform capillary vascular network
 - Differing cytologic features including cellular pleomorphism with increased mitotic figures; multinucleated giant cells in undifferentiated pleomorphic sarcoma; cytoplasmic MUC4 in low-grade fibromyxoid sarcoma; lipoblasts in liposarcoma; rhabdomyoblasts in rhabdomyosarcoma; and atypical chondroblasts in chondrosarcoma are distinctive features for these sarcoma types.

Treatment and Prognosis

- Surgery is the preferred treatment.
- Although soft tissue myxomas lack a discrete capsule, they rarely recur after excision.

BENIGN NEOPLASMS OF THE MIDDLE EAR AND TEMPORAL BONE

MIDDLE EAR ADENOMA (MEA)

(Figs. 24-12 through 24-14)

Definition: Benign glandular neoplasm arising from the middle ear mucosa.

Clinical

- Generally considered an uncommon neoplasm
- No gender predilection; occurs over a wide age range but is most common in the third to fifth decades of life

- Any portion of the middle ear may be affected, including the eustachian tube, mastoid air spaces, ossicles, and chorda tympani nerve.
- Most common symptom is that of unilateral conductive hearing loss:
 - Fullness, tinnitus, and dizziness may also occur.
 - Pain, otic discharge, and facial nerve paralysis rarely occur and may be indicative of a malignant process.
- Otoscopic examination in the majority of cases will identify an intact tympanic membrane with tumor

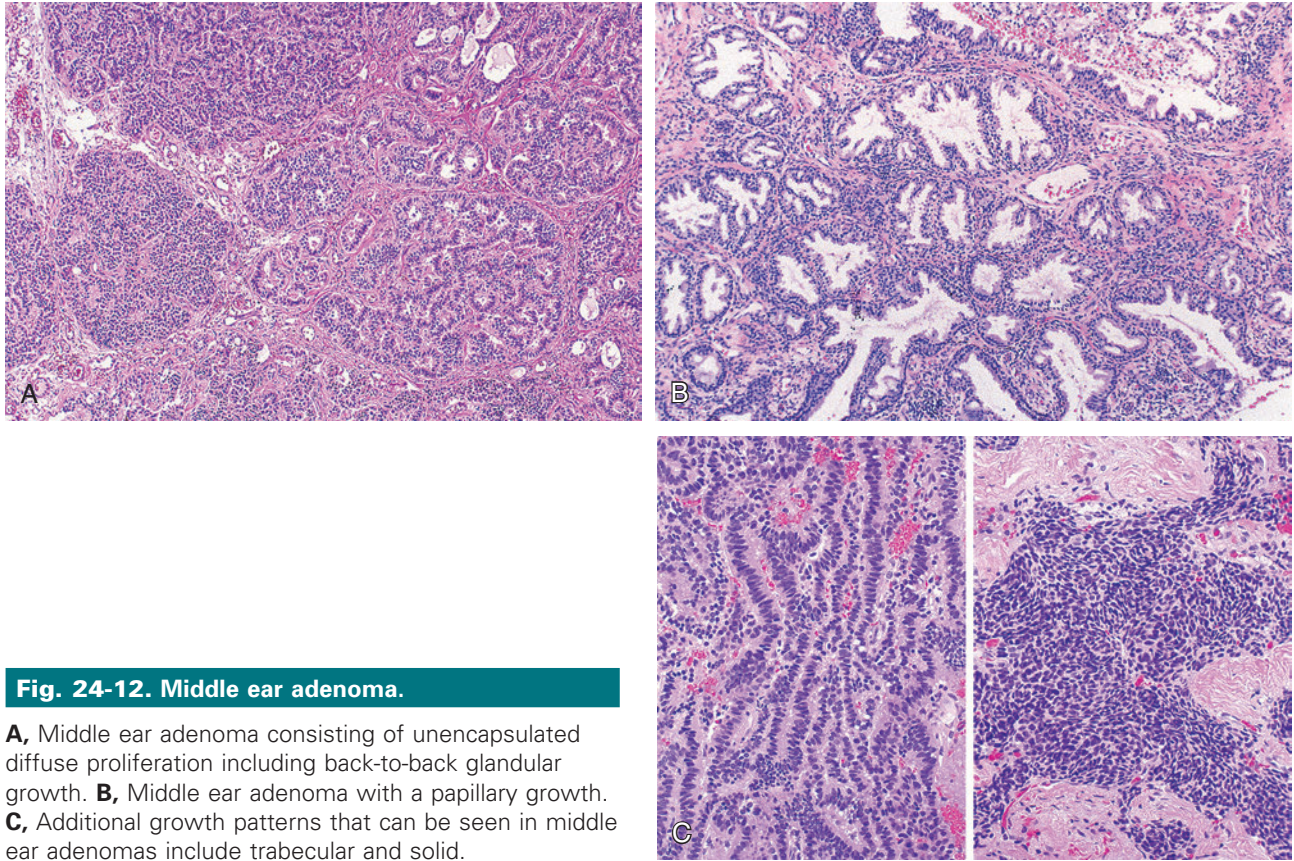


Fig. 24-12. Middle ear adenoma.

A, Middle ear adenoma consisting of unencapsulated diffuse proliferation including back-to-back glandular growth. **B,** Middle ear adenoma with a papillary growth. **C,** Additional growth patterns that can be seen in middle ear adenomas include trabecular and solid.

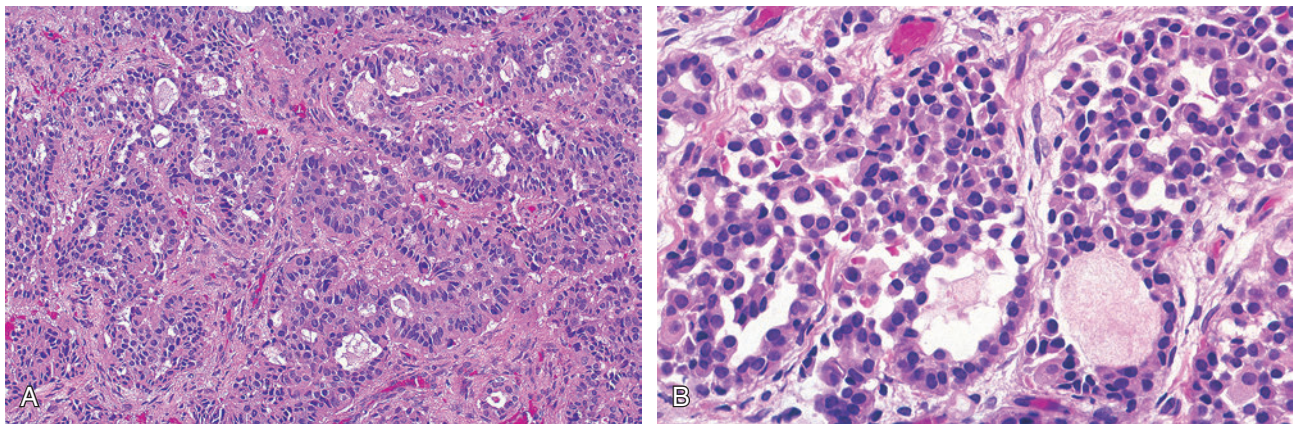


Fig. 24-13. Middle ear adenoma.

A, Middle ear adenoma showing complex growth composed of a single layer of cuboidal to columnar cells with a varying amount of eosinophilic cytoplasm and round to oval nuclei. **B,** Middle ear adenomas often have a cellular component predominated by plasmacytoid cells, as seen in glandular and solid foci. **C,** Diffuse (solid) cellular proliferation composed of dyscohesive plasmacytoid cells. The cells were cytokeratin positive (not shown) and nonreactive with lymphoid/plasma cell markers (e.g., CD20, CD79, CD138).

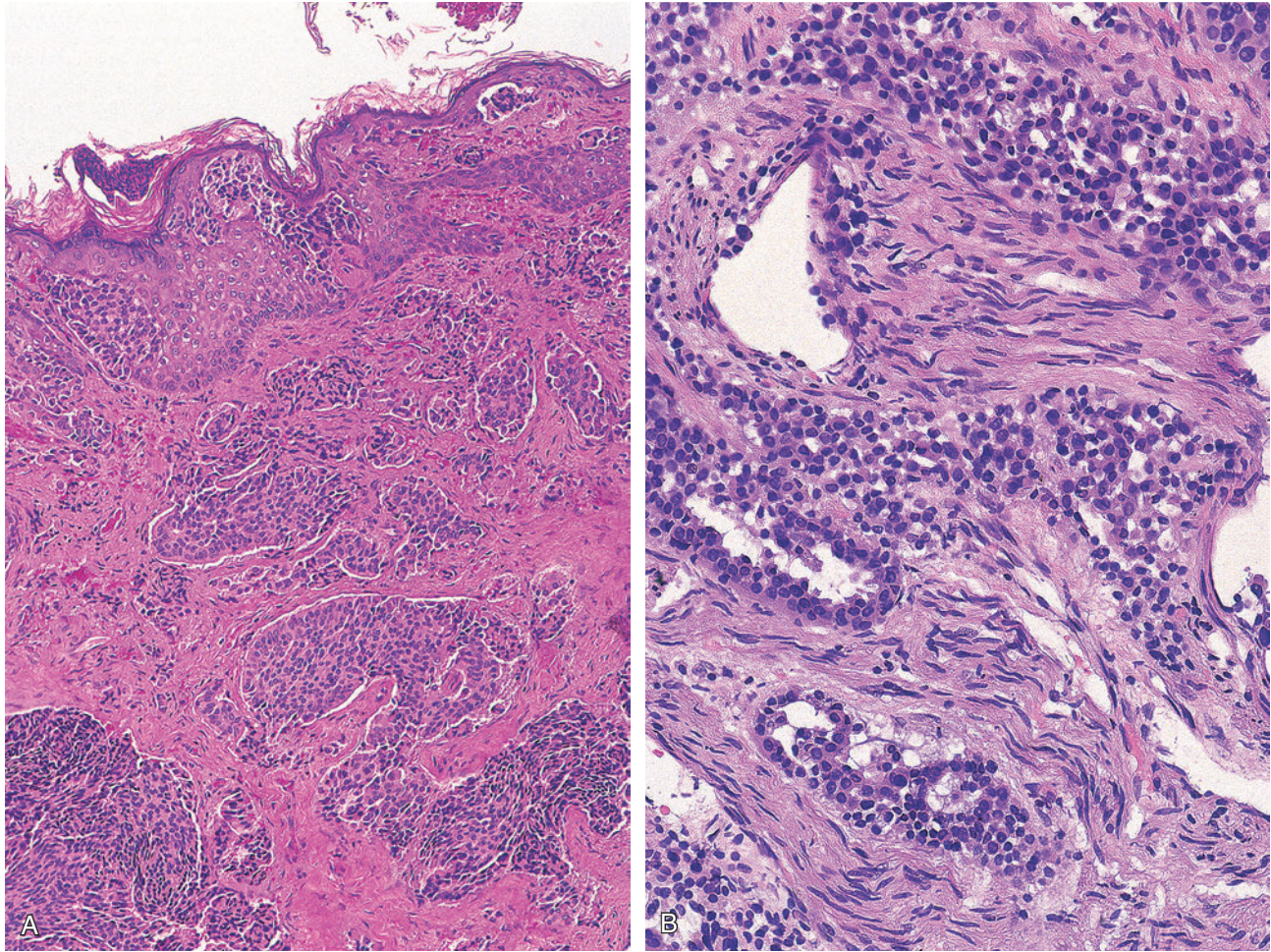


Fig. 24-14. Middle ear adenoma.

A, Middle ear adenoma that perforated the tympanic membrane resulting in a clinical presentation as an external auditory canal lesion; histologically, pagetoid and subepithelial spread of the tumor to the external canal keratinizing squamous epithelium is present. **B,** Given the limited anatomic confines of the middle ear space, middle ear adenomas, as well as other benign middle ear tumors, may have expansive growth including into connective tissue structures; the presence of perineural growth, as seen in this illustration, in an otherwise benign-appearing neoplasm may occur in middle ear adenomas and should not be misinterpreted as a malignancy; additional findings are needed to diagnose a malignancy.

confined to the middle ear space with possible extension to the mastoid; occasionally, the adenoma will perforate through the tympanic membrane with extension into and presentation as an external auditory canal mass.

- No known etiologic factors related to the development of MEA:
 - Not associated with a prior history of chronic otitis media
 - Concurrent cholesteatomas may be seen but there is no known association between these two lesions.
- Radiologic imaging:
 - In its more typical radiologic presentation, appears as a relatively avascular soft tissue density without evidence of destructive, invasive, or erosive properties.

Pathology

Gross

- Gray-white to red-brown, rubbery to firm mass free of significant bleeding on manipulation

Histology

- Unencapsulated lesion with glandular or tubule formation, as well as solid, sheetlike, trabecular, cystic and cribriform (back-to-back) growth patterns; rarely, may show a predominant papillary growth
- Glands are composed of:
 - Single layer of cuboidal to columnar cells with a varying amount of eosinophilic cytoplasm
 - Round to oval nuclei; nucleoli may be seen and are generally eccentrically located

- Nuclear chromatin ranges from densely packed (hyperchromatic) to a more dispersed “salt and pepper” pattern
- Cells typically lack presence of cilia
- Cells often have a prominent plasmacytoid appearance, particularly evident in the more solid areas of growth but also in the cells forming the glandular structures
 - Paranuclear clear zone is not present.
- Cellular pleomorphism may be prominent but mitoses are uncommon.
- Rarely, perineural invasion may occur; in the absence of cytomorphic features of malignancy (see later discussion under middle ear adenocarcinoma) neurotropism is not evidence of malignancy.
- Stromal component is sparse and may appear fibrous or myxoid.
- Histochemistry:
 - Intraluminal but not intracytoplasmic mucin-positive material may be seen.
 - PAS-positive material is not identified.
 - Neoplastic cells may be argentaffin (Fontana stain) and argyrophilic (Churukian-Schenk) positive.
- Immunohistochemistry (see Chapter 25, Table 25-1):
 - Cytokeratins and epithelial membrane antigen are consistently positive:

- AE1/AE3, CAM 5.2, and CK7 are diffusely positive.
- Focal and weak CK20 reactivity may be seen.
- CK5/6 may be present.
- p63 may be present.
- S100 protein, smooth muscle actin negative:
 - Suggests absence of myoepithelial cells in MEA
- Neuroendocrine differentiation may be seen (see below) as identified by the presence of synaptophysin, chromogranin, CD56, and neuron-specific enolase.
- Serotonin and human pancreatic polypeptide also may be present.
- Vimentin staining may be present.
- Desmin and actin are negative.

Middle Ear Adenoma with Neuroendocrine Differentiation (Fig. 24-15)

- MEAs may show neuroendocrine features by light microscopic and immunohistochemical staining, including:
 - Ribbons, cord-like, and organoid growth patterns
 - Cells with dispersed or stippled-appearing (“salt and pepper”) nuclear chromatin

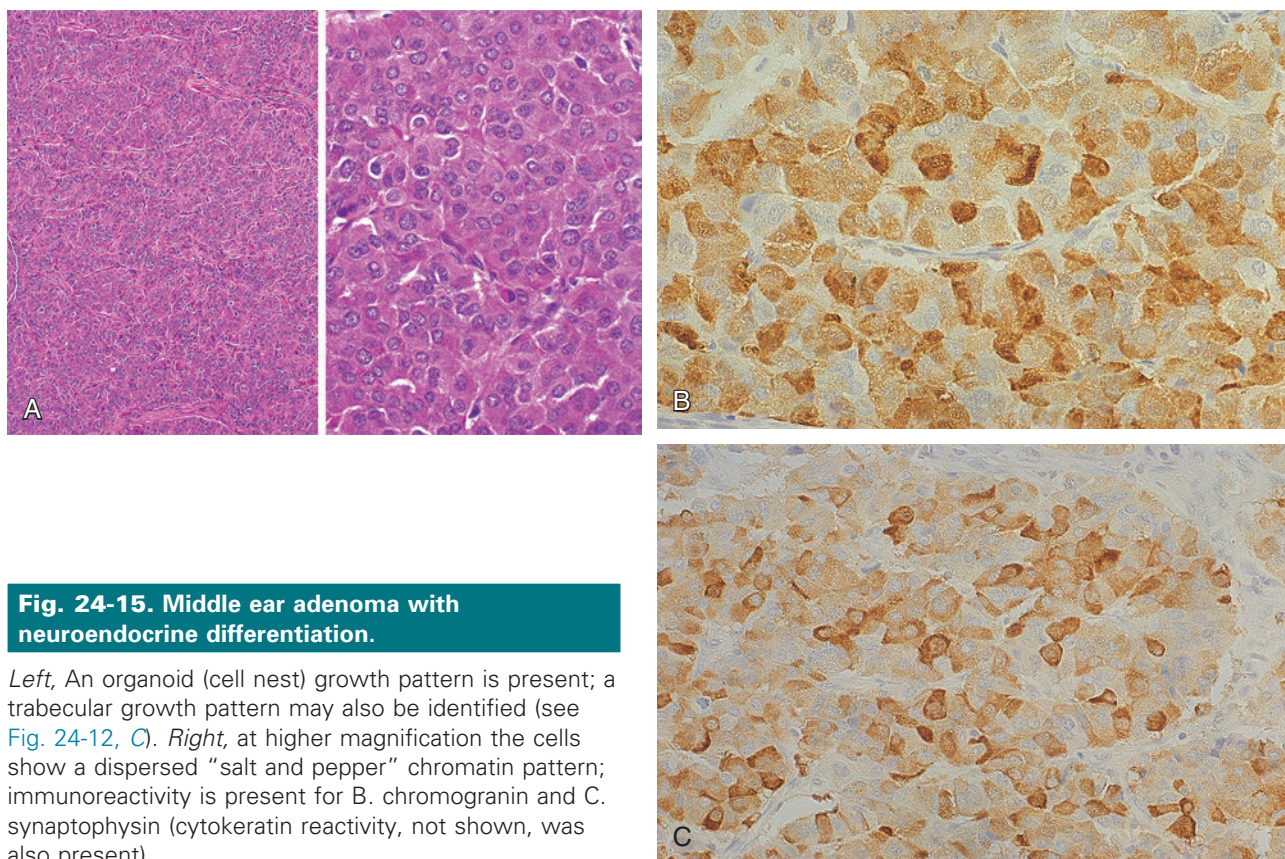


Fig. 24-15. Middle ear adenoma with neuroendocrine differentiation.

Left, An organoid (cell nest) growth pattern is present; a trabecular growth pattern may also be identified (see Fig. 24-12, C). *Right*, at higher magnification the cells show a dispersed “salt and pepper” chromatin pattern; immunoreactivity is present for B. chromogranin and C. synaptophysin (cytokeratin reactivity, not shown, was also present).

- Immunoreactivity with one or more neuroendocrine markers, including synaptophysin, chromogranin, CD56, NSE:
 - Serotonin and human pancreatic polypeptide also may be present.
 - Despite the presence of vasoactive compounds in these tumors, carcinoid syndrome is extraordinarily rare in association with these neoplasms.
- MEAs with neuroendocrine differentiation have been termed carcinoid tumors of the middle ear as well as neuroendocrine adenoma of the middle ear (NAME).
- The issue relative to these tumors is whether they be classified as MEA with neuroendocrine differentiation or carcinoid tumor (also referred to as well-differentiated neuroendocrine carcinoma):
 - Controversy relates to their biologic behavior:
 - Locally recurrent tumor (which may be a function of inadequate initial excision) or regional metastasis have been reported, which support the contention that at least some of these middle ear neoplasms are carcinoid tumors/well-differentiated neuroendocrine carcinomas
 - However, long-term follow-up shows the overwhelming majority of these tumors have a benign biologic course, supporting the contention that these neoplasms are best viewed as being part of the histologic spectrum of MEA, albeit with neuroendocrine differentiation.
 - Presence of chromogranin-positive cells within hyperplastic but not in nonneoplastic middle ear epithelium overlying an MEA supports the inclusion of middle ear glandular tumors with neuroendocrine differentiation within the spectrum of MEA.

Middle Ear Adenoma with Papillary Features (Aggressive Papillary Tumor)

- Another controversial issue relative to MEAs is the presence of papillary growth and whether such papillary middle ear neoplasms represent part of the histologic spectrum of MEAs or whether such tumors in reality are endolymphatic sac papillary tumors (ESPTs).
- Unlike ESPTs, MEAs typically lack papillary architecture and are not associated with evidence of bone destruction:
 - When confronted with a tumor of the middle ear and temporal bone with papillary architecture and destructive growth, the likely diagnosis is that of ESPT, a neoplasm that often is associated with von Hippel-Lindau syndrome (VHL).
 - However, there are documented cases of MEAs with papillary growth confined to the middle ear

space, including the eustachian tube, without destructive growth:

- Such findings support the existence of a middle ear neoplasm with papillary growth originating from the middle ear, occurring sporadically without association to VHL and representing a distinct variant of MEA unrelated to ESPT.

Differential Diagnosis

- Metaplastic glandular proliferation secondary to otitis media:
 - Glandular metaplasia may occur in the setting of chronic otitis media (COM).
 - Metaplastic glands may be misdiagnosed as neoplastic.
 - In contrast to MEA, the glandular proliferation in COM is focal identified or haphazardly arrayed and occurs in the presence of histologic features of COM, including chronic inflammation with fibrosis and calcifications (tympanosclerosis).
 - Identification of cilia supports a diagnosis of metaplastic glands rather than an adenoma.
- Ceruminous gland adenoma:
 - MEAs may perforate the tympanic membrane and appear to represent a neoplasm of the external auditory canal, such as a ceruminous gland adenoma.
 - Histologic features of ceruminous gland adenoma are distinctly different from MEA, including the presence of decapitation-type secretion and intracytoplasmic cerumen.
- Differential diagnosis of MEA is primarily with the other more common middle ear tumors, including jugulotympanic paraganglioma, meningioma, and acoustic neuroma. The pathologic features of these other tumor types are discussed below.
- Endolymphatic sac papillary tumor (ESPT):
 - Occasional MEAs have a predominant papillary architecture.
 - See previous discussion under Middle Ear Adenoma with Papillary Features (Aggressive Papillary Tumor).
 - There is some confusion in the literature regarding these papillary MEAs and their relationship to the endolymphatic sac papillary tumor; as discussed later in this chapter, the histogenesis, clinical presentation, anatomic location, pathologic features, and clinical course of ESPT are decidedly different from MEA.
- Middle ear adenocarcinoma:
 - In contrast to the rare middle ear adenocarcinoma, MEAs lack marked cellular pleomorphism, increased mitotic activity, necrosis or invasion of bone, and other soft tissue structures.
- Rhabdomyosarcoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - Surgery may be conservative if the lesion is small and confined to the middle ear or more radical (mastoidectomy) for larger lesions associated with more extensive structural involvement.
- Recurrence may occur and is usually a function of inadequate excision.
- Some MEAs may be locally aggressive and rarely may invade vital structures, causing death.
- In general, the clinical, radiologic, and pathologic findings indicate that the tumor is benign (absence of associated neural deficits, invasion or destruction of adjacent structures, or pleomorphism and increased mitotic activity); nevertheless, the histologic appearance is not always predictive of the clinical behavior.

JUGULOTYMPANIC PARAGANGLIOMA (JTP)

(Figs. 24-16 through 24-21)

Definition: Benign neoplasm arising from the extra-adrenal neural crest–derived paraganglia specifically located in the middle ear or temporal bone region.

Synonyms: Glomus jugulare tumor; glomus tympanicum tumor

Clinical

- Arguably, considered the most common tumor of the middle ear
- Affect women more than men; most commonly seen in the fifth through seventh decades of life
- Jugulotympanic paragangliomas occur in one of three locations:
 - 85% arise in the jugular bulb (*glomus jugulare tumor*), resulting in a mass lesion in the middle ear or external auditory canal.
 - 12% originate in the posterior auricular branch of the vagus nerve, also known as Arnold's nerve (*glomus tympanicum tumor*), presenting in the middle ear.
 - 3% originate from the tympanic branch of the glossopharyngeal nerve, also known as Jacobson's nerve (*glomus tympanicum tumor*), presenting as a mass in the external auditory canal.
- Most common symptom is conductive hearing loss; other symptoms include tinnitus, fullness, otic discharge, pain, hemorrhage, facial nerve abnormalities, and vertigo.
- Often are locally invasive neoplasms with extension into and destruction of adjacent structures, including the temporal bone and mastoid

- Radiology:
 - CT scan: soft tissue mass often with evidence of extensive destruction of adjacent structures
 - Carotid angiography: vascularized lesion fed by branches of nearby large arteries
 - MR imaging: in tumors larger than 2 cm there is a unique salt-and-pepper pattern of hyperintensity and hypointensity on T1-weighted and T2-weighted imaging.
- Familial (hereditary) paraganglioma:
 - JTPs may be familial (hereditary)
 - Familial JTPs may be multifocal, including jugulotympanic and carotid body.
 - Autosomal dominant pattern of inheritance is favored.
 - Genetic analysis has shown linkage with two different loci, including 11q13.1 and 11q22.3-q23.
 - See Section 4, The Neck, for a more complete discussion.
- Jugular and tympanic paragangliomas have been reported as a single entity (i.e., temporal bone paragangliomas) but their distinction has important clinical and therapeutic implications; as such, classification schemes based on site of origin (Table 24-2) or based on site and origin and extent of tumor involvement have been developed (Table 24-3).

Pathology

Gross

- Polypoid, red, friable mass identified behind an intact tympanic membrane or within the external auditory canal, measuring from a few millimeters to a large mass completely filling the middle ear space
- Typically, paragangliomas bleed profusely on manipulation.

Histology

- Histologic hallmark is the presence of a cell nest, or “zellballen,” pattern characteristic of paragangliomas:
 - Although this pattern is characteristic of paragangliomas, it is not unique to paragangliomas and can be seen in other neuroendocrine tumors, including carcinoid and atypical carcinoid tumors, as well as in middle ear adenoma, carcinomas, and melanoma.
- Stroma surrounding and separating the nests is composed of a prominent fibrovascular tissue.
- Neoplasm is composed of chief cells and sustentacular cells:
 - Chief cells predominate and include round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm.
 - Sustentacular cells represent modified Schwann cells and are situated at the periphery of the cell



Fig. 24-16. Glomus jugulare tumor CT.

A, Axial image shows demineralization of the bony margins of the jugular foramen on the right (*black arrows*). There is demineralization of the fine cortical line usually demonstrated along the lateral aspect of the vascular portion of the jugular foramen. Compare with the intact cortical plate on the opposite side (*white arrow*). Note the demineralization of the bony wall separating the carotid canal from the jugular foramen. **B**, Blown-up axial image shows demineralization of the lateral cortical plate (*arrowhead*), as well as slight demineralization of the bony plate between the carotid canal and the jugular foramen (*white arrow*). Note the proximity of the demineralized bone to the vertical section of the facial nerve canal (*white arrow*). **C**, Axial image enlarged through the normal side shows the intact white cortical line (*arrow*) along the lateral aspect of the jugular foramen. The integrity of this line essentially excludes a glomus jugulotympanicum tumor. **D**, Coronal image shows demineralization of the margins (*arrowheads*) as well as the soft tissue of the intratympanic portion of the tumor (*arrow*). (Courtesy Dr. Hugh D. Curtin. From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 20-120, p 1329)

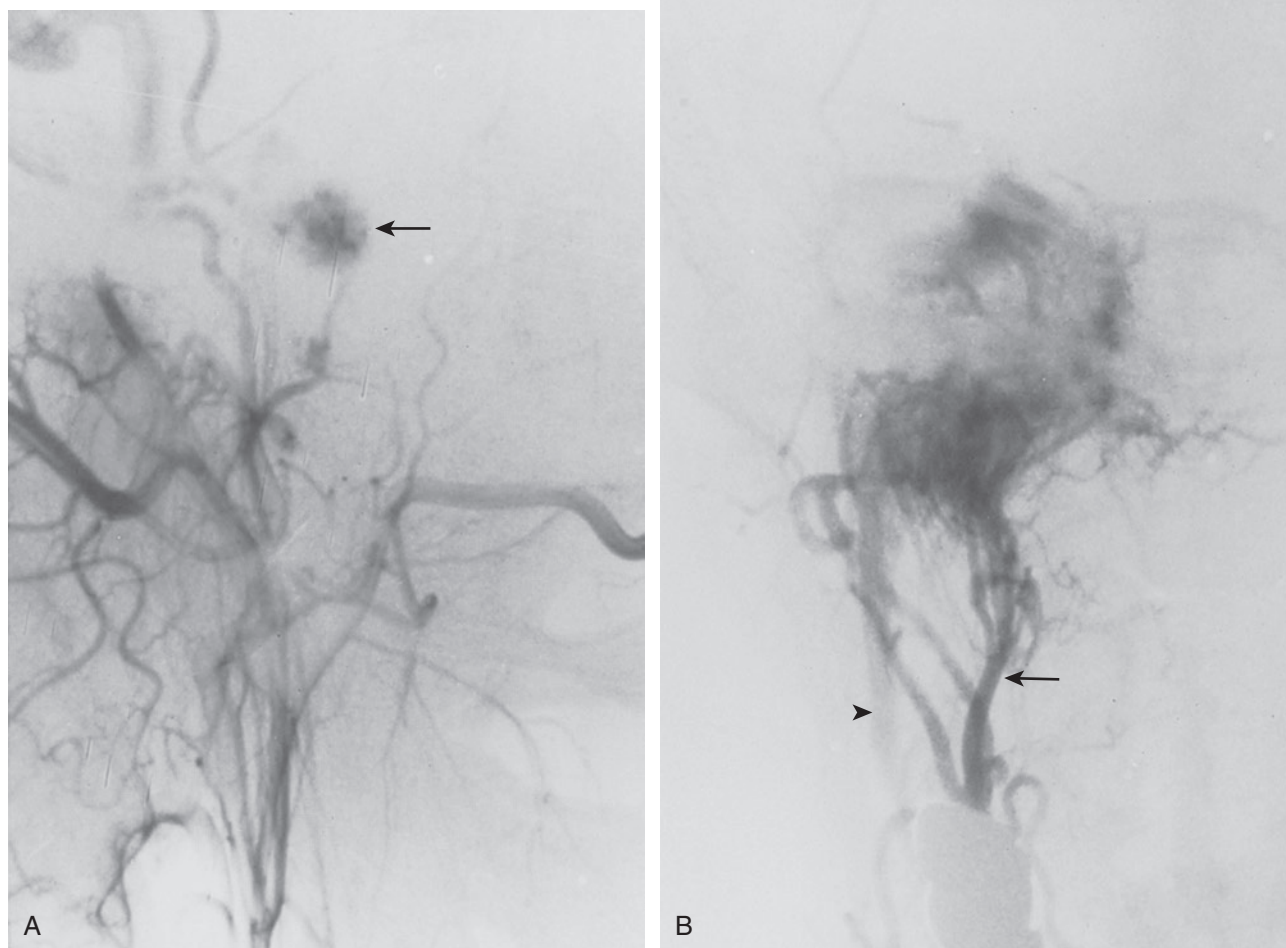


Fig. 24-17. Carotid angiogram of jugulotympanic paraganglioma.

A, Glomus tympanicum tumor. Selective external carotid angiogram. Characteristic hypervascularity (*arrow*) is seen.
B, Glomus jugulare tumor. Selective external carotid angiogram. The characteristically hypervascular tumor is supplied by the hypertrophic ascending pharyngeal artery (*arrow*). Note the early draining vein (*arrowhead*) seen during the midarterial phase. Differential diagnosis includes other hypervascular tumors such as metastatic renal cell carcinoma, metastatic pheochromocytoma, myeloma, and so on. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figs. 20-124 and 20-125, p 1331.)

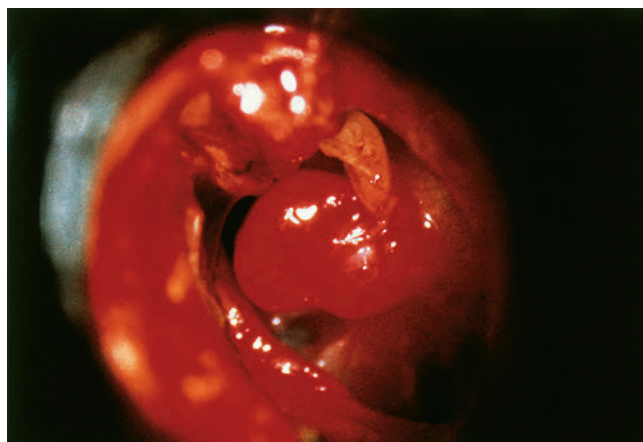


Fig. 24-18. Jugulotympanic paraganglioma.

Jugulotympanic paraganglioma characterized by a bright red polypoid mass originating in the middle ear space.

nests, appearing as spindle-shaped, basophilic cells.

- Are difficult, if not impossible, to identify by light microscopy alone, requiring S100 protein staining for identification
- No glandular or alveolar differentiation is seen.
- Cellular pleomorphism can be seen; mitoses and necrosis are infrequently identified.
- Spindling of the chief cells may be seen and infrequently may predominate.
- Not infrequently, jugulotympanic paragangliomas do not display the characteristic cell nest or organoid growth but appear compressed due to artifactual distortion secondary to surgical manipulation (“squeezing”) of the tissue during removal:
 - In addition to the loss of an organoid pattern of growth, jugulotympanic paragangliomas may be

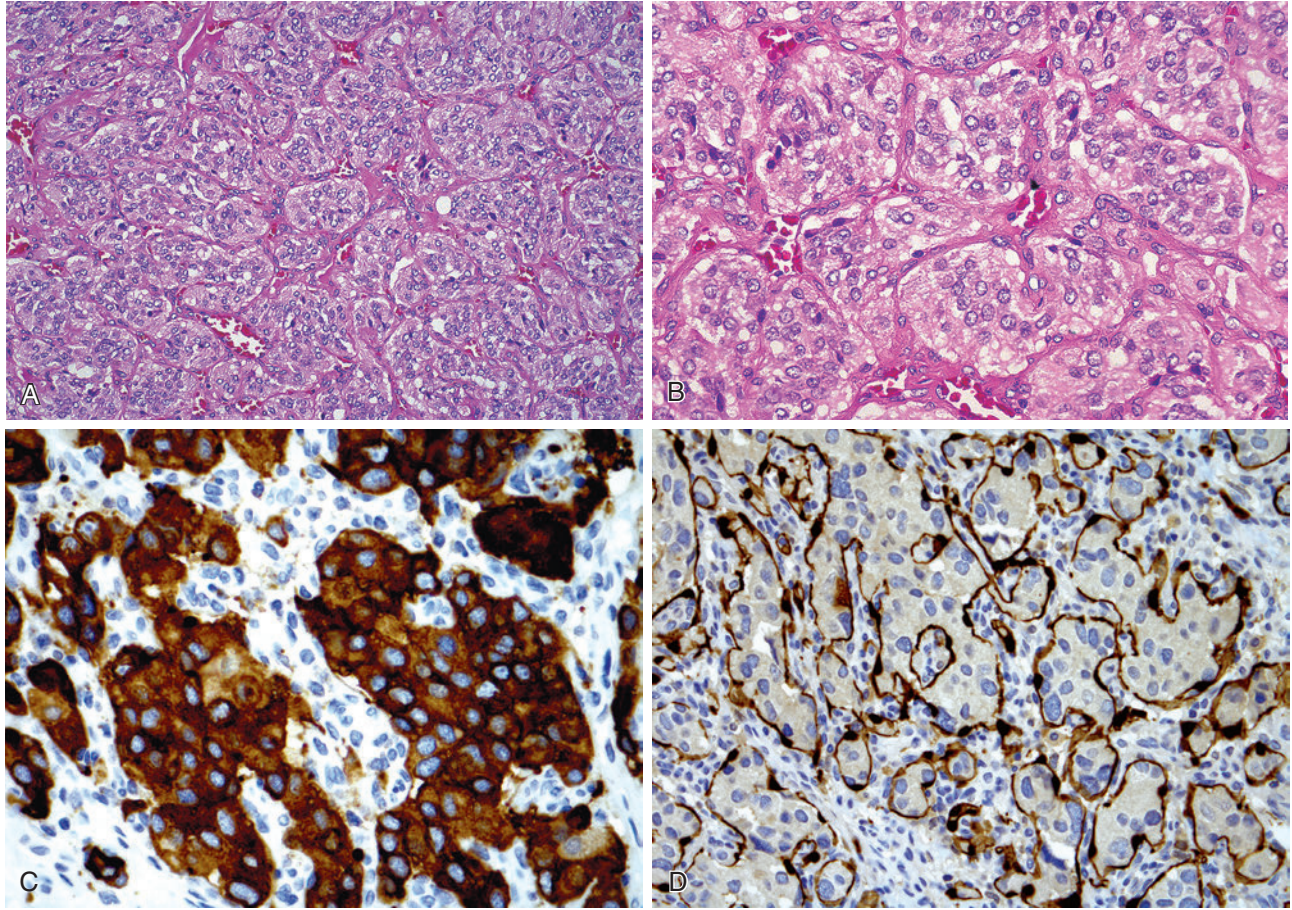


Fig. 24-19. Jugulotympanic paraganglioma.

A, Jugulotympanic paraganglioma showing characteristic histologic appearance including the presence of a cell nest (organoid) growth pattern separated by fibrovascular stroma. **B**, Higher magnification shows the tumor to be predominantly composed of chief cells, which are round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm; the peripherally located sustentacular cells are difficult to identify by light microscopy and appear as spindle-shaped cells with a basophilic appearance. Immunohistochemical confirmation of paraganglioma includes the presence of immunoreactivity for neuroendocrine markers, with **(C)** diffuse synaptophysin (and chromogranin, not shown) reactivity and **(D)** S100 protein staining highlighting the peripherally situated sustentacular cells.

- associated with a dense fibrous stroma and an appearance of infiltrative growth.
 - These findings may result in overlooking a diagnosis of JTP, resulting in an erroneous interpretation including other benign middle ear neoplasms or even a malignant neoplasm.
 - Awareness of this occurrence and use of appropriate special stains should allow for a correct diagnosis.
- Histochemistry:
 - Reticulin staining may better delineate the cell nest growth pattern with staining of the fibrovascular cores surrounding the neoplastic nests.
 - Tumor cells are argyrophilic (Churukian-Schenk).
 - Argentaffin (Fontana), mucicarmine, and periodic acid-Schiff stains are negative.
- Immunohistochemistry (see Chapter 25, Table 25-1):
 - Chief cells: synaptophysin, chromogranin, CD56, neuron-specific enolase, neurofilaments, and a variety of peptides positive
 - Sustentacular cells: S100 protein and SOX10 positive:
 - Characteristic peripheral pattern for staining correlating to the location of the sustentacular cells
 - Vimentin is variably reactive in the chief cells and sustentacular cells.
 - In general, epithelial markers, including cytokeratins, as well as HMB-45 and mesenchymal markers (desmin and other markers of myogenic differentiation), are negative; rare examples of cytokeratin-reactive paragangliomas have been reported.

- Electron microscopy:
 - The hallmark of the EM findings is the presence of neurosecretory granules.

Differential Diagnosis

- Middle ear adenoma with or without neuroendocrine differentiation
- Acoustic neuroma
- Meningioma

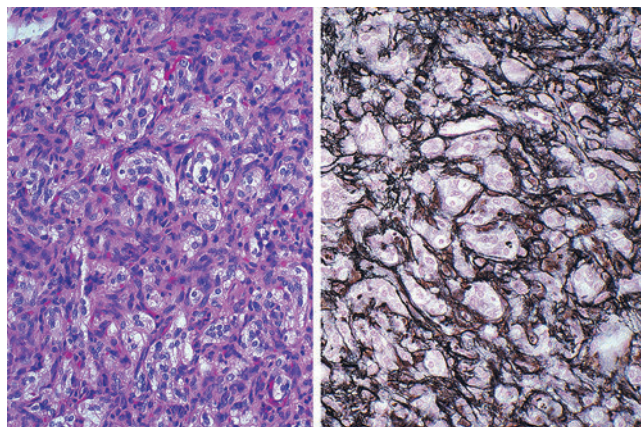


Fig. 24-20. Jugulotympanic paraganglioma.

A, The histologic appearance of jugulotympanic paragangliomas can be distorted or masked secondary to artifactual changes, but the characteristic cell nest appearance is usually focally maintained and **(B)** reticulin staining is helpful in delineating the cell nest growth by staining the fibrovascular stroma surrounding the tumor nests.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - Paragangliomas confined to the middle ear (Glasscock-Jackson type I; Fisch class A) can be approached through a transcanal approach.
 - If the margins of tumor are not discernible but the bone over the jugular bulb and the carotid canal is intact (i.e., Glasscock-Jackson types II and III, Fisch class B), a postauricular transmastoid approach and extended facial recess approach provides excellent exposure for tumor resection.
 - Involvement of the jugular bulb requires a combined transmastoid and transcervical approach.
 - Limited involvement of the jugular bulb without carotid artery involvement requires a complete mastoidectomy and an extended facial recess approach.
 - More extensive involvement of the jugular bulb or involvement of the intrapetrous internal carotid artery requires an infratemporal fossa approach.
- Preoperative embolization has been advocated as useful to decrease the vascularity of the tumor and allow for safer surgery:
 - Main objective is to direct the embolism material to selectively permeate only the vascularity of the paraganglioma without proximal occlusion of the feeding artery and also avoiding distal migration of emboli into the systemic circulation.
 - Postembolization angiography should document absence of tumor “blush” with continued patency of the external carotid systems.

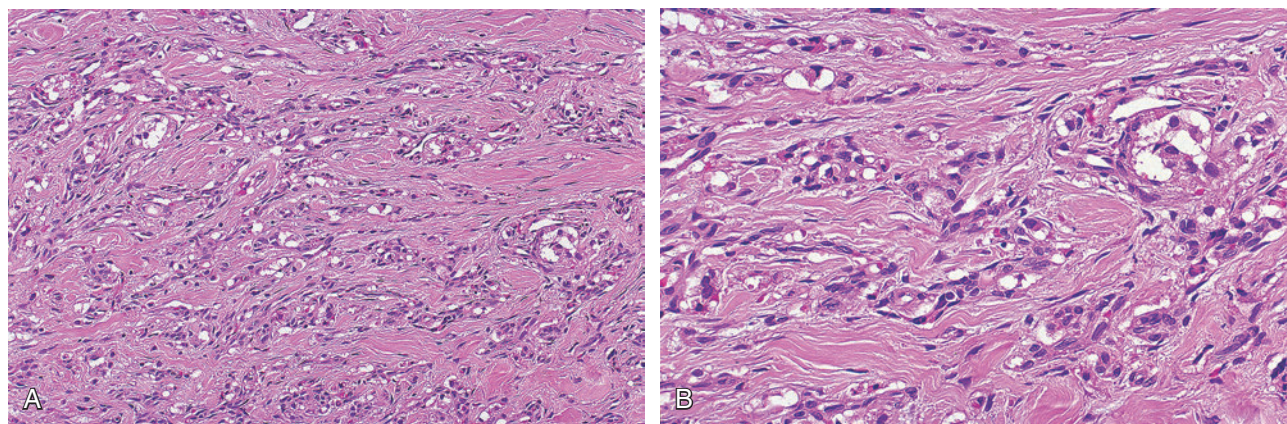
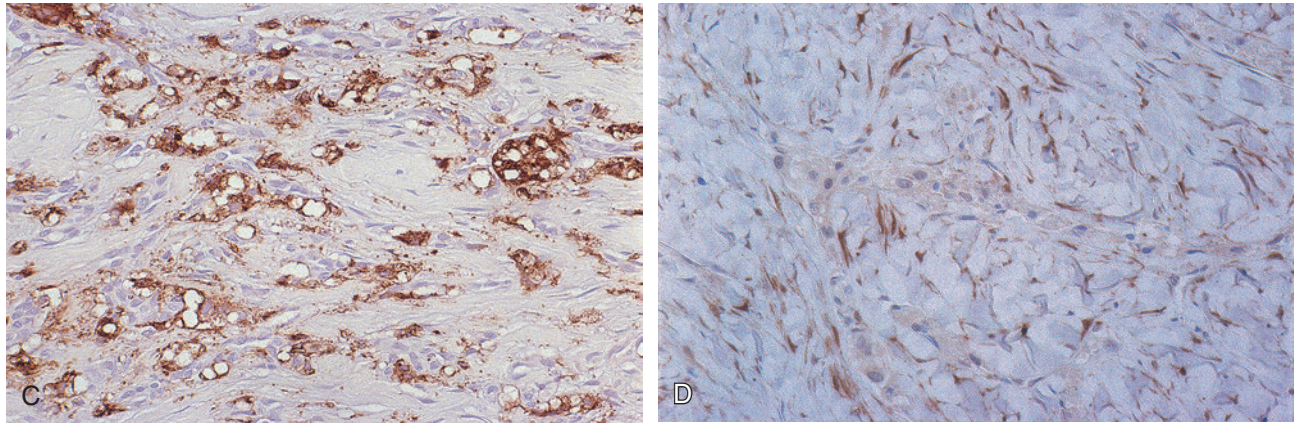


Fig. 24-21. Jugulotympanic paraganglioma.

A and **B**, Another example of a jugulotympanic paraganglioma in which tumor nests show an “invasive” growth with associated dense fibrotic stroma; the absence of discrete cell nest growth pattern is associated with extensive fibrosis. These findings, especially when coupled to radiographic evidence of bone erosion, may result in the erroneous interpretation as a malignant neoplasm. Immunohistochemical stains assist in the diagnosis as evidenced by

**Fig. 26-21, cont'd**

(C) synaptophysin and (D) S100 protein immunoreactivity, the latter limited to the peripherally located sustentacular cells.

TABLE 24-2 Fisch Classification of Jugulotympanic Parangliomas

Class A	Tumors arising along the tympanic plexus on the middle ear promontory
Class B	Tumors arising from the inferior tympanic canal of the hypotympanum; may invade the middle ear and mastoid; cortical bone over jugular bulb is intact; carotid canal is intact
Class C	Tumors arising in dome of jugular bulb and involving the overlying cortical bone
C1	Tumors eroding the carotid canal but not involving the carotid artery
C2	Tumors involving the vertical carotid canal
C3	Tumors involving the horizontal carotid canal; foramen lacerum is free of tumor
C4	Tumors involving the foramen lacerum and the cavernous sinus
Class D	Tumors with intracranial extension of posterior fossa
De1	Extradural tumor of less than 2 cm medial dural displacement
De2	Extradural tumor of more than 2 cm medial dural displacement
Di1	Intradural tumor of less than 2 cm
Di2	Intradural tumor of more than 2 cm
Di3	Neurosurgically unresectable tumor

TABLE 24-3 Glasscock-Jackson Classification of Glomus Tumors

Glomus Tympanicum	
Type I	Small mass limited to promontory
Type II	Tumor completely filling the middle ear space
Type III	Tumor filling the middle ear and extending into the mastoid
Type IV	Tumor filling the middle ear, extending into the mastoid or through the tympanic membrane to fill the external auditory canal; may also extend anterior to the internal carotid artery
Glomus Jugulare	
Type I	Small tumor involving the jugular bulb, middle ear, and mastoid
Type II	Tumor extending under the internal auditory canal; may have intracranial extension
Type III	Tumor extending into petrous apex; may have intracranial extension
Type IV	Tumor extending beyond the petrous apex into the clivus or infratemporal fossa; may have intracranial extension

- Experienced vascular radiology team must be thoroughly familiar with the complexities and possible variations in head and neck vascular anatomy.
- Not all paragangliomas should be embolized:
 - Decision is dependent on the location and extent of tumor and the experience of the surgeon and interventional radiologist.
 - Paragangliomas confined to the middle ear cavity do not require preoperative

embolization if the patient is being treated by an experienced otologic surgeon.

- Other types of paragangliomas can be treated by preoperative embolization.
- Location and invasive nature of these lesions often preclude the capability of complete surgical eradication, and in such situations radiotherapy is a useful adjunct to surgery:
 - Unresectable paragangliomas include those with extensive skull base involvement or intracranial extension.
 - Patients who might be poor surgical candidates, including medically infirm and elderly
 - Radiotherapy results in a decrease or ablation of vascularity and promotes fibrosis.
 - Radiotherapy has been used primarily to treat jugular paragangliomas of the temporal bone.
 - Because there is rarely total resolution of the tumor following radiotherapy, successful treatment of paragangliomas with radiotherapy is defined as local control in the form of stability or regression of tumor size and nonprogression or improvement of neurologic symptoms.
- Local recurrence of the tumor can be seen in as many as 50% of the cases.
- Although these are slow-growing neoplasms, prognosis is guarded because they often infiltrate and invade adjacent structures.
- Although malignancy is rare, these neoplasms may result in increased morbidity and mortality as a result of invasion of vital structures (e.g., cranial cavity).
- Histologic appearance of paragangliomas does not correlate to the biologic behavior of the tumor.
 - JTPs are slow-growing tumors but may be locally invasive with extension into and destruction of adjacent structures, including the temporal bone and mastoid.
 - Intracranial extension may occur in up to 15% of cases.
- Neurologic abnormalities, including cranial nerve palsies, cerebellar dysfunction, dysphagia, and hoarseness, may be seen and correlate to the invasive capabilities of this neoplasm.
- Functioning JTPs as evidenced by endocrinopathic manifestations occur but are extremely uncommon.
- Malignant JTPs occur and are associated with histologic criteria of malignancy, including:
 - Increased mitotic activity
 - Necrosis usually seen within the center of the cell nests
 - Vascular invasion
 - Metastasis to cervical lymph nodes, lungs, and liver
- In general, DNA ploidy studies by image analysis are not predictive of the behavior of paragangliomas.

ACOUSTIC NEUROMA (AN)

(Figs. 24-22 through 24-24)

Definition: Benign neoplasm arising from Schwann cells specifically originating from the eighth cranial nerve.

Synonyms: Acoustic schwannoma; benign peripheral nerve sheath tumor; neurilemmoma

Clinical

- Account for up to 10% of all intracranial neoplasms and for up to 90% of all tumors of the cerebellopontine angle
- More common in women than in men; may occur at any age but are most common in the fourth to seventh decades of life
- Majority involve the superior or vestibular portion of the eighth nerve as compared with involvement of the cochlear portion of the eighth nerve.
- Typically develop at the neuroglial-neurolemmal junction termed the Rednik-Obersteiner line identified immediately inside the meatus of the internal auditory canal; however, the site of this junction varies and so too does the site of acoustic neuromas.
- Symptoms include progressive (sensorineural) hearing loss, tinnitus, and loss of equilibrium; with



Fig. 24-22. Acoustic neuroma.

Axial CT air cisternogram of acoustic neuroma: intrathecally injected air outlines a left intracanalicular tumor (arrows), which extends into the cerebellopontine angle. The left internal auditory canal (arrowheads) is slightly enlarged, a typical feature of eighth nerve schwannomas. MR imaging has virtually replaced invasive diagnostic techniques.

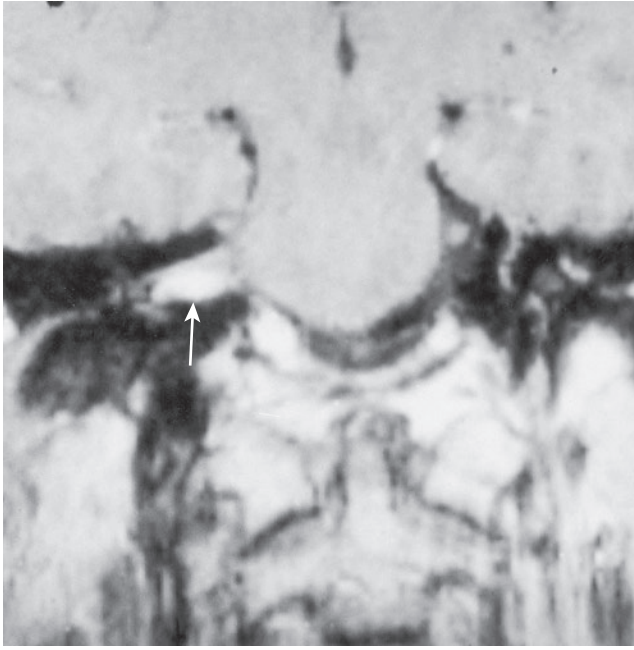


Fig. 24-23. Acoustic neuroma.

Coronal MR T1-weighted image, enhanced, of an acoustic neuroma: contrast-enhanced tumor (*arrow*) largely confined by the right internal auditory canal. Contrast-enhanced MR is now the preferred imaging modality for evaluation of neurosensory hearing loss and suspected cerebellopontine angle masses.

progression the tumor enlarges and may compress adjacent cranial nerves (V, VII, IX, X, XI), the cerebellum and the brainstem leading to facial paresthesia and numbness, headaches, nausea, vomiting, diplopia, and ataxia.

- Up to 8% may be bilateral; bilaterality is a potential marker of neurofibromatosis type 2 (NF-2):
 - NF-2 is an autosomal-dominant condition.
 - Gene for NF-2 mapped to the long arm of chromosome 22 (22q12)
 - Hallmark of NF-2 is bilateral acoustic neuromas.
 - Patients with NF-2 have an increased incidence of developing a meningioma.
 - Patients with acoustic neuroma (or meningioma) who are under 30 years of age should raise concern for a diagnosis of NF-2:
 - Seen in more than 90% of patients with NF-2
 - Accounts for approximately 5% of all vestibular neuromas
 - Symptoms of neurofibromatosis may be seen in up to 16% of patients and those with neurofibromatosis who develop acoustic neuromas generally are symptomatic at an earlier age (teenage years or early third decade of life) and

have a higher incidence of bilateral acoustic neuromas.

- Symptoms include:
 - Early: hearing (sensorineural) loss, tinnitus, dizziness
 - Late: headache, facial pain and/or weakness, others
- Occasionally, unilateral vestibular (acoustic) neuroma may occur in patients with NF-2 in the absence of other criteria necessary for a diagnosis of NF-2.
- Approximately 50% to 67% of patients with NF-2 develop cutaneous schwannomas.
- Patients with NF-2 also experience increased incidence of multiple, separately occurring meningiomas in intra- and extracranial meningiomas.
- Radiology:
 - CT and MRI: flaring, asymmetric widening, or erosion of the internal auditory canal; these techniques are capable of detecting tumors with dimensions of 1 cm and less.

Pathology

Gross

- Unilateral, circumscribed, tan-white, rubbery to firm mass, which may appear yellow and have cystic change
- Sizes range from a few millimeters up to 4 to 5 cm in greatest diameter.

Histology

- Unencapsulated tumors are composed of alternating regions composed of compact spindle cells (so-called Antoni A areas), and loose, hypocellular zones (so-called Antoni B areas); in a given tumor, the proportion of these components varies.
- Cells are arranged in short, interlacing fascicles and whorling or palisading of nuclei may be seen:
 - Nuclear palisading with nuclear alignment in rows are called Verocay bodies.
- Nuclei are vesicular to hyperchromatic, elongated, and twisted with indistinct cytoplasmic borders.
- Antoni B areas display a disorderly cellular arrangement, myxoid stroma, and a chronic inflammatory cell infiltrate.
- Increased vascularity is prominent, composed of large vessels with thickened (hyalinized) walls.
- Mitoses, usually sparse in number, and cellular pleomorphism with hyperchromasia can be identified but are not evidence of malignancy.
- Cellularity may vary and some benign schwannomas can be very cellular, conferring the name cellular schwannoma.
- Retrogressive changes may be present, including cystic degeneration, necrosis, hyalinization, calcification, and hemorrhage.

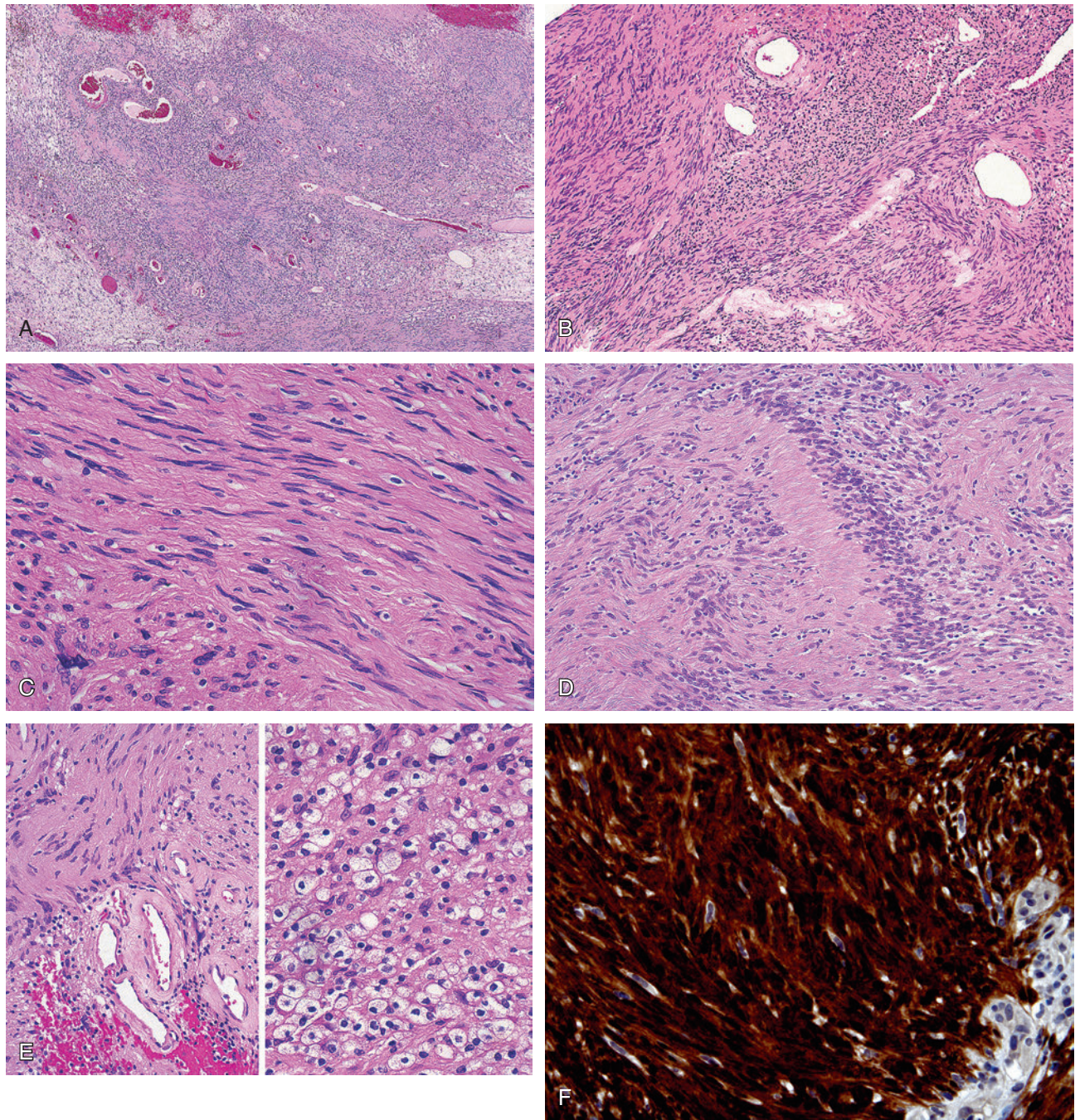


Fig. 24-24. Acoustic neuroma.

A, Acoustic neuroma is unencapsulated and composed of central cellular zone of spindle-shaped cells (Antoni A areas) and loose, hypocellular zones (Antoni B areas) along the outer aspects. **B**, Fascicular growth of spindle-shaped cells; vascular hyalinization is seen. **C**, The cellular component includes elongated and twisted (buckled or wavy) nuclei with indistinct cytoplasmic borders. **D**, Nuclear palisading (Verocay bodies) may be seen. **E**, Degenerative changes including perivascular hyalinization (*left*) and foamy histiocytes (*right*) may be present. **F**, Diffuse and intense S100 protein immunoreactivity is characteristically present.

- Immunohistochemistry (Chapter 25, Table 25-1):
 - Diffuse and intense S100 protein positivity
 - SOX10 immunoreactivity:
 - Transcription factor involved in neural crest development and differentiation of neural crest cells into melanocytic and schwannian differentiation
 - Sensitive marker for melanoma:
 - ◻ Diffuse and strong nuclear staining
 - ◻ Expression reported in more than 85% to 90% of melanomas
 - Reactivity also present in:
 - ◻ Schwannomas (100%)
 - No immunoreactivity for cytokeratins or the neuroendocrine markers chromogranin and synaptophysin
 - Most common sites of occurrence of the ectopically located meningiomas is the head and neck region, including:
 - Middle ear and temporal bone (internal auditory canal, jugular foramen, geniculate ganglion, roof of the eustachian tube, sulcus of the greater petrosal nerve)
 - Sinonasal cavity
 - Orbit, oral cavity, and parotid gland
 - Symptoms vary according to site and in the middle ear and temporal bone area clinically simulate an acoustic neuroma with symptoms including progressive loss of hearing, loss of equilibrium, headaches, cerebellar dysfunction, and cranial nerve abnormalities
 - May be associated with neurofibromatosis type (NF-2):
 - Patients with NF-2 have an increased incidence of developing a meningioma.
 - Patients with NF-2 also experience increased incidence of multiple, separately occurring meningiomas in intra- and extracranial meningiomas.
 - The hallmark of NF-2 is bilateral acoustic neuromas.
 - Patients with an acoustic neuroma or meningioma who are under 30 years of age should raise concern for a diagnosis of NF-2.
 - Radiologic findings include:
 - Soft tissue mass with variable vascularity
 - A feature that correlates to the histology and is considered a pathognomonic feature for meningioma in this location is the presence of speckled calcification in a soft tissue mass.

Differential Diagnosis

- Middle ear adenoma
- Jugulotympanic paraganglioma
- Meningioma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Alternative nonmicrosurgical treatment (i.e., radiotherapy) for smaller tumors may play an increasingly important role in the future.
- Death may occur secondary to herniation of the brainstem in untreated and/or large neoplasms.
- Malignant AN (malignant peripheral nerve sheath tumors) are exceedingly rare and, if present, neurofibromatosis should be suspected.

MENINGIOMA (Figs. 24-25 and 24-26)

Definition: Benign neoplasms arising from arachnoid cells forming the arachnoid villi seen in relation to the dural sinuses.

Clinical

- Represent 13% to 18% of all intracranial tumors
- Represent the second most common tumor of the cerebellopontine angle
- More common in women than in men; occur over a wide age range but are most commonly seen in the fifth decade of life and infrequently occur in children
- Occurrence outside the central nervous system is considered ectopic and is divided into:
 - Primary meningioma with no identifiable CNS connection
 - Secondary meningioma with CNS connection
- Development of meningiomas in the middle ear and temporal bone results either by direct extension or from the presence of arachnoid cells ectopically located.

Pathology

Gross

- Lobular-appearing, tan-white to gray, rubbery to firm mass with a gritty consistency
- In contrast to their intracranial counterparts, which are well-delineated and circumscribed lesions, meningiomas of the middle ear tend to be infiltrative with extension and invasion of adjacent structures.

Histology

- Four histologic variants have been described and include:
 - Syncytial or meningothelial
 - Fibroblastic
 - Transitional (combination of syncytial and fibroblastic)
 - Angioblastic
- In the middle ear the most common histologic subtype is the meningothelial type, which has the following features:
 - Lobular growth with tumor nests separated by a variable amount of fibrous tissue

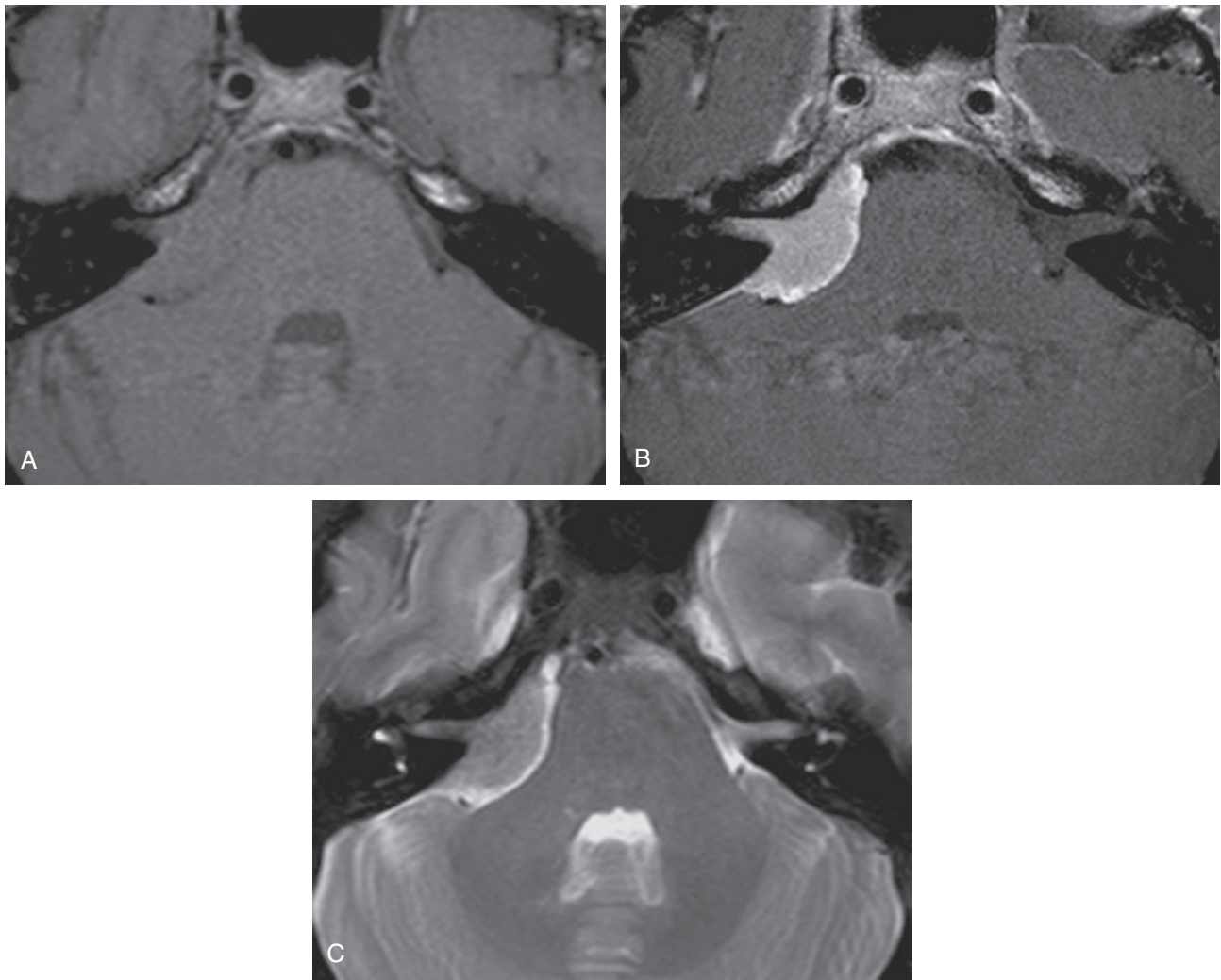


Fig. 24-25. CPA meningioma with intracanalicular extension.

A and B, T1-weighted images before and after contrast enhancement. Typical hemispheric meningioma with intracanalicular extension. The meningioma is eccentric to the IAC, has a broad dural base, and the cisternal component forms an obtuse angle with the posterior border of the petrous bone. The dural tail of the tumor extending posteriorly is best seen on the post-contrast-enhanced image. **C,** The tumor is homogeneously isointense to gray matter. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 20-22, p 1276.)

- Cells have a whorled appearance and are composed of round to oval or spindle-shaped nuclei with pale staining cytoplasm and indistinct cell borders.
- Characteristically, the nuclei have a punched-out or empty appearance resulting from intranuclear cytoplasmic inclusions.
- Psammoma bodies, typical and numerous in intracranial meningothelial meningiomas, may be seen but are not as often found in meningiomas occurring in the middle ear region.
- Mild cellular pleomorphism may be seen; mitoses are uncommon.
- Immunohistochemistry (see Chapter 25, Table 25-1):
 - Immunoreactivity with vimentin and epithelial membrane antigen (EMA)
 - Typically S100 protein negative but occasionally may be positive, particularly in the fibroblastic variant
 - Cytokeratins can be positive:
 - As a whole may be positive in 20% of cases
 - May approach 40% positivity in epithelial variants
 - D2-40 (podoplanin) positive in majority of cases
 - Neuroendocrine markers (i.e., chromogranin, synaptophysin, others) negative

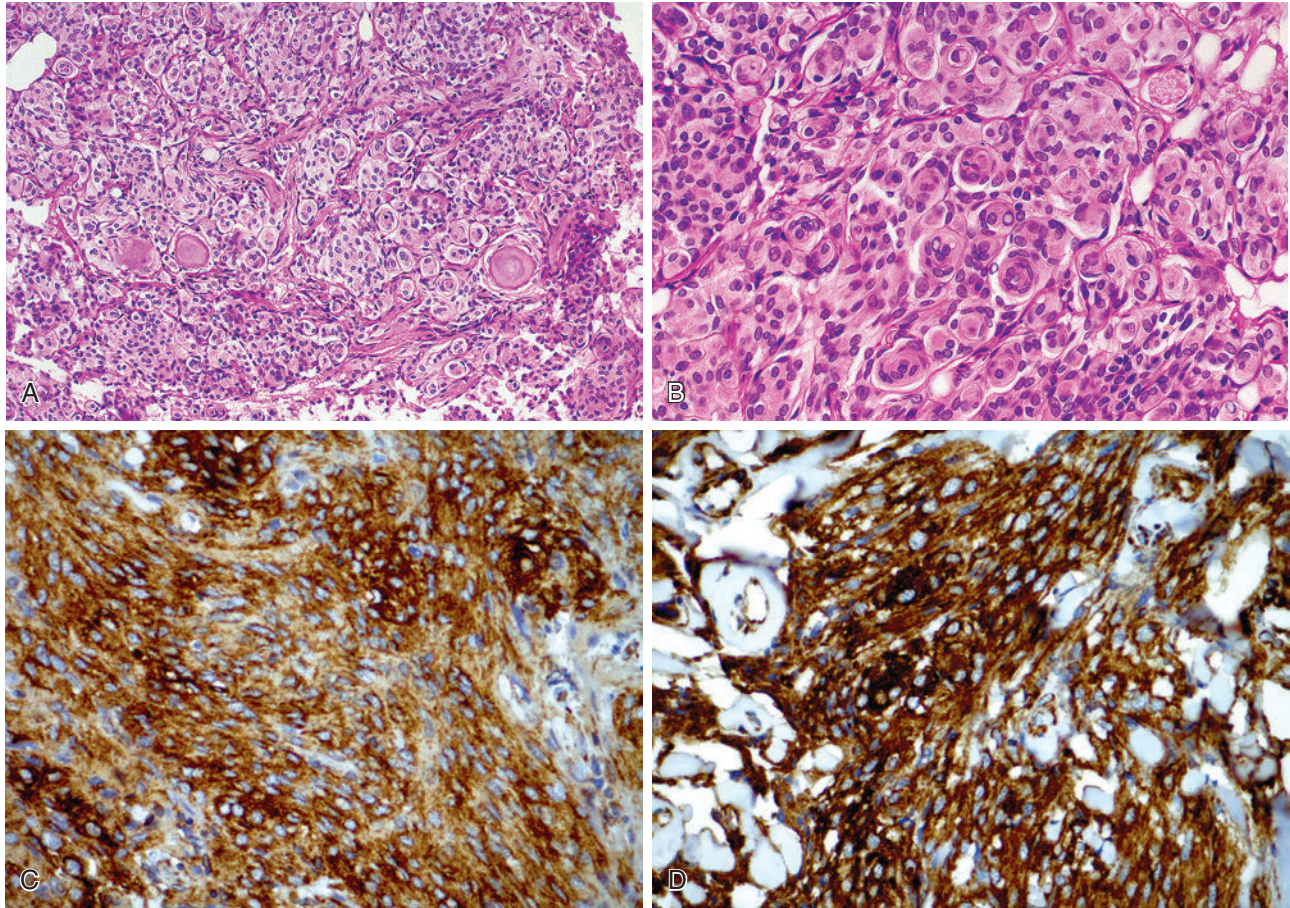


Fig. 24-26. Meningioma.

A, The histology of meningioma includes a lobular growth with tumor nests separated by a variable amount of fibrous tissue; psammoma bodies are seen. **B**, The neoplastic cell nests have a whorled appearance and are composed of round to oval nuclei with pale staining cytoplasm and indistinct cell borders; characteristically, the nuclei have a punched-out or empty appearance resulting from intranuclear cytoplasmic inclusions; immunoreactivity is present from **C**. Epithelial membrane antigen (EMA) and **(D)** vimentin.

- Low proliferation rate (usually less than 3%) by Ki67 (MIB1) staining

Differential Diagnosis

- Middle ear adenoma
- Jugulotympanic paraganglioma
- Acoustic neuroma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Local recurrence relates to inadequate excision.
- Malignant change rarely, if ever, occurs.
- A diagnosis of middle ear meningioma should be made only after clinical evaluation to exclude secondary extension from an intracranial neoplasm.
- There is no correlation between the histologic subtype and clinical behavior, except for the angio-blastic variant, which has been associated with a more aggressive behavior.

OTHER BENIGN TUMORS OF THE MIDDLE EAR AND TEMPORAL BONE (Fig. 24-27)

- Although uncommon, a number of other primary benign tumors can be found in the middle ear or temporal bone.
- Middle ear papillary epithelial neoplasms that are histologically identical to sinonasal or Schneiderian papillomas may rarely be identified:
 - Referred to as Schneiderian-type mucosal papillomas of the middle ear
 - More common in women than in men
 - Occur over a wide age range with an average age of occurrence in the fifth decade of life
 - Presentation may include conductive hearing loss, otalgia, and otorrhea.
 - Often occur in patients with a history of chronic otitis media

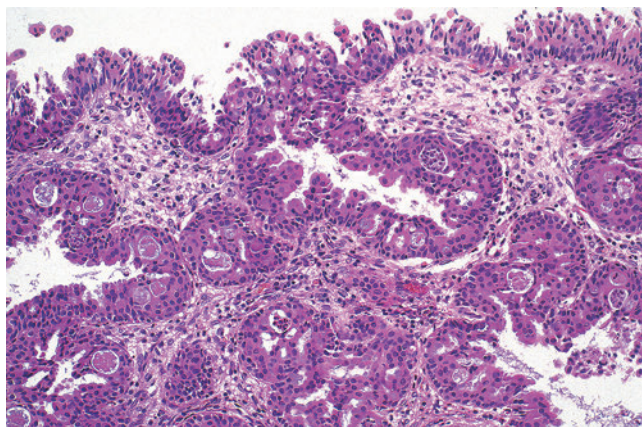


Fig. 24-27. Middle ear Schneiderian-type papilloma.

Middle ear papilloma with histologic features of a sinonasal (Schneiderian) type of cylindric cell papilloma.

- Arise de novo without evidence of sinonasal tract papillomas but some have occurred in patients with sinonasal tract papillomas
- Histology identical to that of inverted-type and cylindrical-type Schneiderian papillomas
- Associated squamous cell carcinoma has been reported.
- Complete excision usually necessitating radical tympanomastoidectomy is the preferred treatment.
- Other uncommon primary benign tumors of the middle ear and temporal bone are primarily mesenchymal, including:
 - Hemangiomas, lipoma, osteoma, osteoblastoma, chondroblastoma, and teratomas

MALIGNANT NEOPLASMS OF THE EXTERNAL EAR

BASAL CELL CARCINOMA (BCC) (Figs. 24-28 through 24-30)

Definition: Slow growing, locally infiltrative malignant neoplasm of the skin and subcutaneous adnexal tissue.

Synonym: Basal cell epithelioma

Clinical

- Represents the most common cutaneous malignancy
- More common in men than in women; generally a tumor affecting adults and is most commonly seen in the seventh decade of life
- Sun-exposed areas of the head and neck are the most frequent sites of occurrence:
 - May occur in virtually all cutaneous sites of this region
 - More common locations include the nose, eyelids, nasolabial area, and the auricular area (pinna).
- In general, basal cell carcinomas are asymptomatic; presentation usually occurs because the patient notices a growth.
- Basal cell carcinomas of the external auditory canal are uncommon; however, when this area is involved it typically has extensive subcutaneous involvement, which may not be clinically appreciated.
- Basal cell carcinomas take origin from a pluripotent cell in either the basal cell layer of the surface epithelium or in the epithelium of the subcutaneous adnexae.
- Etiology is related to prolonged sun exposure with resulting actinic damage.
- Basal cell carcinomas may be inherited in the autosomal dominant disorder called nevoid basal cell

carcinoma syndrome (Gorlin syndrome) which includes:

- Autosomal dominant inherited condition with high penetrance and variable expressivity
- Multiple basal cell carcinomas most commonly involving the nose, mouth, eyes, and ear regions
- Occurrence in childhood
- Association with palmar and plantar pitting, odontogenic keratocysts of the jaws, skeletal developmental abnormalities (bifid ribs, brachy-metacarpalism and vertebral anomalies), ectopic calcification in dermal and soft tissue sites, and neurologic abnormalities (mental retardation)
- Caused by mutations in *patched (PTCH)*, a tumor suppressor gene mapped to chromosome 9q22.3q31; in few cases, the syndrome is due to a microdeletion at 9q22.
- Bazex syndrome:
 - Autosomal dominant inherited condition
 - Characterized by:
 - Multiple basal cell carcinomas of the face
 - Follicular atrophoderma
 - Localized or generalized hypohidrosis
 - Hypertrichosis
 - May be associated with other solid malignant neoplasms of varying organs, including those of the head and neck (e.g., squamous cell carcinoma)

Pathology

Gross

- Initially, the lesion is a raised papule or nodule with a waxy or translucent appearance covered by a fine capillary network (telangiectasia).



Fig. 24-28. Basal cell carcinoma.

The clinical appearance of basal cell carcinoma of the external ear may include (A) raised papule or nodule on the helix as well as involving the concha and (B) ulcerated lesions surrounded by raised borders creating a papulonodular ulcerative ("rodent ulcer") lesion on the cutaneous surface behind the ear. (Images courtesy Mark Persky, MD.)

- With time, the central portion ulcerates and is surrounded by raised, pearly appearing borders, creating the typical papulonodular ulcerative lesion referred to as rodent ulcer.

Histology

- Unlike squamous cell carcinoma, basal cell carcinomas do not have a premalignant counterpart.
- Although a variety of histologic growth patterns are identified, all basal cell carcinomas arise in continuity with the basal cell layer of the epithelium or from the adnexae.
- Nodulocystic BCC:
 - Most common histologic type
 - Composed of fairly uniform cells with hyperchromatic, oval or elongated nuclei, scant cytoplasm, and palisading appearance of the nuclei at the periphery of the tumor nests
 - Connected to the overlying epidermis by narrow cords or broad trabeculae
 - Stroma is fibromyxoid and characteristically retracts (separates) from the peripheral portions of the tumor nests.
 - Solar elastosis typically presents in surrounding dermis.
- Various growth patterns include:
 - BCC, solid type:
 - Made up of islands or sheets of tumor cells
 - BCC, morphea-like or sclerosing type:
 - Most frequently occurs on the face, particularly the cheek, forehead, and temples
 - Clinically resembles localized scleroderma
 - Histologically shows tumor cells in elongated strands embedded in a dense, sclerotic stroma

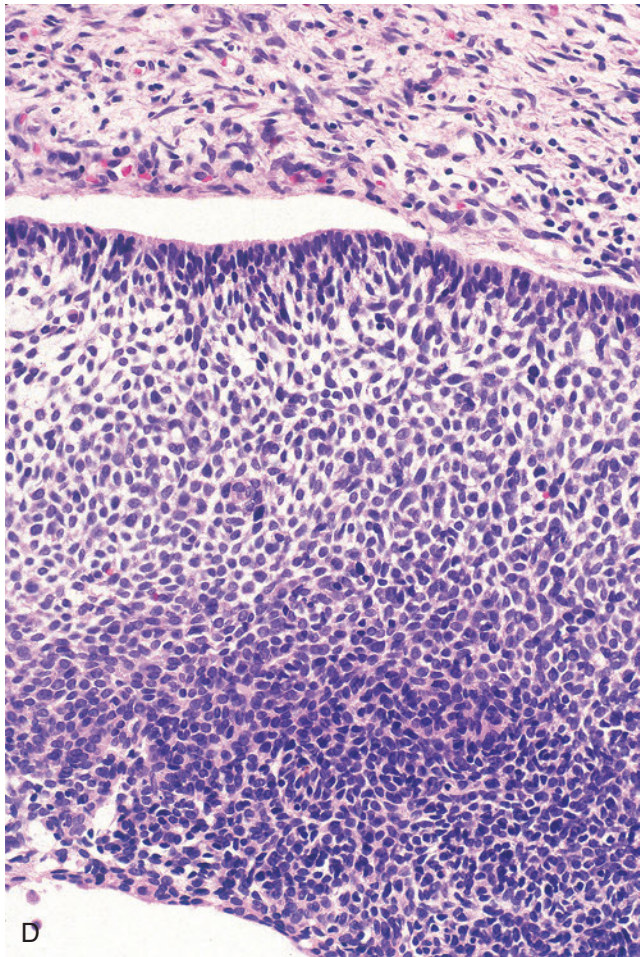
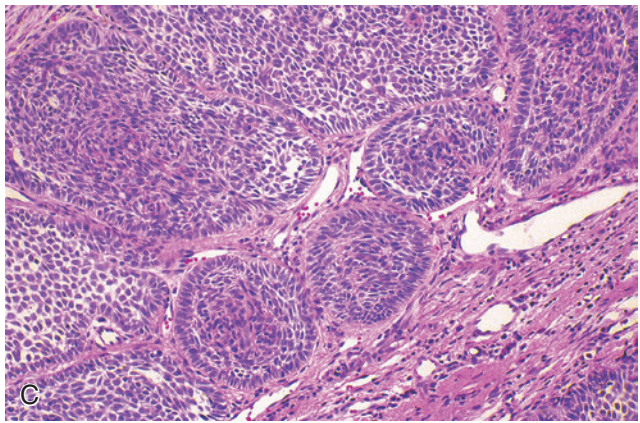
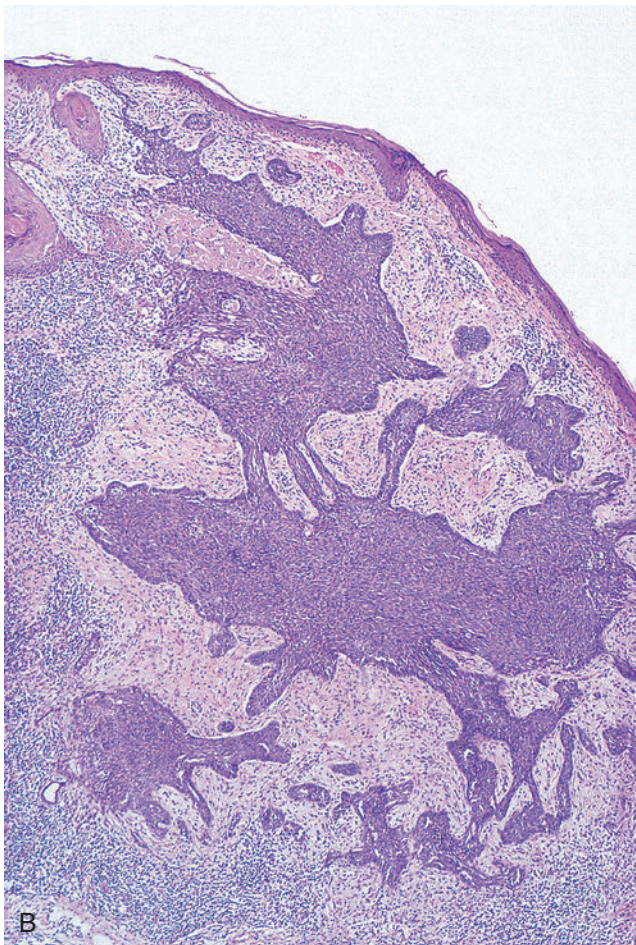
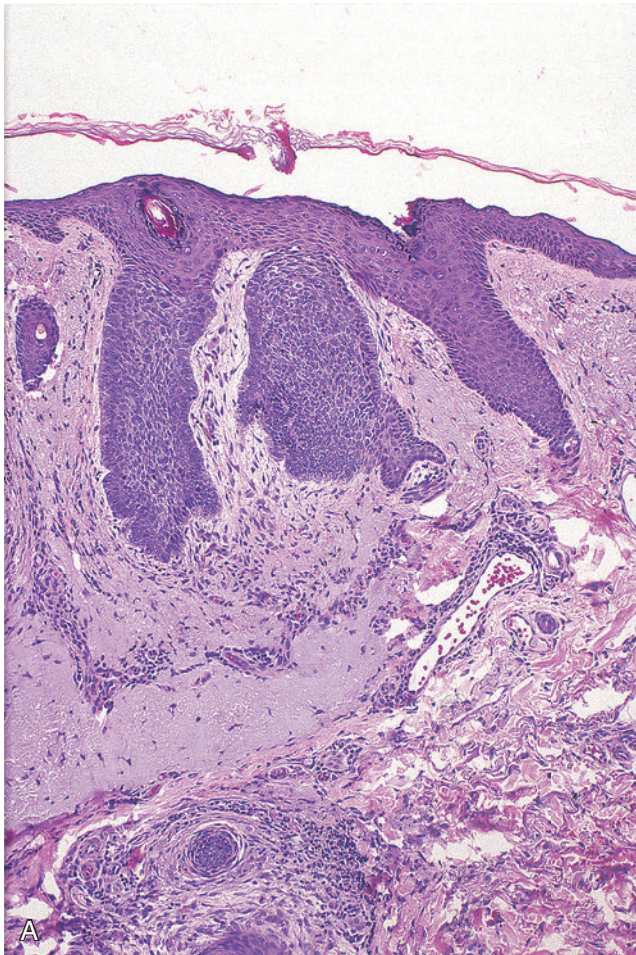


Fig. 24-29. Basal cell carcinoma.

A, Superficial basal cell carcinoma characterized by small nests arising from the basal epidermis. **B**, Nodulocystic BCC arising from the basal epidermis; even at this magnification peripheral nuclear palisading and retraction from surrounding stroma can be seen. **C**, Rounded nests of basaloid cells with peripheral nuclear palisading. **D**, Higher magnification shows the peripheral nuclear palisading characterized by the parallel alignment of the nuclei at the periphery of the tumor nest; note the retraction or separation of the surrounding stroma from the peripheral portions of the tumor nest.

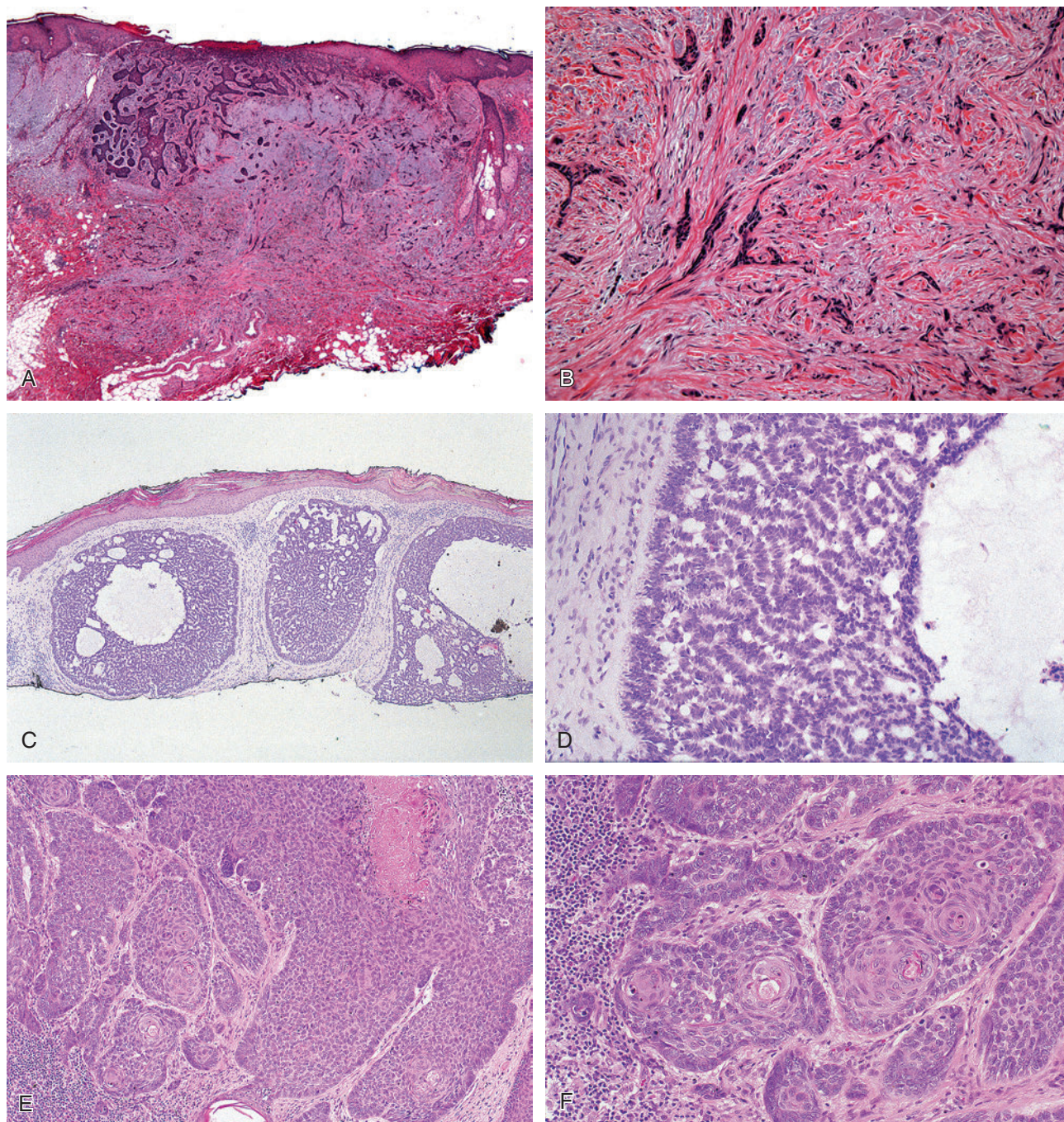


Fig. 24-30. Basal cell carcinoma.

Various types of basal cell carcinoma include (A) Morphea-like (sclerosing) basal cell carcinoma showing conventional basal cell carcinoma in the superficial aspect of the specimen and the invasive component of strands of tumor extending deep into the depth of the dermis and subcutis. B, At higher magnification the morphea-like component is comprised of tumor cells in elongated strands embedded in a dense, sclerotic stroma. C and D, Adenoid basal cell carcinoma in which the tumor islands are arranged in anastomosing cords, creating a lace-like or adenoid pattern. E and F, Metatypical or basosquamous carcinoma composed of a basal cell carcinoma with squamous cell differentiation.

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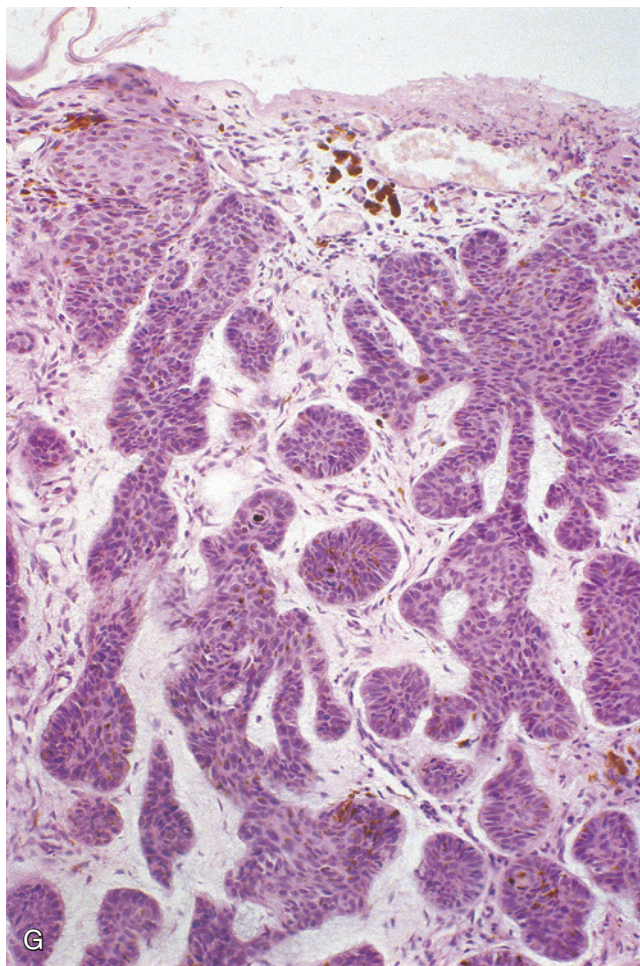


Fig. 24-30, cont'd

G, Melanin pigmentation in tumor nests may impart a brown-to-black appearance and clinically simulate a malignant melanoma.

- Continuity between the tumor strands and surface epithelium rarely seen
- BCC, adenoid type:
 - Adenoid type in which the tumor islands are arranged in anastomosing cords, creating a lace-like or adenoid pattern
- BCC, keratotic (pilar) type:
 - Composed of keratin microcysts or horn cysts lined by flattened, parakeratotic cells identified within the tumor islands
- Additional histologic variants of basal cell carcinoma include:
 - Metatypical or basosquamous carcinoma:
 - Most often occur on face, in particular ear and nose
 - Composed of a basal cell carcinoma with squamous cell differentiation, less pronounced nuclear palisading, irregular lobules, and more stromal proliferation
 - Basal cell and squamous differentiated tumors lie adjacent to one another or are admixed.
 - Squamous component includes keratinization (individual cell or horn pearl formation) and intercellular bridges.
 - Metastatic rate is similar to squamous cell carcinoma.
- Adamantinoid basal cell carcinoma:
 - Most frequently occurs on face (around eyes and glabella)
 - Histologically composed of stellate basaloid cells, resulting in cribriform pattern
- Keloidal basal cell carcinoma:
 - Simulates a keloid
 - Histologically shows a typical basal cell carcinoma admixed with thick sclerotic collagen bundles
- Pleomorphic basal cell carcinoma:
 - Most often occurs in head and neck
 - Occasionally seen in nevroid basal cell carcinoma syndrome
 - Histologically has typical basal cell carcinoma pattern but includes pleomorphic and multinucleated cells
- Rarely, a sarcomatous histologic variant has been reported (so-called sarcomatoid basal cell carcinoma).
- In any one lesion multiple growth patterns may be identified.
- Cellular pleomorphism, increased mitoses, and necrosis may be seen and vary from case to case.
- Melanin pigmentation may be seen in tumor islands.

Differential Diagnosis

- Adnexal neoplasms:
 - Trichoepithelioma
- Merkel cell carcinoma (see later in chapter):
 - Basal cell carcinoma may coexist with Merkel cell carcinoma.
- Squamous cell carcinoma

Treatment and Prognosis

- Complete surgical excision is the preferred treatment:
 - Given indolent behavior, local excision (e.g., Mohs surgery) provides long-term cure in more than 90% of cases.
 - Similar treatment applicable for even large BCCs.
- Prognosis is excellent following complete excision.
- Local recurrences are not uncommon and are especially high in the morphea or sclerosing type of basal cell carcinoma.
- Metastases are rare except for:
 - Neglected or long-standing tumors that attain large sizes and become deeply and extensively infiltrative

- Basosquamous carcinoma, which for all intents and purposes behaves as a squamous cell carcinoma:
 - Metastatic rates seen in approximately 6% of patients
 - This form of basal cell carcinoma requires a more aggressive surgical approach and a closer follow-up than other types of basal cell carcinomas.
- When metastases occur, spread is usually to regional lymph nodes and to the lungs; metastatic disease is associated with poor prognosis irrespective of any therapeutic intervention.
- Basal cell carcinomas of the external auditory canal are notorious for extensive local invasion and extension to the middle ear, mastoid region, temporal bone, and potentially into the cranial cavity; radical surgical excision may be necessary to eradicate tumors in this location.
- Aside from the metatypical and sclerosing types, histology does not correlate with the biologic behavior.
- Invaluable aid in the diagnosis of squamous cell carcinoma of the external auditory canal, especially in the presence of a well-differentiated squamous epithelial lesion that histologically is bland appearing and may appear to be limited to the auditory canal, belying its invasive nature
- Squamous cell carcinoma of the external auditory canal:
 - CT accurately predicts tumor extent.
 - Evidence of destruction of adjacent structures can be seen, including bone and other soft tissue structures, extension into the middle ear and extradural growth into middle cranial fossa, mastoid involvement, and extension into soft tissues beneath the temporal bone.

Pathology

Gross

- External ear: polypoid, rubbery to firm nodules frequently with ulceration
- External auditory canal: visualization is difficult given the location and concealment by any purulent or hemorrhagic exudates

Histology

- In general, squamous cell carcinomas in this region tend to be well differentiated and composed of infiltrating nests of cells with keratinization (keratin pearl formation, individual cell keratinization) and intercellular bridges:
 - Nuclear atypia is present but it is variable.
 - Increased mitotic activity may be present and may include atypical forms.
 - Frequently, invasive growth is seen, varying from superficial invasion with irregular budding of the basal epithelium from the skin surface to the more obvious invasion characterized by irregular tongues of tumor projecting downward from the surface epithelium and irregular strands of atypical epithelial cells extending between the dermal collagen fibers.
 - Limited tissue sampling as well as tangential sectioning can compromise the ability to definitively identify invasive growth, creating problems in diagnosing carcinoma and differentiating it from benign lesions such as inverted follicular keratosis (see below under differential diagnosis).
- Less differentiated squamous cell carcinomas may occur:
 - Moderately differentiated squamous cell carcinoma usually lacks keratin pearls but does have scattered individual keratinized cells.
 - Poorly differentiated SCC, keratinization is extremely difficult to identify, and classification as SCC is based on features such as associated squamous epithelial dysplasia, a pavement-like

SQUAMOUS CELL CARCINOMA OF THE EXTERNAL EAR AND EXTERNAL AUDITORY CANAL (Figs. 24-31 through 24-34)

Definition: Malignant epithelial tumor arising from the surface epithelium.

Synonym: Epidermoid carcinoma

Clinical

- Accounts for approximately 25% of all squamous cell carcinomas of the head and neck.
- Squamous cell carcinoma of the external ear (i.e., auricular skin):
 - More common in men than in women; most frequently seen in the seventh to eighth decades of life
 - Present with a nonhealing sore
- Squamous cell carcinoma of the external auditory canal:
 - More common in women than in men; most frequently seen in the sixth to seventh decades of life
 - Symptoms mimic those of a chronic otitis media with pain, hearing deficits, and otorrhea (bloody or purulent).
- Suspicion for the presence of a malignancy should be considered in patients with chronic ear infections who suddenly have a change in symptoms, including pain, bleeding, or facial paralysis.
- Usually unilateral but may uncommonly be bilateral
- Radiology:

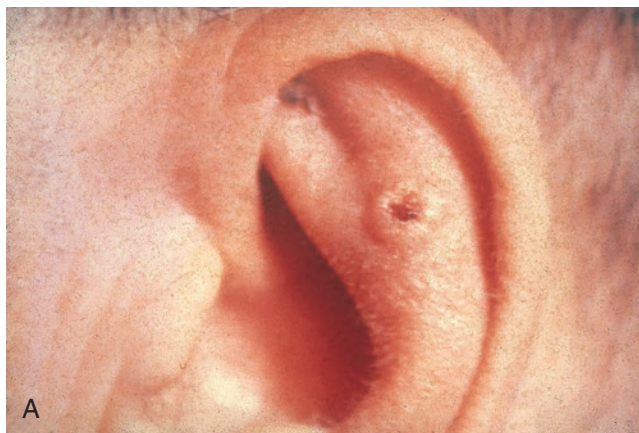


Fig. 24-31. Squamous cell carcinoma.

The spectrum of clinical appearances of squamous cell carcinoma of the external ear identified in various sites.
(Images courtesy Mark Persky, MD.)



Fig. 24-31, cont'd

- squamoid cellular pattern or foci in which intercellular bridges or some evidence of keratinization is seen.
- Adenoid variant:
 - Unusual variant of SCC with a propensity to occur on the face and scalp and especially on the periauricular area
 - “Adenoid” designation refers to a pseudoglandular appearance that results from tumor cell acantholysis.
 - These tumors have been alternatively referred to as adenoid squamous cell carcinoma, acantholytic squamous cell carcinoma, and adenoacanthoma.
 - Islands of tumor cells show central acantholysis, in which cohesiveness is lost and the tumor cells crumble apart, leaving a relatively intact peripheral rim of more cohesive tumor cells and simulating the presence of a glandular lumen.
 - Acantholytic cells in the false “lumen” often show the deeply eosinophilic cytoplasm that is common in exfoliated dyskeratotic cells.
- Tumor can usually be seen emanating from dysplastic surface epithelium, further supporting its squamous origins.
- Glandlike spaces often contain some amorphous basophilic material; however, histochemically, no evidence of epithelial mucin is found.
- Treatment, prognosis, and grading are the same as conventional squamous cell carcinoma.
- Spindle cell squamous carcinoma:
 - A predominant or exclusive spindle cell morphology may be seen.
 - Spindle cell squamous carcinomas arising on the external ear may:
 - Show little to absent evidence of squamous differentiation (e.g., epithelial dysplasia, carcinoma in situ, infiltrating foci of differentiated squamous cell carcinoma)
 - Frequently have surface ulceration
 - Continuity of the tumor with the overlying epithelium may be seen in those cases not associated with ulceration.

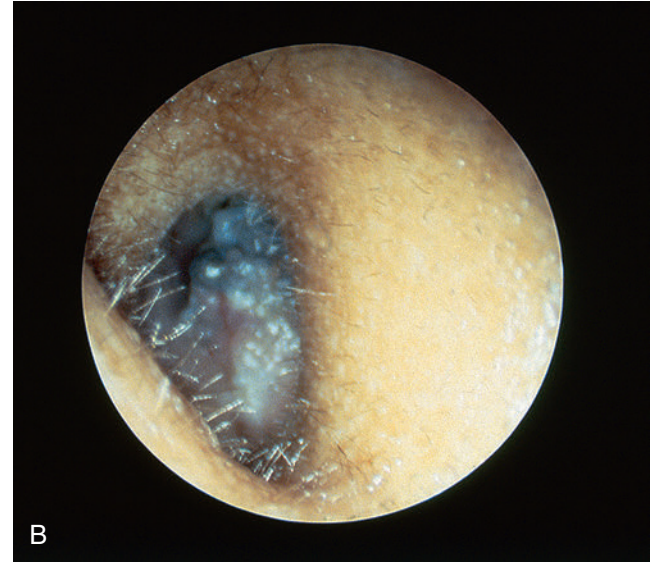


Fig. 24-32. Squamous cell carcinoma.

A, Squamous cell carcinoma appearing as a fleshy polypoid mass protruding from the external auditory canal. **B**, External auditory canal squamous cell carcinoma within the depth of the canal appearing as a gray-white, pearly-appearing polypoid lesion filling the canal. The superficial presentation of these lesions may belie their extensive invasive growth as can be seen in appropriate imaging studies (see next image).

- Infiltrating but demarcated tumor composed of interlacing bundles or fascicular growth pattern
- Histologically composed of cells with elongated hyperchromatic nuclei, cellular pleomorphism with giant cells, increased mitotic activity, including atypical mitoses and a variable amount of amphophilic to eosinophilic cytoplasm
- Heterologous elements including bone and cartilage may be present.
- Immunoreactivity:
 - Cytokeratins (AE1/AE3, CAM5.2, CK5/6, OSCAR), p63, and EMA variably positive:
 - Multiple epithelial markers should be performed in each case to increase potential yield of positive staining;
 - Vimentin invariable positive
 - S100 protein, melanoma markers (HMB-45, melan A, tyrosinase, MART-1 [melanoma antigen recognized by T cells-1], microphthalmia transcription factor [MITF], SOX10) and vascular endothelial markers (CD31, Factor VIII-related antigen, CD34, ERG, Fli1) negative

Differential Diagnosis

- Pseudoepitheliomatous hyperplasia and other reactive hyperplasias
- Cholesteatoma of the external auditory canal
- Seborrheic keratosis and inverted follicular keratoma:
 - Inverted follicular keratosis (IFK): (Fig. 24-35)
 - Variant of seborrheic keratosis
 - Endophytic proliferation of mature squamous epithelium with spongiosis and numerous whorls of eosinophilic flattened squamous cells referred to as squamous eddies; the latter differ from horn cysts by their large number, small size, and circumscription
 - Downward squamous cell proliferation may extend below the adjacent normal epidermis that is typically seen in nonirritated seborrheic keratosis.
 - Inflammation below epithelial proliferation is usually mild or absent, differing from irritated seborrheic keratosis.
 - Diagnostic challenges in differentiation IFK from SCC directly relate to limited tissue sampling.

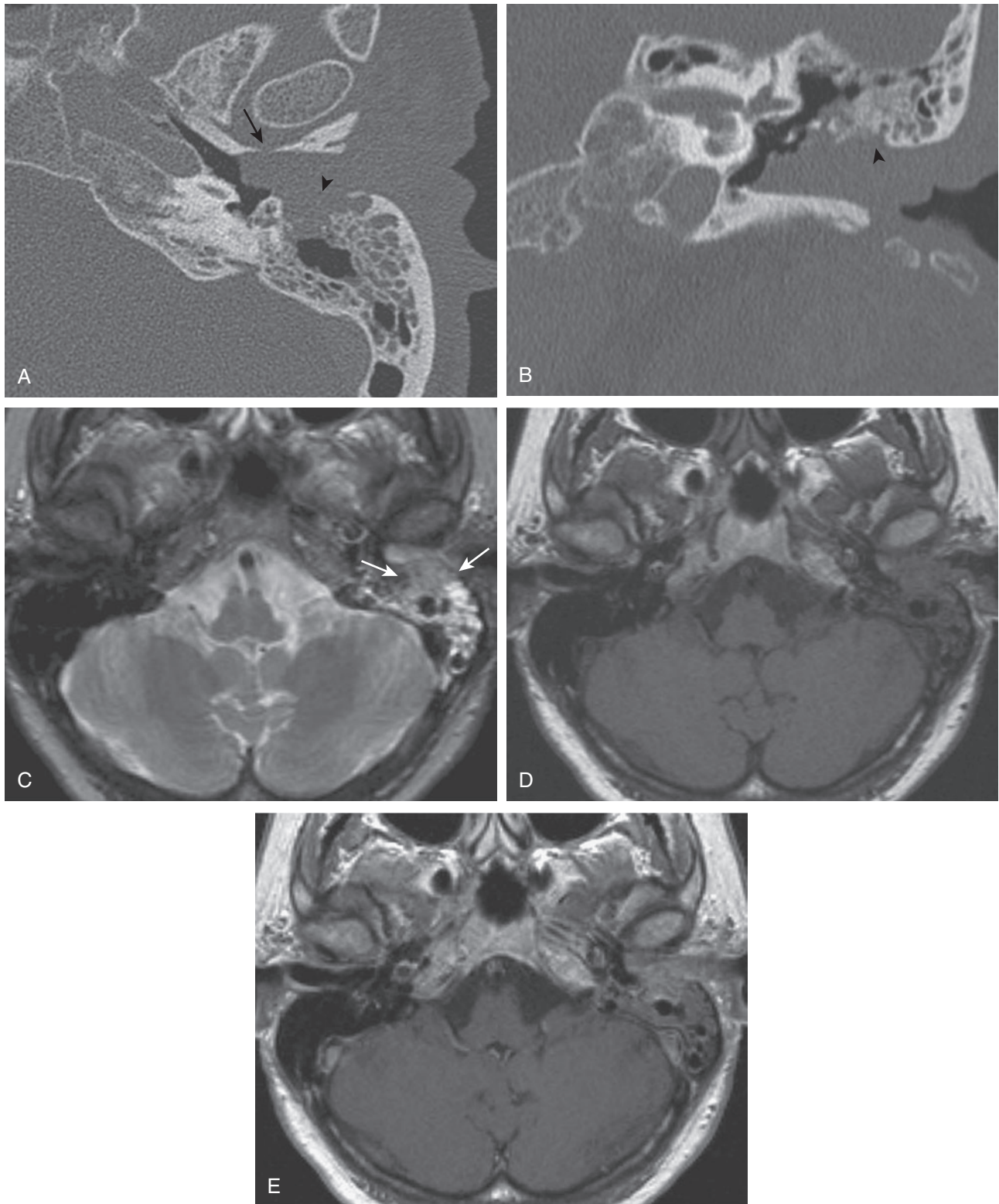


Fig. 24-33. EAC squamous cell carcinoma.

A and **B**, Axial and coronal CT images in bone algorithm. Tumor fills the EAC lumen. There is destruction of the anterior (arrow in **A**) and superoposterior (arrowheads in **A** and **B**) margins of the EAC. There is extension through the posterior defect to invade the mastoid. **C**, Axial T2-weighted image. The tumor is heterogeneously hypointense to CSF. Note invasion of the mastoid (arrows) by tumor, which can be distinguished from fluid in the mastoid air cells by the tumor's lower signal intensity. **D** and **E**, Pre- and post-contrast-enhanced T1-weighted images, demonstrating enhancement. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia: Elsevier, Fig. 20-199, p 1384.)

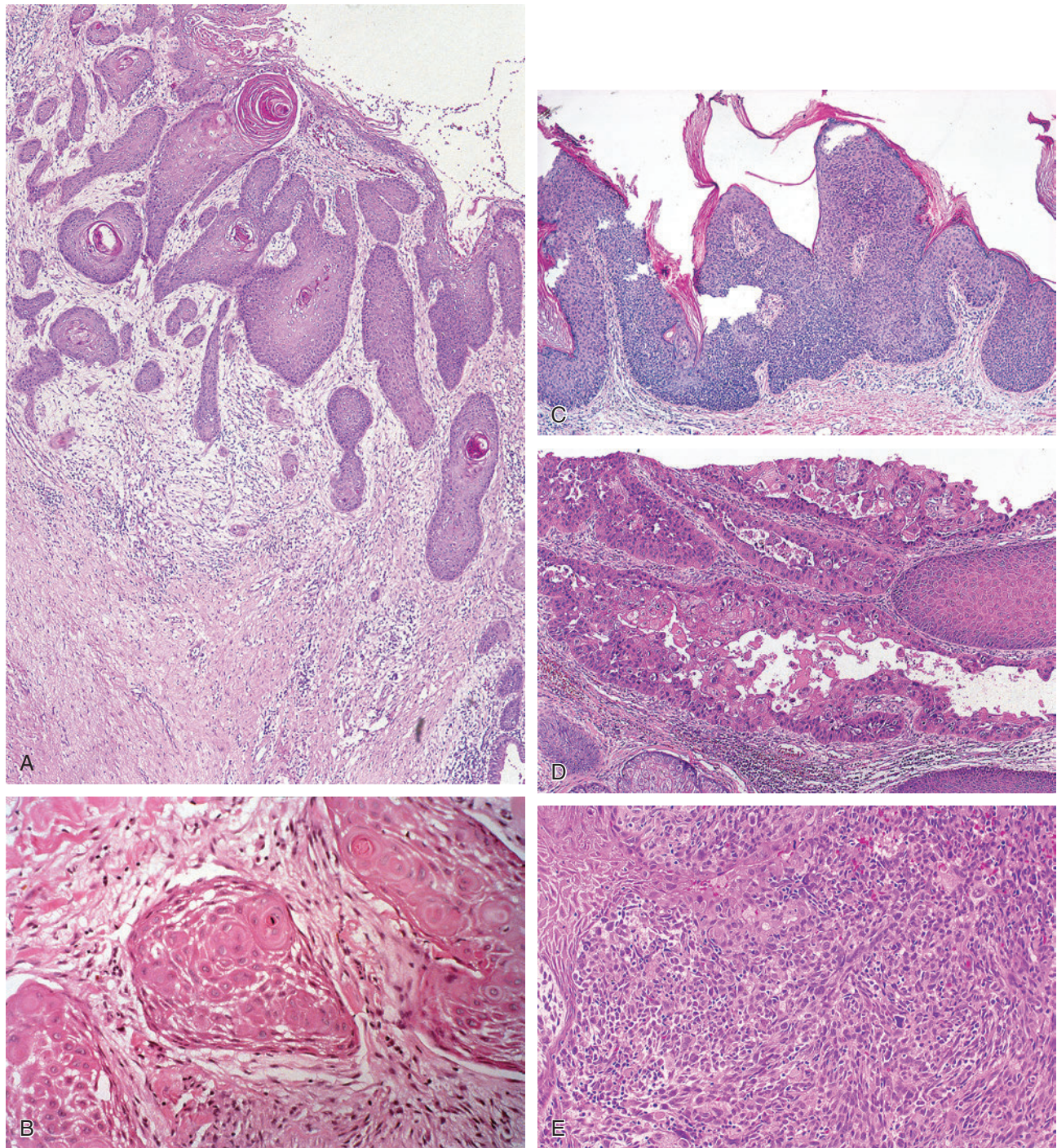


Fig. 24-34. Squamous cell carcinoma.

A, Infiltrating well-differentiated squamous cell carcinoma of the external auditory canal originating from the surface epithelium. **B**, Higher magnification shows infiltrating well-differentiated squamous cell carcinoma with keratinization and intercellular bridges. **C**, In some cases, carcinoma in situ or bowenoid dysplasia (Bowen's disease) may be identified. **D**, Adenoid squamous cell carcinoma is a morphologic variant of squamous cell carcinoma that is more often seen in cutaneous rather than mucosal-based squamous cell carcinoma; the adenoid changes represent a degenerative phenomenon. **E**, Spindle cell squamous carcinoma of the external cutaneous skin. The malignant spindle-shaped and pleomorphic cells originate from the surface epithelium (*left*), the latter showing dysplastic changes. The neoplastic cells were immunoreactivity for cytokeratins (AE1/AE3, CAM5.2, OSCAR, CK5/6) and p63 (not shown), confirming the diagnosis.

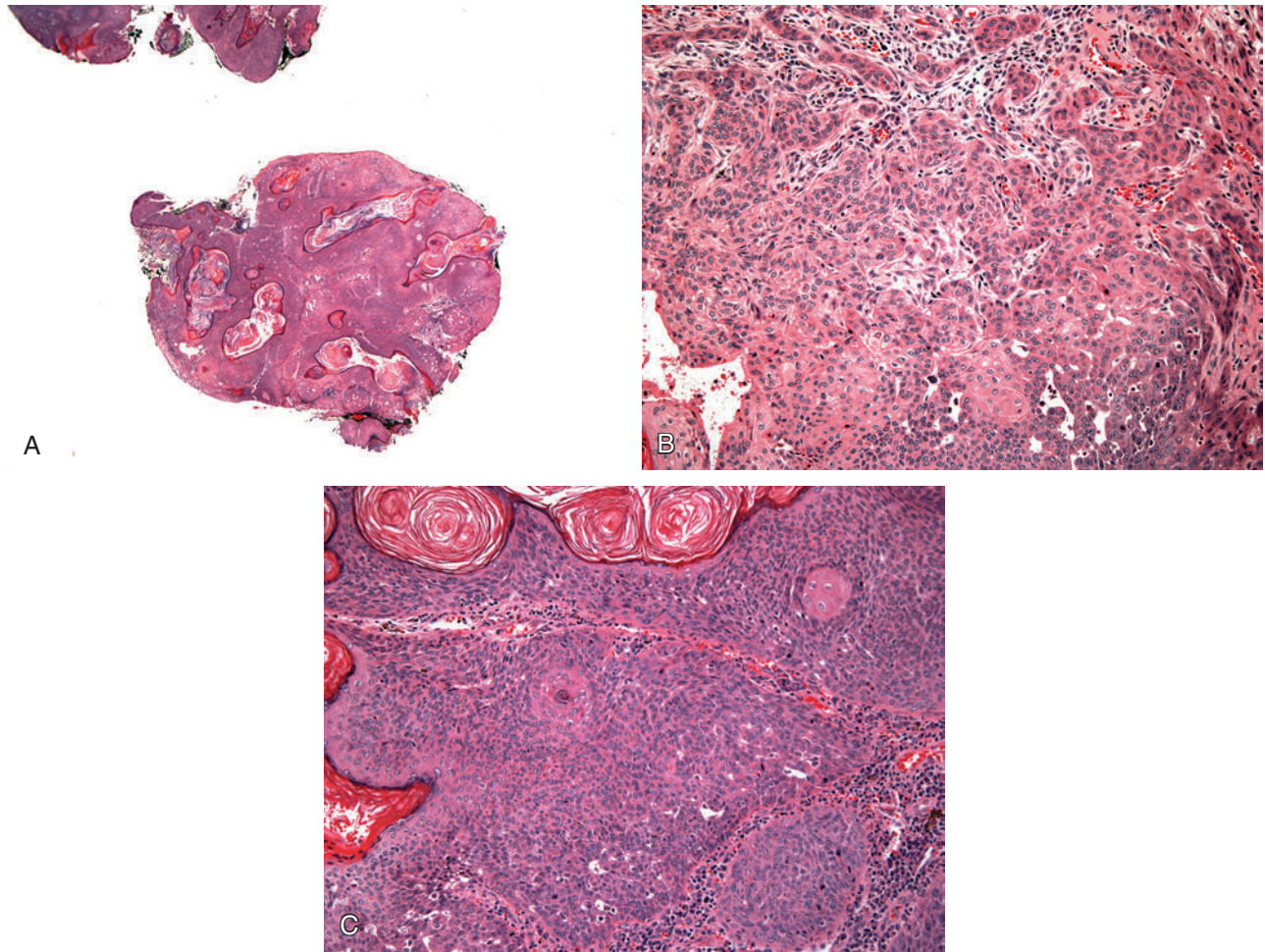


Fig. 24-35. Inverted follicular keratosis.

Seborrheic keratosis (inverted follicular keratoma) of the external auditory canal. **A**, Polypoid-appearing squamous epithelial proliferation characterized by hyperkeratosis, acanthosis, and horn cysts. **B**, Higher magnification shows an epithelial proliferation composed of squamous cells and basaloid cells. **C**, In the depth of the lesion there is an endophytic proliferation of mature squamous epithelium with squamous eddies.

- Key differentiating feature is the absence (IFK) or presence (SCC) of stromal invasion, which is not as simple to determine in practice as it is in theory:
 - In equivocal cases, identification of lesion extent by radiologic imaging may be the critical determinant in the diagnosis.
 - Tissue sampling including deeper tissues is recommended and may be necessary in rendering a definitive diagnosis.
 - Presumptively, if tissue is sampled from deeper portions of the canal and/or deeper to the lesion itself, then the presence of squamous epithelium even with limited cytologic atypia likely represents well-differentiated squamous cell carcinoma; such epithelium would not be expected to be located in the setting of IFK.
- Atypical fibroxanthoma (see below)
- Malignant melanoma:
 - In general, differentiating squamous cell carcinoma from malignant melanoma is straightforward, but problems may occur in certain circumstances such as in differentiating spindle cell squamous carcinoma from spindle cell malignant melanoma; among the features found in malignant melanoma not identified in carcinoma would be the presence of melanin pigment and immunohistochemical reactivity for S100 protein, HMB45, melan A, tyrosinase, MART-1, MITF and/or SOX10, and absence of epithelial markers.

- Dermatofibrosarcoma protuberans (see below)
- Other sarcomas

Treatment and Prognosis

- External ear:
 - Complete surgical excision is the preferred treatment with or without adjunctive radiotherapy.
 - In general, early detection and complete removal result in good prognosis; however, prognosis depends on the extent of disease and the presence or absence of metastasis.
 - Conservative (limited) local resection can be performed for small lesions limited in extent without osseous invasion or invasion of the middle ear.
 - Some authorities recommended radiotherapy in the treatment of early (T1) lesions.
 - For advanced (higher stage) squamous cell carcinomas, more aggressive management is recommended, including radical surgical resection plus radiotherapy and/or chemotherapy.
 - Elective parotidectomy necessary in advanced SCC:
 - For control of occult parotid node metastasis
 - To secure adequate margins
 - Local recurrence may occur in up to 25% of patients and may correlate to tumor size.
 - Fatal outcomes are seen when tumor has spread beyond the auricle.
- External auditory canal:
 - Complete surgical excision is the preferred treatment:
 - Often requires a radical procedure (mastoidectomy or temporal bone resection)
 - Radiotherapy may be indicated depending on the extent of disease.
 - Prognosis is considered poor with approximately 25% 5-year survival rates.
 - Histologic differentiation does not correlate with prognosis.
 - Squamous cell carcinomas in this location often go undetected for long periods time and presentation is with advanced disease involving the mastoid and/or middle ear.
 - Regional lymph node metastases are seen infrequently, and death is generally attributed to invasion of regional structures, particularly intracranial extension.
 - In general, early detection and complete removal result in good prognosis:
 - 3-year estimated survival for T1 and T2 lesions of 100%
 - 5-year estimated survival for T3 and T4 of 80% and 35%, respectively
 - Prognosis is dependent on the extent of disease (i.e., stage), completeness of surgery with tumor-free margins, recurrence, and metastasis.

- Local recurrence may occur in up to 25% of patients and may correlate with tumor size.
- Owing to the low risk of nodal metastasis occurring in less than 20% of patients, elective neck dissection is not advocated.
- Pathologic factors linked to propensity for local recurrence and metastases include:
 - Carcinomas measuring greater than 2 cm in diameter, greater than 4 mm in depth
 - Perineural invasion
 - Development within a scar
 - Previously treated squamous carcinoma in the site
 - Host immunosuppression
 - Histologic differentiation does not necessarily correlate with prognosis.
- Death is generally attributed to invasion of regional structures, particularly intracranial extension.
- On the basis of clinical radiographic-histopathologic correlation, a TNM staging system for external auditory meatus carcinoma (referred to as the Pittsburgh classification system) was proposed (Table 24-4), using preoperative computed tomography and physical examination:
 - 2-year determinant survival in this classification includes:
 - Stage I (T1N0): 100%
 - Stage II (T2N0): 80%
 - Stage III (T3N0M0, T1 or T2 or T3N1M0): 50%

TABLE 24-4 TNM Staging System for External Auditory Meatus Carcinoma (Pittsburgh Classification System)

Stage	Status
T1	Tumor limited to EAM without bony erosion or evidence of soft tissue extension
T2	Limited EAM erosion (not full thickness), or radiographic findings consistent with limited (<5 mm) soft tissue involvement
T3	Erosion into the EAM (full thickness) with limited (<5 mm) soft tissue involvement, or tumor involving the middle ear and/or mastoid, or presence of facial paralysis
T4	Tumor eroding the cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or with extensive (>5 mm) soft tissue involvement
N	As described by the American Joint Committee for classifying lymph node involvement in head and neck neoplasms. However, any node involvement is considered to be advanced disease: stage III, T1, N1; stage IV, T2, T3, T4, N1
M	Any metastasis is considered to be advanced disease: stage IV, M1

EAM, External auditory meatus.

Data from Gaudet et al: Applicability of the Pittsburgh Staging System for advanced cutaneous malignancy of the temporal bone, *Skull Base*, 20(6):409–441, 2010.

TABLE 24-5 T Staging of Squamous Cell Carcinoma of the External Auditory Canal

Stage	Definition
T1	Tumor limited to external auditory canal without erosion of bone or extension into soft tissue
T2	Tumor with limited bone erosion (not full thickness) of the external auditory canal or radiographic evidence of limited (less than 0.5 cm) of soft tissue involvement (includes tumors extending through cartilaginous fissures or bone-cartilaginous junction of the external auditory canal)
T3	Tumor eroding the osseous external auditory canal (full thickness) with limited (less than 0.5 cm) of soft tissue involvement or tumor involving the middle ear or mastoid, or presentation with facial paralysis
T4	Tumor involving the cochlea, dura, medial wall of the middle ear, petrous apex, or surrounding soft tissue

Modified from Arriaga M et al: Staging proposal for external auditory meatus carcinoma based on preoperative clinical examination and computed tomography findings, *Ann Otol Rhinol Laryngol* 99(9 Pt 1):714-721, 1990.

- Stage IV (T1 or T2 or T3N2M0, T4AnyNM0, AnyTAnyNM1) less than 20%
- Using the T system, mortality rates at 2 years reported as follows:
 - T1 and T2: 0%
 - T3: 44%
 - T4: 83%
- Staging system based on T staging (Table 24-5) found 2-year survival rates for primary squamous cell carcinoma of the external auditory canal included:
 - T1: 100%
 - T2: 80%
 - T3: 50% (survival for T3 tumors was 75% with postoperative radiotherapy, compared with 0% with surgery alone)
 - T4: 7%
 - 2-year survival data directly correlated with the staging system and the use of adjuvant radiotherapy increased survival rate in patients with a T3 lesion.

MERKEL CELL CARCINOMA (MCC) (Fig. 24-36)

Definition: Neuroendocrine carcinoma of the skin, primarily arising from Merkel cells, which may be clinically mistaken for a basal cell carcinoma when it occurs on the face of elderly patients.

Synonyms: Trabecular carcinoma of skin; neuroendocrine carcinoma of skin; undifferentiated carcinoma of skin; small cell neuroepithelial tumor of skin; primary small cell carcinoma of skin

Clinical

- No gender predilection; most common in the seventh to eighth decades of life
- Slow-growing tumor with predilection for cutaneous sites of the head and neck (face), extremities (upper and lower), and buttocks:
 - Propensity to occur in the periocular skin area with about 10% of MCC occurring in this area
- Most present as solitary lesions, but multifocal primary tumors may occur synchronously or metachronously.
- Incidence rates increase with sun exposure and after immunosuppression and organ transplantation:
 - MCC may occur in immunosuppression associated with HIV infection, patients with hematologic malignancies (e.g., CLL, other).
- A significant proportion of MCC has been reported to occur in intimate association with malignant epithelial neoplasms, including:
 - Basal cell carcinoma
 - Squamous cell carcinoma
- Genetic mechanisms underlying the development and tumor progression of MCC are poorly understood, sharing pathogenetic mechanisms with other neoplasms of neural crest derivation.
- Etiology:
 - Merkel cell polyomavirus (MCPyV) considered as the etiologic agent of MCC
 - MCPyV is a member of the human polyomavirus (HPyV) family consisting of 10 members including BK virus (BKV), JC virus (JCV), KI virus (KIPyV), WU virus (WUPyV), HPyV6, HPyV7, trichodysplasia spinulosa virus (TSPyV), HPyV9, and MWPyV.
 - In contrast to the other HPyVs, MCPyV to date is unique in its association with a cancer and thus is the first example of a human oncogenic polyomavirus.
 - MCPyV infection is common, and seroprevalence studies indicate that widespread exposure begins early in life.
 - Majority of adults have anti-MCPyV antibodies and there is a growing body of evidence that healthy human skin harbors resident or transient MCPyV, suggesting that MCPyV infection persists throughout life.
 - Mode of transmission, host cells, and latency characteristics of MCPyV remain unclear.
 - Still not clear whether MCPyV is associated with diseases or lesions other than MCC.

Pathology

Gross

- Usually dome-shaped or nodular lesion with a smooth surface and a red to violaceous appearance; vary in size from 0.5 cm to 9 cm

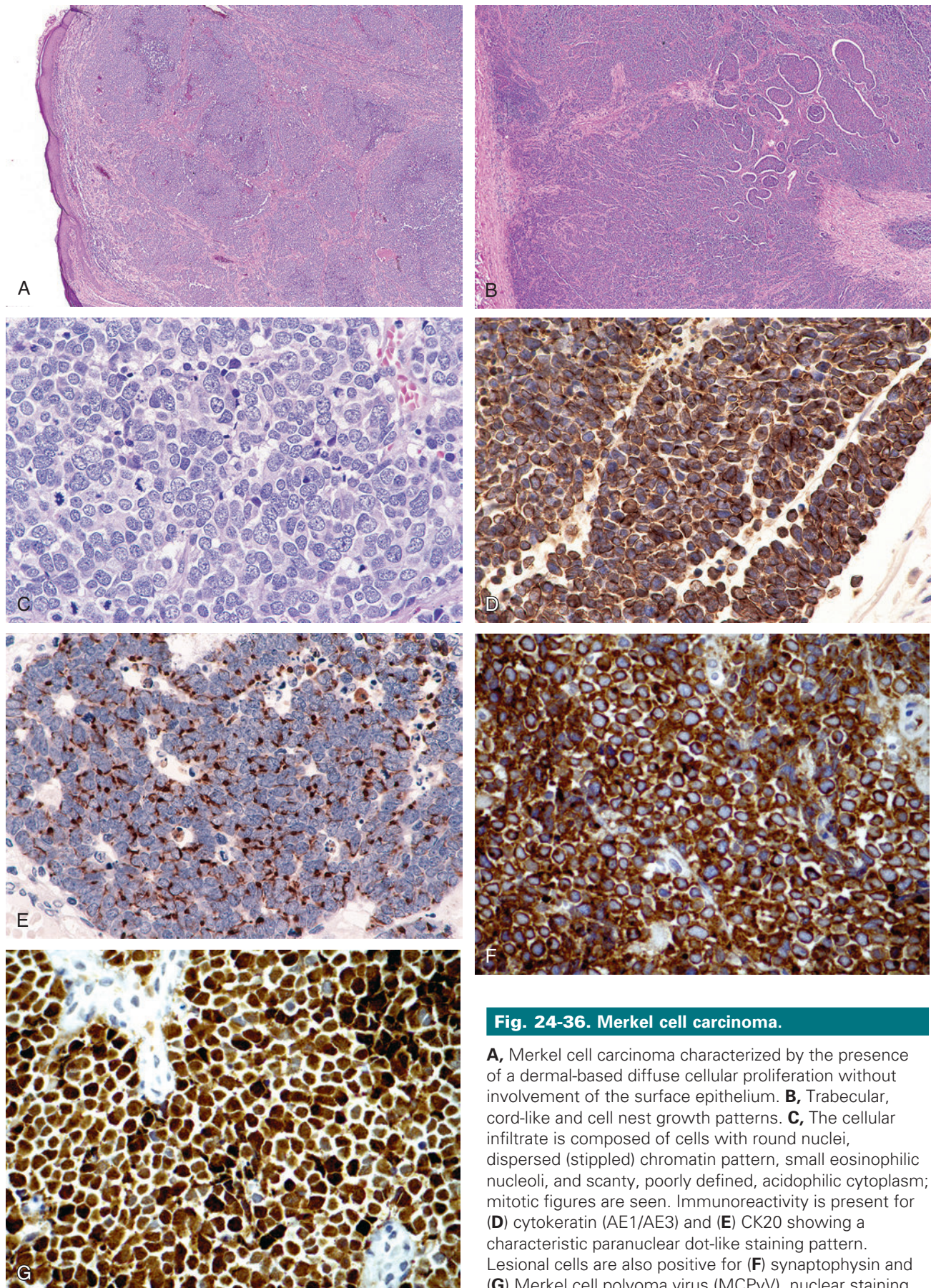


Fig. 24-36. Merkel cell carcinoma.

A, Merkel cell carcinoma characterized by the presence of a dermal-based diffuse cellular proliferation without involvement of the surface epithelium. **B**, Trabecular, cord-like and cell nest growth patterns. **C**, The cellular infiltrate is composed of cells with round nuclei, dispersed (stippled) chromatin pattern, small eosinophilic nucleoli, and scanty, poorly defined, acidophilic cytoplasm; mitotic figures are seen. Immunoreactivity is present for **(D)** cytokeratin (AE1/AE3) and **(E)** CK20 showing a characteristic paranuclear dot-like staining pattern. Lesional cells are also positive for **(F)** synaptophysin and **(G)** Merkel cell polyoma virus (MCPyV), nuclear staining.

Histology

- Characterized by an undifferentiated malignant small cell infiltrate primarily seen in the dermis and subcutaneous tissues and, generally, not involving the epidermis from which the cellular infiltrate is separated by a narrow rim of papillary dermis (Grenz zone):
 - Epidermotropism including intraepidermal growth as single cells or cell clusters forming Pautrier-like microabscesses or rarely with extensive intraepidermal pagetoid spread uncommonly present
 - Intraepithelial involvement may result in ulceration.
- Growth patterns include trabecular, insular, anastomosing cords, and/or diffuse densely packed cellular infiltrate; neural-type rosettes may be identified.
- Most tumors are composed of intermediate sized cells with rather uniform (monomorphic appearing) round nuclei with delicate, dispersed (stippled or dusty) chromatin pattern creating a pale “washed out” appearance with scanty, poorly defined cytoplasm:
 - Small nucleoli may be seen.
 - Nuclear molding may be present but is not prominent.
- Less often the tumor is composed of predominantly diffusely infiltrating small tumor cells.
- Numerous mitotic figures and necrosis (individual cell and confluent foci) can be seen; crush artifact is usually absent.
- Foci of squamous differentiation, horn pearl formation, and pseudoglandular structures may be seen.
- Invasive growth including lymph-vascular space invasion and invasion into connective tissue structures (muscle, fascia, nerves) may be present.
- A sparse to dense associated mixed inflammatory cell infiltrate composed of mature lymphocytes and plasma cells may be seen in the surrounding connective tissue.
- Histochemistry:
 - Argyrophilia may be seen.
- Immunohistochemistry:
 - Keratin (AE1/AE3, CAM 5.2, OSCAR) positive with a punctate (stippled or dotlike pattern) paranuclear staining
 - Cytokeratin 20 (CK20) positive
 - EMA positive
 - Neuroendocrine markers including synaptophysin, chromogranin (less than 50% of cases), CD56, NSE positive
 - Merkel cell polyoma virus (MCPyV) positive (nuclear staining)

- Increased proliferation rate of greater than 90% seen by Ki67 staining.
- Calcitonin and CD117 (c-kit) may be positive.
- S100 protein, melanoma markers (HMB45, melan A, tyrosinase, MART-1, MITF, SOX10), CD45 (leukocyte common antigen), TTF-1, vimentin, desmin, actin, and CD99 typically negative
- Electron microscopy:
 - Neurosecretory granules; perinuclear whorls of intermediate filaments

Differential Diagnosis

- Basal cell carcinoma:
 - Immunohistochemical findings allow for differentiation.
- Hematolymphoid malignancies
 - Immunohistochemical findings allow for differentiation.
- Metastatic small cell neuroendocrine carcinoma (e.g., pulmonary origin):
 - In contrast to Merkel cell carcinoma, small cell carcinomas of pulmonary origin are CK20 negative; staining for other keratins and neuroendocrine cell markers is essentially the same.

Treatment and Prognosis

- Wide local surgical excision is the preferred treatment, with lymph node dissection when palpable nodes are present.
- Radiotherapy may be beneficial in conjunction with surgery.
- Aggressive tumor that has a tendency to recur in approximately one-third of cases.
- Sentinel lymph node positivity is helpful in predicting the risk of recurrence or metastasis in patients with MCC.
- MCC of the head and neck is often associated with nodal metastasis:
 - Regional lymph node metastases commonly occur (approximately 50%).
 - Distant (visceral) metastasis occurs in approximately 15% and most often spreads to lung, liver, bone, and brain:
- 5-year survival rates of 30% to 64% have been reported.
- Overall mortality rate is approximately 11%.

CERUMINAL GLAND ADENOCARCINOMA

(Figs. 24-37 and 24-38)

Definition: Malignant neoplasm of cerumen-secreting modified apocrine glands (ceruminal glands) located in the external auditory canal.

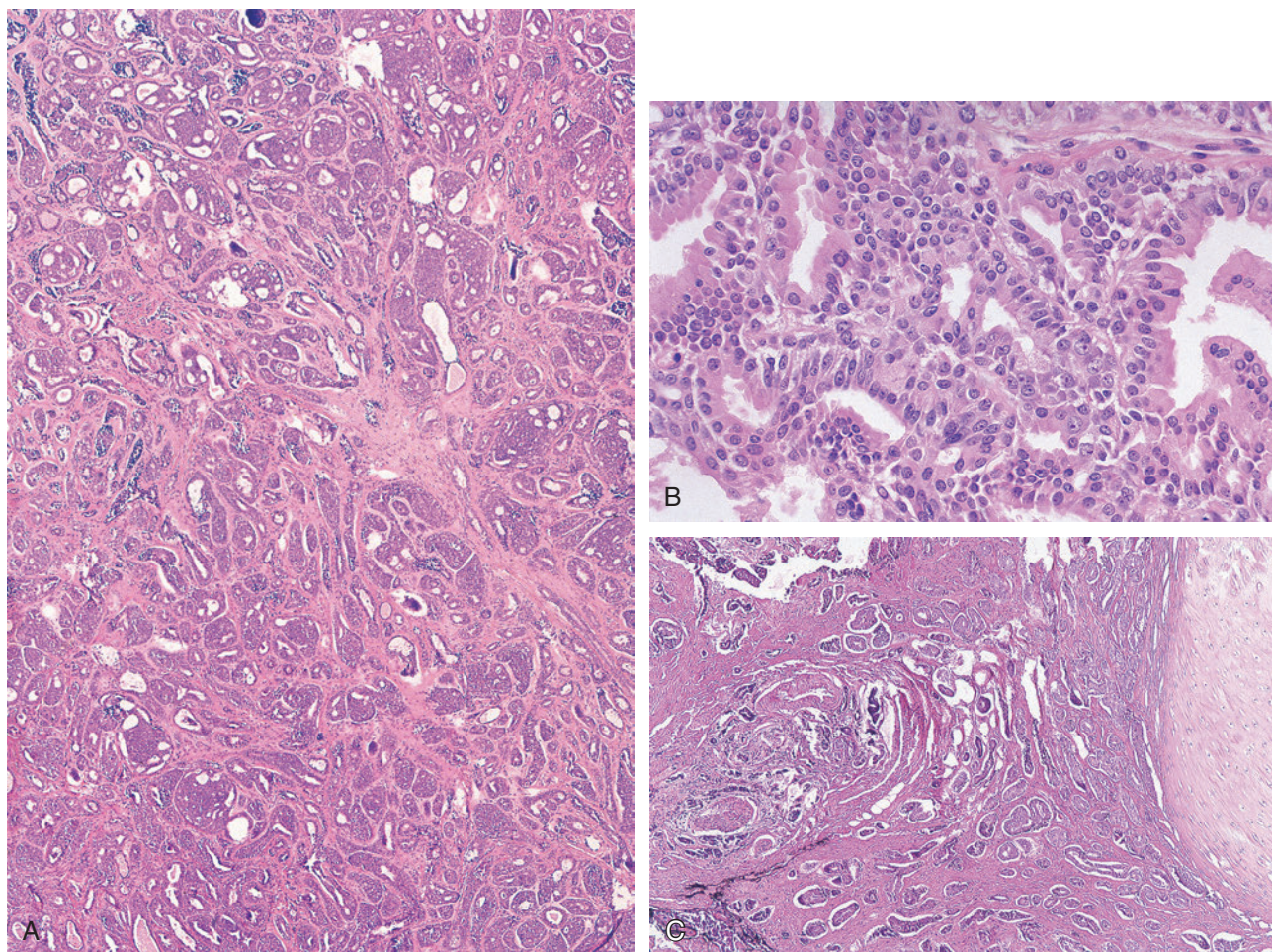


Fig. 24-37. Ceruminal gland adenocarcinoma.

A, Ceruminal gland adenocarcinoma that at low magnification appears infiltrative with glandular, cribriform, and solid growth patterns. **B**, In contrast to ceruminal adenomas, the adenocarcinomas display loss of nuclear polarity, loss of the glandular double cell layer with identification of only the inner or luminal epithelial cell, cellular pleomorphism, anaplasia, and mitoses; the decapitation-type secretion (apical “snouts”) is focally seen but may not be apparent. **C**, In addition to the other features, ceruminal gland adenocarcinomas may demonstrate perineural invasion (*lower left*), as well as invasion of the auricular elastic cartilage (*right*).

Clinical

- More common in men than in women; occurs over a wide age range but is most frequently seen in the fifth to sixth decades of life
- In addition and in contrast to the symptoms of ceruminal gland adenomas, which include a mass in the external auditory canal, hearing difficulty, and otic discharge, ceruminal gland adenocarcinomas are associated with pain as a more characteristic feature.

Pathology

Gross

- Ulcerated, polypoid, or rounded mass ranging in size from 1 to 4 cm in diameter

Histology

- Well-differentiated ceruminal gland adenocarcinomas may appear similar to their benign counterparts and are differentiated only on the basis of invasive growth.
- Features of adenocarcinoma that differ from the adenomas include:
 - Loss of the glandular double cell layer with identification of only the inner or luminal epithelial cell
 - Cells vary in appearance from those with minimal pleomorphism and atypia to cells with pleomorphism, nuclear anaplasia, and mitoses; the decapitation-type secretion (apical “snouts”) may or may not be apparent.
 - Tissue invasion and destruction

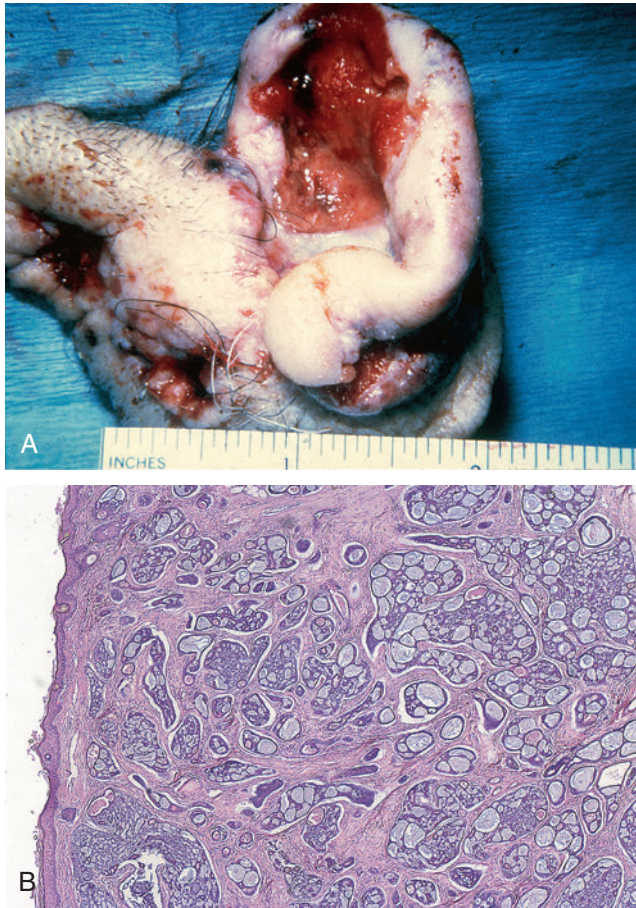


Fig. 24-38. Ceruminal gland adenoid cystic carcinoma.

A, Part of a tympanomastoidectomy showing extensive involvement of the external auditory canal by a malignant neoplasm that proved to be an adenoid cystic carcinoma of ceruminal gland origin. **B**, The histology of the resection specimen included a diffusely infiltrative adenocarcinoma of the subcutaneous tissues of the external auditory canal showing classic cribriform growth pattern of adenoid cystic carcinoma. Although not depicted here, the cell types included a predominant myoepithelial (abluminal) cell proliferation with limited but identifiable admixed true glandular (luminal) cells that typify adenoid cystic carcinoma.

- At the other end of the spectrum, poorly differentiated ceruminal adenocarcinomas occur and are recognized on the basis of their localization in the external auditory canal.
- Immunohistochemistry:
 - In cases retaining dual cell population:
 - Luminal cells are CK7 positive.
 - Basal cells are p63, S100 protein, and CK5/6 positive.
- In addition to the more “conventional” type of ceruminal gland adenocarcinomas, other types of ceruminal gland malignant tumors include:

- Adenoid cystic carcinoma (ACC) and mucoepidermoid carcinoma (MEC) of ceruminal gland origin
- These tumors are morphologically identical to their salivary gland counterparts (see Section 6).
- Ceruminal gland ACC and MEC are extremely uncommon and may in fact represent a primary parotid gland tumor presenting in the external auditory canal.

Differential Diagnosis

- Ceruminal gland adenoma
- Given the proximity of the parotid gland to the external auditory canal, the differential diagnosis for ceruminal gland adenoid cystic carcinoma and mucoepidermoid carcinoma includes direct extension of similar tumors of primary parotid origin:
 - Parotid gland adenoid cystic carcinoma and mucoepidermoid carcinoma should be excluded prior to diagnosing such tumors as being of primary ceruminal gland origin.

Treatment and Prognosis

- En bloc surgical resection is the preferred treatment:
 - Middle ear or temporal bone involvement necessitates more radical surgery.
- Supplemental radiotherapy is recommended.
- Recurrence primarily relates to inadequate surgical excision.
- 5-year overall survival of approximately 50%
- Metastases are rare and include regional lymph nodes and the lung.
- For ceruminal gland adenoid cystic carcinoma and mucoepidermoid carcinoma, wide surgical resection is the recommended treatment with or without supplemental radiotherapy.
- Prognosis for ceruminal gland adenoid cystic carcinoma generally is similar to their salivary gland counterparts, including relatively good short-term (i.e., 5-year) survival but poor long-term (i.e., 10- to 20-year) survival:
 - Metastasis from ceruminal gland adenoid cystic carcinoma may include lungs, kidney, liver, and brain.

ATYPICAL FIBROXANTHOMA (AFX) (Fig. 24-39)

Definition: Pleomorphic predominantly dermal mesenchymal tumor found on actinic-damaged cutaneous sites of older age patients.

Synonyms: Undifferentiated pleomorphic sarcoma of skin; superficial (low-grade) malignant fibrous histiocytoma; pseudosarcoma of skin; pseudosarcomatous dermatofibroma

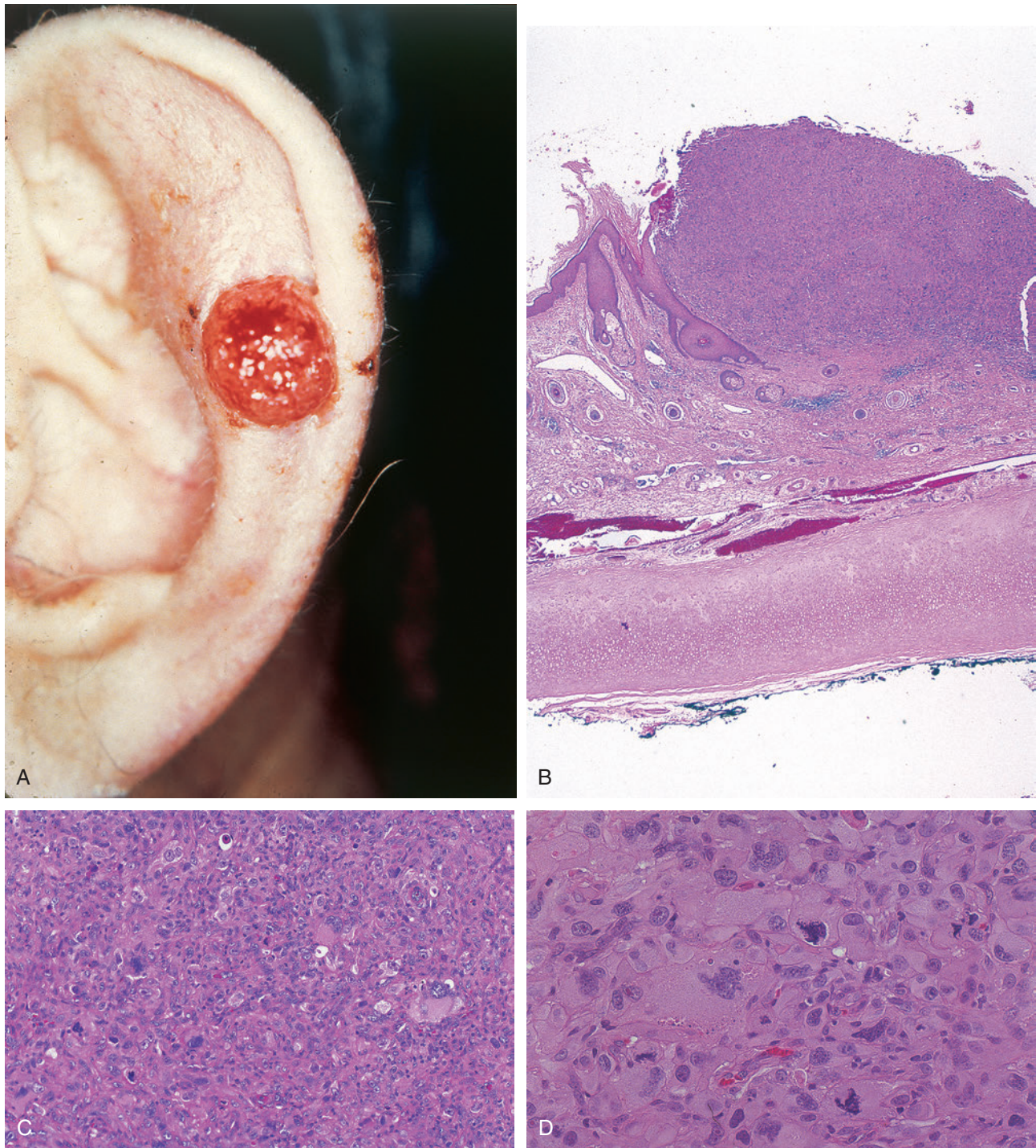


Fig. 24-39. Atypical fibroxanthoma.

A, Atypical fibroxanthoma (AFX) appears as a solitary, delineated nodular or polypoid mass on the external ear. **B**, The lesion is superficial with surface ulceration and limited depth of invasion and appears as unencapsulated but circumscribed. **C**, The neoplasm is characterized by the presence of a diffuse cellular infiltrate composed of strikingly bizarre and pleomorphic cells with spindle-shaped to oval hyperchromatic nuclei often with multiple nuclei, and prominent foamy cytoplasm (xanthomatous cells) and numerous mitoses including atypical forms. **D**, Higher magnification shows the xanthomatous cells with pleomorphic and hyperchromatic nuclei, large eosinophilic nucleoli, prominent foamy cytoplasm, and the presence of atypical mitotic figures.

Clinical

- No gender predilection; elderly patients
- Commonly involving the head and neck including ears, cheeks, and nose
- Prior consideration of a second, less common form affecting younger patients involving superficial sites on the limbs and trunk now considered to be examples of atypical fibrous histiocytoma
- Present as an asymptomatic solitary growth on the affected body site:
 - Bleeding, pruritus, and pain may occur.
- Etiology related to solar and therapeutic radiation supported by:
 - Common occurrence on sun-damaged skin
 - Frequent association with other actinic lesions, including basal cell carcinoma and squamous cell carcinoma
 - Identification of ultraviolet related mutations (p53) and photoproducts
 - Incidence of previous radiation varies from less than 5% to more than 50%.
 - Latent period of approximately 10 years between previous radiation and development of AFX in keeping with radiation-induced tumors.
- May occur in immunosuppressed patients in association with:
 - HIV infection
 - Transplant patients on immunosuppressive agents

Pathology

Gross

- Solitary, firm nodule frequently associated with ulceration and measuring from 1 to 2 cm in diameter

Histology

- Unencapsulated but generally circumscribed neoplasm arising in the dermis and characterized by a bizarre cellular component arranged in a vague fascicular pattern; a storiform growth pattern is infrequently seen.
- Junctional activity between the neoplasm and the overlying epidermis is absent:
 - Grenz zone of uninvolved dermis present
 - Surface atrophy or ulceration may be present.
- Cells are strikingly pleomorphic and bizarre, varying from spindle-shaped, plump, or rounded with hyperchromatic nuclei often with multiple nuclei and large acidophilic nucleoli.
 - Larger cells may have foamy cytoplasm that is reminiscent of lipid-rich histiocytic cells.
 - In some cases, a pleomorphic component may be absent.
- Multiple, atypical, multipolar mitotic figures are present.

- Necrosis is rarely seen.
- Secondary findings may include:
 - Mild chronic inflammatory cell infiltrate
 - Prominent stromal myxoid change
 - Hemorrhage and hemosiderin deposition
 - Osteoclast-like giant cells
 - Osteoid deposition
 - Chondroid material may rarely be present.
- Multinucleated, osteoclastic-like giant cells, as well as osteoid may rarely be present:
 - Osteoclastic-like multinucleated giant cells are intimately associated with atypical, large pleomorphic, and multinucleated cells.
 - Immunostaining of the multinucleated cells shows variable CD68 and actin (HHF35 and smooth muscle actin).
 - Osteoclast-like multinucleated giant cells show variable expression for receptor activator of factor- κ B (RANK), a tumor necrosis factor receptor family member normally expressed in plasma membrane of osteoclasts and their precursors, and indicate greater support that these cells are neoplastic rather than reactive, representing transformation and/or fusion of recruited non-neoplastic histiocytes.
- Superficial areas adjacent to the tumor show solar elastosis and vascular proliferation:
 - Prominent stromal sclerosis may be present.
 - Keloid-type collagen may be present.
- Histochemistry:
 - Intracytoplasmic diastase-resistant, PAS-positive granular material may be seen.
- Immunohistochemistry:
 - Variable staining for CD68 (KP1), muscle-specific actin, smooth muscle actin
 - Strong CD10 reactivity:
 - Lacks specificity
 - CD99, CD163, and CD117 may be present.
 - Absent staining for cytokeratins and S100 protein:
 - Rare cases are cytokeratin positive but typically negative for CK5/6 and p63, although focal p63 (and EMA) staining may be present.
 - Dendritic cells in association with the neoplasm will be S100 protein positive.
 - Negative for desmin and melanoma markers (e.g., HMB-45, Melan-A, tyrosinase, MART-1, MITE, SOX10):
 - Aberrant HMB45 and MART-1 (melanoma antigen recognized by T cells-1) staining reported limited to the large, multinucleated cells with vacuolated cytoplasm.
 - Absence of endothelial markers including CD31, factor VIII-related antigen, CD34, ERG1, Fli1:
 - Histiocytes may be CD31 positive.

- Electron microscopy:
 - Ultrastructural variability with evidence of fibrohistiocytic and myofibroblastic features and to a lesser extent features of Langerhans cells
 - Absence of features indicative of epithelial differentiation (e.g., prominent intercellular bridges, tonofibrils) or melanocytic differentiation (e.g., premelanosome, melanosomes)
- Cytogenetics and molecular biology:
 - Deletions on chromosomes 9p and 13q;
 - Similar to genetic alterations in undifferentiated high-grade pleomorphic sarcoma suggesting common pathogenetic pathway
 - Statistically significant differences of genetic alterations between AFX and undifferentiated high-grade pleomorphic sarcoma concerning deletions on 1q, 3p, 5q, 11p, 11q; gains on 7q and 12q; and high-level gains on 5p and 11q;
 - Genetic differences may contribute to the different biological behavior of these two tumors.
- Unusual variants of AFX include:
 - Clear cell variant characterized by:
 - Sheets of large cells with foamy cytoplasm and hyperchromatic, polyploid nuclei with frequent mitoses, including atypical mitoses
 - Clear cells express CD68 but not CD3, CD20, CD34, S100 protein, muscle-specific actin, factor XIIIa, melan-A, carcinoembryonic antigen, or cytokeratin.
 - Differentiation from balloon cell melanoma, sebaceous carcinoma, pleomorphic liposarcoma, chordoma, parachordoma, tricholemmal carcinoma, and clear cell squamous cell carcinoma predicated on differentiating immunohistochemical staining.
 - Granular cell variant
 - Spindle cell, nonpleomorphic variant:
 - Frequently immunoreactive for SMA and calponin
- Uncommonly, pigmentation may occur:
 - These lesions have been termed pigmented atypical fibroxanthoma.
 - Pigmented atypical fibroxanthoma can be easily mistaken for malignant melanoma clinically and histopathologically.
 - Pigmentation is felt to represent hemorrhage with neoplastic cells ingesting and degrading erythrocytes following intratumoral hemorrhage and to accumulate hemosiderin in their cytoplasm.
 - Pigment stains for iron
- Pseudoangiomatous features and aberrant expression of CD31 and Fli1 may be present, creating potential diagnostic difficulties with cutaneous angiosarcoma:
 - Staining for CD34, ERG is negative.
 - S100, HMB-45, desmin, p63, and cytokeratins negative.

Differential Diagnosis

NOTE: The diagnosis of atypical fibroxanthoma is one of exclusion.

- Spindle cell squamous carcinoma (SCSC):
 - Presence of a differentiated squamous cell component ranging from dysplasia to carcinoma in situ to invasive carcinoma in conjunction with a malignant spindle and/or epithelioid cell component is diagnostic for SCSC.
 - Immunoreactivity for epithelial/squamous cell markers (keratins, p63) differentiates spindle cell squamous carcinoma from AFX.
- Malignant melanoma:
 - Nested growth pattern, junctional changes, and melanin pigment are features of malignant melanoma and not AFX.
 - Presence of S100 protein and melanocytic markers allows for differentiation.
- Dermatofibrosarcoma protuberans (DFSP):
 - Contrasting histologic features should allow for differentiation.
 - DFSPs are CD34 positive.
- Angiosarcoma:
 - Presence of endothelial-related markers (CD31, Factor VIII-related antigen, CD34, ERG, Fli1)
- Leiomyosarcoma:
 - Immunohistochemical stains should allow for separating AFX from leiomyosarcoma, the latter tumor showing reactivity for myogenic markers, including actins (muscle specific and smooth muscle actin) and desmin.
- Undifferentiated pleomorphic sarcoma (UPS):
 - If a tumor has the histologic features of AFX but is large (greater than 2 cm in diameter), extensively involves the subcutis, is deeply infiltrative (penetrates fascia and muscle), shows necrosis or vascular invasion, then it should be considered as a UPS.
 - This distinction is important as therapy for UPS includes surgery with supplemental irradiation.
 - UPS has a propensity for recurrences and metastases and a poor prognosis.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment and is curative.
- Prognosis is excellent.
- Local recurrence is uncommon (7%) and is related to incomplete excision.
- Recurrent tumors may present as a large mass in the deep soft tissue and these neoplasms should be considered and treated as a bona fide UPS.
- AFX may metastasize but these metastasizing AFX may in fact represent (superficial) UPS.

DERMATOFIBROSARCOMA PROTUBERANS (DFSP) (Fig. 24-40)

Definition: Nodular cutaneous fibrohistiocytic tumor of intermediate malignancy characterized by storiform pattern with a tendency for local recurrence but infrequently metastasizes.

Synonyms: Progressive and recurrent dermatofibroma

Clinical

- More common in men than in women; typically present in early or middle adults:
 - May occur in pediatric ages
 - Most frequently occur on the trunk and upper and lower extremities (approximately 85% of cases) but
- approximately 15% occur in cutaneous sites of the head and neck.
 - Clinical presentation is typically that of a slow but persistent growth over extended periods of time (months to years).
 - Clinical appearance of the lesion is usually that of a firm, nodular, or plaque-like cutaneous lesion often with surrounding red to blue discoloration:
 - Less commonly, multiple small subcutaneous nodules are present.
 - Rarely, may appear an area of atrophy (atrophic variant of DFSP)
 - Nodular or plaque-like lesion remains stable for a period of time and then may rapidly develop into one or more nodules, creating the “protuberant” clinical appearance:
 - May reach large sizes especially if neglected

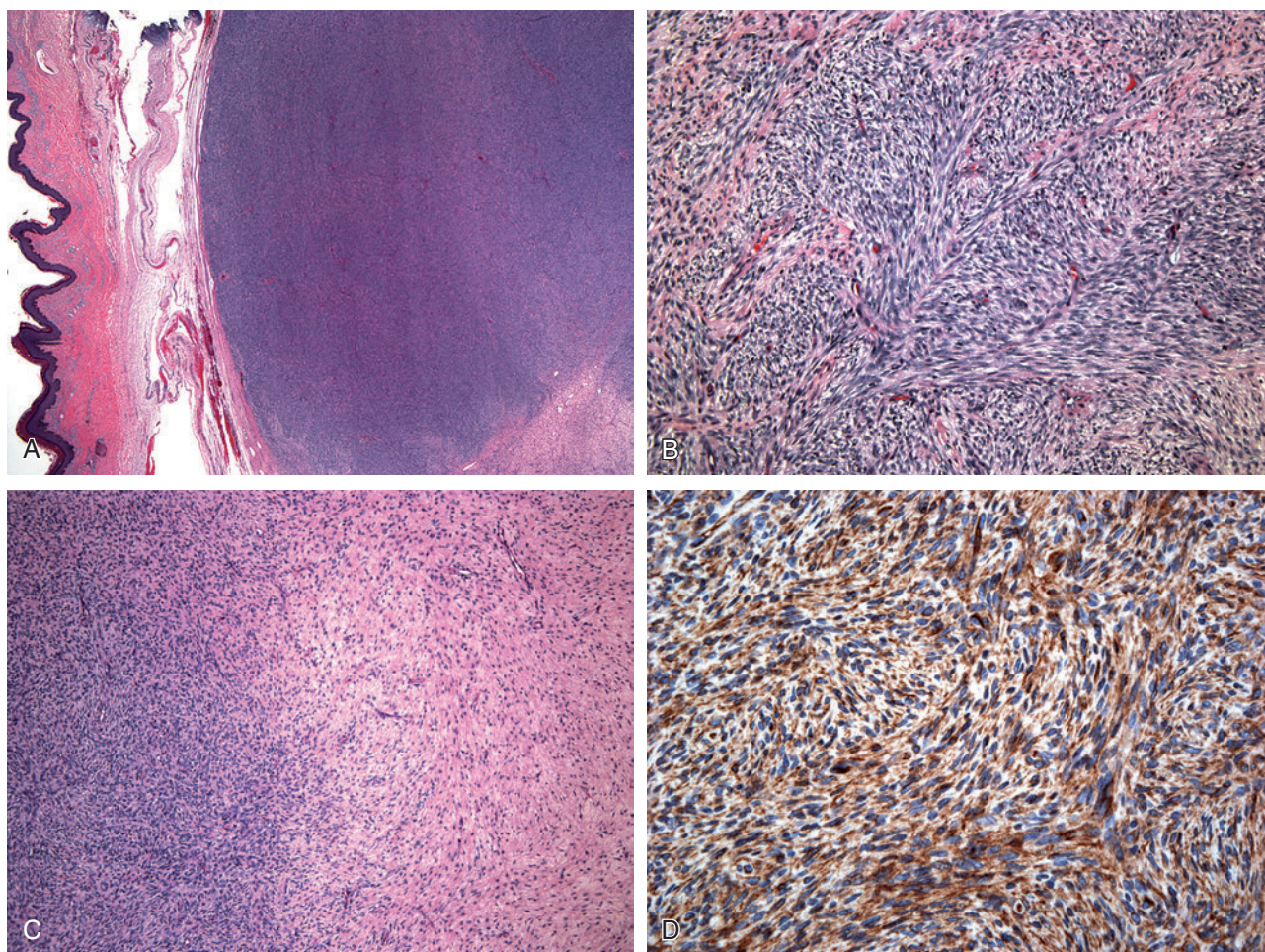


Fig. 24-40. Dermatofibrosarcoma protuberans.

A, Dermatofibrosarcoma protuberans characterized by the presence of a hypercellular subcutaneous proliferation separated from the dermis; unlike the epithelium in dermatofibroma, the overlying epithelium in DFSP usually is not hyperplastic. **B,** Higher magnification shows characteristic storiform growth of relatively uniform-appearing spindle-shaped cells and presence of a rather inconspicuous vascular pattern. **C,** DFSP may show hypocellular and myxoid foci seen here adjacent to a more cellular area. **D,** Diffuse CD34 reactivity.

- No specific link to known etiologic factors, although DFSP has occurred in association with prior trauma, acrodermatitis enteropathica, BCG vaccination site, exposure to arsenic, rapid enlargement during pregnancy, and acanthosis nigricans.

Pathology

Gross

- Solitary, gray-white, circumscribed nodular subcutaneous mass varying in size but with an average size of approximately 5 cm; may achieve extremely large sizes
- Recurrent lesions are often characterized by the presence of multiple discrete nodules.
- Overlying skin may be ulcerated.
- Extension into adjacent structures such as skeletal muscle is uncommon; also, rare tumors may be limited to the subcutis without dermal involvement.
- Degenerative changes, including cyst formation, hemorrhage, and myxoid change may be present but necrosis is rare.

Histology

- Cellular neoplasm diffusely infiltrating the dermis and subcutis:
 - May reach epidermis or not involve the dermis separated by an uninvolved zone of dermis
 - Overlying epidermis typically lacks hyperplastic changes as seen in cutaneous fibrous histiocytomas (dermatofibromas).
 - In its depth the tumor spreads along connective tissue septa or infiltrates adipose tissue in an interdigitating pattern, creating a lace-like appearance.
- Main portion of the tumor shows the presence of a cellular proliferation of slender spindle-shaped cells arranged in a characteristic storiform growth pattern and inconspicuous vascular pattern:
 - Spindle-shaped cells are relatively uniform (monotonous), with little nuclear pleomorphism, low to moderate mitotic activity (fewer than 5 mitoses per 10 high-power fields), and absence of necrosis.
- Multinucleated giant cells and xanthoma cells are uncommon but may be present.
- An associated inflammatory cell infiltrate and myxoid change may be seen:
 - Myxoid areas may be pronounced and when prominent the storiform pattern becomes less distinct with a more prominent vascular pattern resembling features of a myxoid liposarcoma.
- Peripheral portions of the tumor may appear deceptively bland as a result of attenuation of the neoplastic cells at the advancing edge of the tumor;

superficially, the neoplastic cells may or may not reach the epidermis.

- An unusual feature that can rarely be seen is the presence of a nonneoplastic myoid nodule or ball centered around a vascular structure; this finding may represent an unusual vascular response.
- Histology of metastatic foci is similar to that of the primary tumor.
- Immunohistochemical findings include:
 - Consistent CD34 and vimentin positive
 - Muscle-specific actin positive in approximately 80%
 - Factor XIIIa, cytokeratin, S100 protein, HMB45, melan-A, and desmin negative
- Ultrastructure:
 - Elaborate cell processes, desmosomes, and incomplete basal lamina
- Cytogenetics and molecular biology:
 - Supernumerary ring chromosomes consisting of low-level amplification of sequences from chromosomes 17 and 22, and 8 or linear translocation:
 - Ring chromosomes in adult cases
 - Linear translocation derivative in pediatric cases
 - Breakpoints from the rings and translocations fuse exon 2 of the platelet-derived growth factor β -chain (PDGF- β) gene to exons on collagen type 1 α 1 gene (*COL1A1*), resulting in fusion transcript *COL1A1-PDGF- β* consistently identified in DFSP
 - Approximately 8% of DFSP are fusion negative.

Differential Diagnosis

- Benign fibrous histiocytoma (dermatofibroma), which in contrast to DFSP:
 - Commonly occurs on extremities
 - Less distinct storiform growth
 - Presence of plump spindle cells often admixed with inflammatory cells, giant cells, and siderophages
 - Typically CD34 negative
 - Typically lacks subcutaneous extension
- Undifferentiated pleomorphic sarcoma (UPS), which in contrast to DFSP shows:
 - Greater nuclear pleomorphism, mitotic activity, and necrosis
 - Deeper location
 - More rapid growth
- Diffuse neurofibroma, which in contrast to DFSP:
 - Lacks highly cellular areas and increased mitotic activity
 - May show features of neural differentiation (e.g., tactoid structures)
 - Show S100 protein reactivity

- Myxoid liposarcoma, which in contrast to DFSP:
 - Are CD34 negative
 - Include presence of lipoblasts
 - Are typically present in deeper locations

Treatment and Prognosis

- Wide surgical excision is the preferred treatment to include at least 2- to 3-cm margins.
- In the head and neck, approximately 50% to 75% recur as compared with a recurrence rate of 20% to 55% from all other sites:
 - Adequate initial surgical resection essential for minimizing recurrences
 - Risk of recurrence correlates with extent of wide excision:
 - Excision margin of 3 cm or more recurrence rate of 20%
 - Excision margin of 2 cm or less recurrence rate of 41%
 - Recurrences usually develop within 3 years of initial surgery but approximately one-third of patients may develop recurrence after 5 years.
- Mohs surgery advocated in treatment of DFSP:
 - Offers potential to achieve clear margins with minimal excision of normal tissue
 - Local recurrence rates following Mohs reported to be less than 10%
- Imatinib is a potent and specific inhibitor of several protein-tyrosine kinases, including the PDGFRs:
 - Neo-adjuvant use of imatinib in DFSP is efficacious and well tolerated.
 - Imatinib may provide an alternative for the treatment of unresectable or partially resectable tumors, thereby possibly improving the effectiveness of surgery.
- Radiotherapy recommended for:
 - Large, unresectable tumors
 - Postoperatively in margin-positive cases
- Conventional DFSP (in the absence of sarcomatous transformation) infrequently metastasizes:
 - May be a late event in the disease course such that long-term follow-up may reveal increased metastatic rates
 - Approximately 75% of metastases occur via hematogenous spread including to the lungs:
 - Due to low-grade behavior, resection of isolated lung metastases is advocated.
 - Other sites of metastatic spread include brain and bones.
 - Approximately 25% have locoregional lymph node metastasis; as such regional node dissection is generally not indicated.
 - Metastasis usually occurs in the setting of tumor recurrence.
- Sarcoma arising in DFSP:
 - Referred to as fibrosarcomatous variant of DFSP
 - Characterized by the presence of foci of conventional fibrosarcoma within a DFSP
 - Shares clinical features of DFSP
 - Histologically include sarcomatous foci in at least 5% to 10% of the tumor characterized by fascicular growth pattern, high nuclear grade features, increased mitotic activity (more than 7 mitoses per 10 high-power fields), and decreased CD34 immunoreactivity
 - Increased proliferation rate as determined by Ki67 (MIB1) staining
 - Increased p53 immunoreactivity
 - Aggressive biologic behavior as might be suggested by presence of sarcomatous component is debatable:
 - With wide local excision including clear margins, local recurrence rates similar to DFSP with no metastasis

Additional Facts

- Giant cell fibroblastoma is closely related to DFSP and might represent the juvenile form of DFSP based on:
 - Shared clinical and histologic findings with DFSP
 - Presence of CD34 reactivity
 - Rearrangement of chromosomes 17 and 22
- Bednar tumors also referred to as pigmented dermatofibrosarcoma protuberans are:
 - Tumors that resemble DFSP with the additional presence of melanin
 - Uncommon tumors
 - Share clinical, pathologic (gross, microscopic), and genetic features to DFSP
 - Overall behavior considered similar to DFSP
 - May display fibrosarcomatous areas
 - Rare examples of metastatic tumor to the lungs
- Perineurial cell differentiation in DFSP has been suggested based on:
 - Expression of epithelial membrane antigen (EMA)
 - Ultrastructural findings of perineurial cell features, such as thin long bipolar cytoplasmic processes, pinocytotic vesicles, fragments of external lamina and/or external lamina-like material, attachment plaques, and desmosome-like junctions may be present.
 - However, the presence of claudin-1 in perineuromas and absence of claudin-1 in DFSP weigh against perineurial cell differentiation in DFSP.

MALIGNANT NEOPLASMS OF THE MIDDLE EAR (Fig. 24-41)

MIDDLE EAR SQUAMOUS CELL CARCINOMA (ME-SCC)

Definition: Malignant epithelial tumor of epidermoid cells arising as a primary neoplasm from the middle ear mucosal epithelium.

Clinical

- No gender predilection; most commonly seen in the sixth to seventh decades of life
- Majority of patients have a long history of chronic otitis media usually greater than 20 years in duration.
- Development of a middle ear squamous cell carcinoma should be suspected in patients with a long

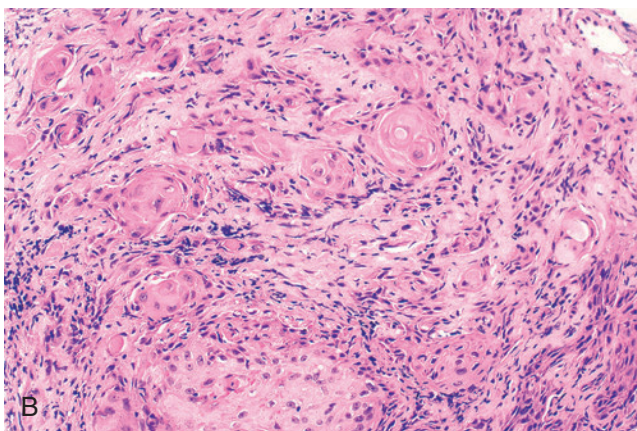
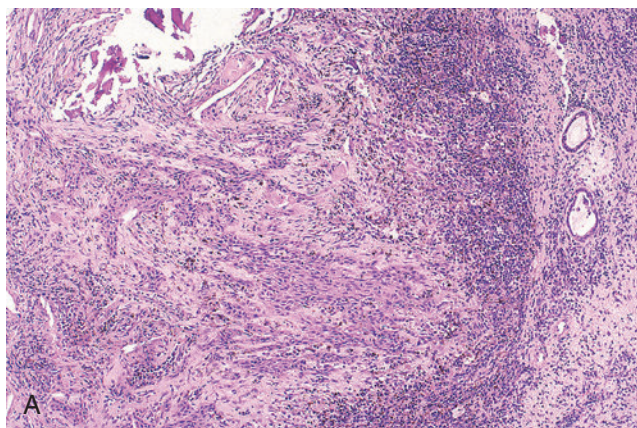


Fig. 24-41. Middle ear squamous cell carcinoma.

A, Middle ear squamous cell carcinoma showing an infiltrative neoplasm occurring in the background of chronic otitis media, the latter including a chronic inflammatory cell infiltrate, glandular metaplasia (*extreme right*), and tympanosclerosis (*upper left*). **B,** At higher magnification the squamous cell carcinoma is keratinizing and well differentiated.

history of chronic otitis media with the following clinical manifestations:

- Sudden onset of pain out of proportion to the clinical extent of disease
- Onset or increase of otorrhea, which is often hemorrhagic
- Lack of clinical resolution following therapeutic doses of antibiotics
- Early symptoms include pain with radiation to the scalp and face and hearing impairment; late symptoms include facial palsies and vertigo.
- Etiology linked:
 - To radiation treatment for intracranial neoplasms and, although no longer used, radiotherapy for middle ear inflammatory conditions
 - The high-risk human papillomavirus types 16 and 18 identified in middle ear squamous cell carcinomas raises HPV as a possible etiologic factor in the development of middle ear squamous cell carcinoma, although a direct cause and effect has not been established.
- Although concomitant cholesteatomas can be seen in up to 25% of cases, there is no correlation between cholesteatomas and the development of a middle ear squamous cell carcinoma.

Pathology

Histology

- Varies from well to poorly differentiated squamous cell carcinoma with morphologic features identical to squamous cell carcinomas of other sites.
- Carcinoma may or may not be seen arising from the middle ear mucosa.
- Often evidence of chronic otitis media is seen in association with the infiltrating carcinoma as demonstrated by the presence of a chronic inflammatory cell infiltrate, calcifications (tympanosclerosis), and glandular metaplasia.
- Desmoplastic stromal response is often present.
- Evidence of a cholesteatoma may be present.
- Subtypes such as undifferentiated (lymphoepithelial-like) carcinoma of the middle ear identified: (Fig. 24-42)
 - Histologically similar to nasopharyngeal counterpart
 - In situ hybridization for Epstein-Barr encoded RNA (EBER) positive

Differential Diagnosis

- Cholesteatoma
 - Cholesteatoma is characterized by a bland keratinizing squamous epithelium lacking cytomorphic atypia or invasive growth.

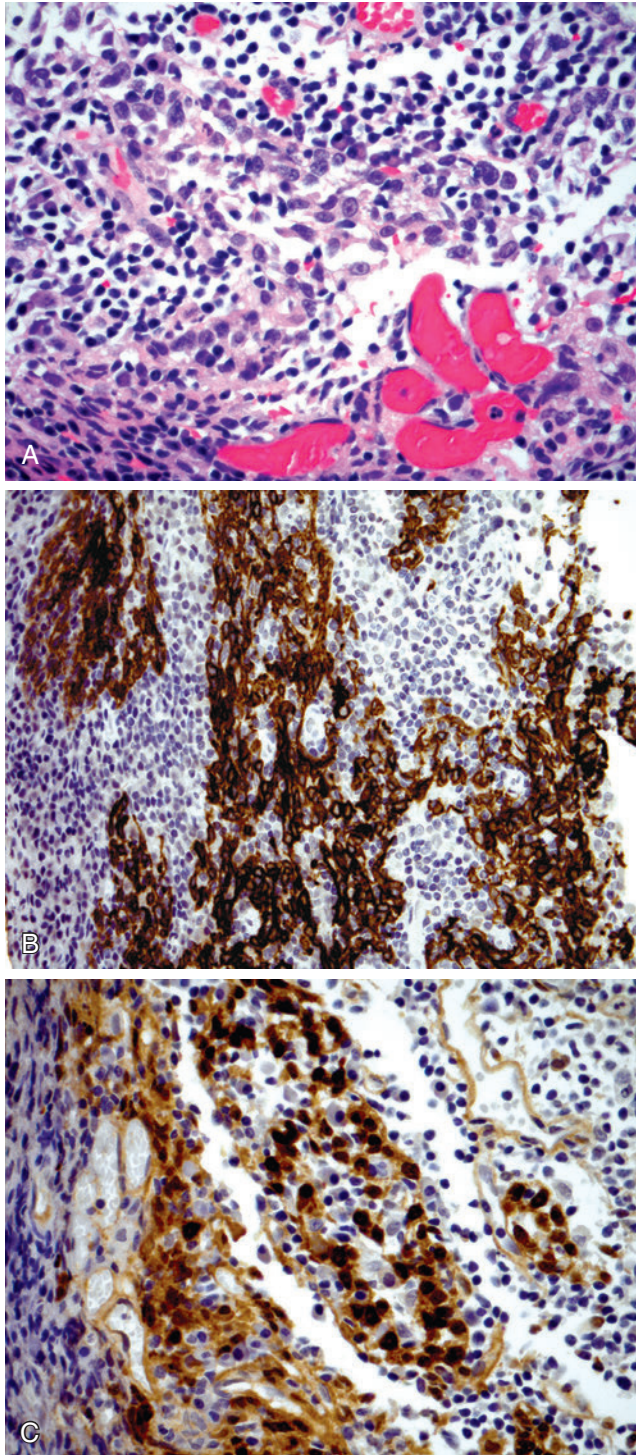


Fig. 24-42.

A, Lymphoepithelial-like carcinoma of the middle ear characterized by scattered epithelioid cells with enlarged nuclei surrounded by mixed lymphoplasmacytic cell infiltrate; **B**, the lesional cells are immunoreactive for cytokeratin (CAM5.2) and **(C)** in situ hybridization for Epstein-Barr–encoded RNA (EBER). The patient presented with conductive hearing loss with the identification of a mass wholly confined to the middle ear space without extension from a primary nasopharyngeal neoplasm.

- Metastatic squamous cell carcinoma from a distant site or extension from a squamous carcinoma from an adjacent site (external ear, nasopharynx, parotid gland, or skin):
 - Clinical evaluation to exclude one of these possibilities is indicated prior to rendering a diagnosis of a primary middle ear squamous cell carcinoma.

Treatment and Prognosis

- Radical surgery (i.e., radical mastoidectomy, temporal bone resection) with postoperative radiotherapy is the treatment of choice.
- Combined radical surgery and radiotherapy are the preferred treatment modalities, radical radiotherapy (55 Gy in 20 daily fractions) alone achieves comparable results in terms of local control and cancer-specific survival and is a viable option in the treatment of ME-SCC.
- In advanced disease, chemotherapy may be of benefit.
- Prognosis is poor with 5- and 10-year survival rates of 39% and 21%, respectively.
- Reported 5-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) of 77%, 79%, and 52%, respectively
- Upfront complete resection (i.e., lateral temporal bone resection), when combined with postoperative radiation therapy, may improve survival and decrease recurrence.
- Neoplasms often present in advanced stages with extensive bone destruction and spread to the eustachian tube, external auditory canal, mastoid, jugular fossa, internal auditory canal, and brain.
- Metastases may occur but are considered uncommon.
- Bony capsule of the labyrinth is resistant to the spread of tumor.

MIDDLE EAR ADENOCARCINOMA (Fig. 24-43)

Definition: Malignant glandular neoplasm arising from the middle ear mucosa.

Clinical

- Rare neoplasm:
 - Metastases to the middle ear from adenocarcinomas of other (distant) sites must be considered.
- No gender predilection; occurs over a wide age range between the second to sixth decades of life.
- Symptoms are typically present for many years and include progressive hearing loss and a unilateral draining ear; pain and vestibular manifestations are uncommon.

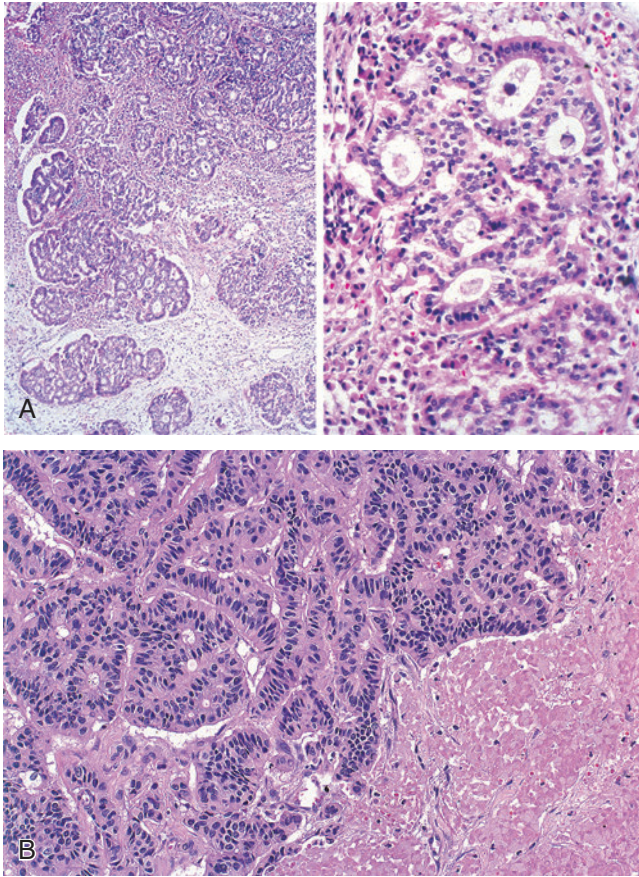


Fig. 24-43. Middle ear adenocarcinoma.

A, (left) Middle ear neoplasm that is gland forming and infiltrative that at higher magnification **(right)**, has a complex growth, including a cribriform or back-to-back pattern with cellular pleomorphism. **B,** Another example showing complex growth, including a cribriform or back-to-back pattern with cellular pleomorphism, mitotic figures, and confluent area of tumor necrosis **(lower right)**.

- Otoloscopic examination in the majority of cases will identify an intact tympanic membrane with tumor confined to the middle ear space with possible extension to the mastoid; occasionally, and similar to the middle ear adenoma, the adenocarcinoma will perforate through the tympanic membrane with extension into and presentation as an external auditory canal mass.
- Etiology is unknown:
 - No association between chronic otitis media and the development of middle ear adenocarcinoma

Pathology

Gross

- Variation in appearance from gray-white to red-brown, rubbery to firm mass to spongy and cystic appearing

- May attain large sizes filling the middle ear space and encasing the ossicles

Histology

- Unencapsulated lesion with diffuse proliferation of glands showing complex gland-in-gland (cribriform) growth composed of cells with marked nuclear pleomorphism and increased mitotic activity:
 - Mucocytes are not identified.
- Extensive infiltration of surrounding soft tissue structures including perineural and perivascular invasion and invasion of bone is usually identified.
- Papillary and cystic variant (papillary cystadenocarcinoma) lined by cells with hyperchromatic nuclei and vacuolated cytoplasm containing luminal eosinophilic secretions with scalloped edges can be identified.
- Histochemistry:
 - Intraluminal but not intracytoplasmic mucin positive material may be seen.
- Immunohistochemistry:
 - Cytokeratin and epithelial membrane antigen are consistently positive.
 - Immunoreactivity absent for neuroendocrine markers, organ specific markers and/or markers reactive in other adenocarcinomas:
 - Thyroid: thyroglobulin, TTF-1, PAX8
 - Prostate: prostate specific antigen (PSA), prostatic acid phosphatase (PAP), prostein
 - Kidney: renal cell carcinoma antibody, CD10, PAX2, PAX8, CAIX
 - Breast: mammaglobin, BRST-2, GATA3
 - Lung: Naspin A, TTF1
 - Colorectal: CDX2, CK20, villin

Differential Diagnosis

- Middle ear adenoma.
- Confinement to the middle ear space and association with the middle ear mucosa are supportive evidence of origin from the middle ear; nevertheless, metastatic adenocarcinoma from a separate site must be excluded prior to treatment:
 - Metastases to the middle ear and temporal bone can be seen from all sites but are most common from breast, lung, kidney, gastrointestinal tract, larynx, skin (melanoma), and prostate gland.

Treatment and Prognosis

- Complete surgical excision is the preferred treatment.
- In general, these are slow-growing neoplasms that are locally aggressive but do not metastasize.
- Papillary cystadenocarcinomas are considered low-grade malignant tumors.
- Death may occur as a result of direct intracranial extension.

RHABDOMYOSARCOMA (RMS)

Definition: Malignant neoplasm showing skeletal muscle differentiation.

Clinical

- In the head and neck, RMS is primarily but not exclusively a disease of the pediatric population
- In the head and neck, parameningeal tumors are the most common:
 - Most frequent sites in the head in neck include nasopharynx > middle ear and mastoid > sinonasal tract > soft tissues of the neck > oral cavity (tongue, lip, palate).

- For more complete discussion including images, see Section 3, The Pharynx.

ENDOLYMPHATIC SAC PAPILLARY TUMOR (ELSPT)

(Figs. 24-44 through 24-46)

Definition: Uncommon but distinct neoplasm of probable endolymphatic sac epithelial origin possibly representing a manifestation of von Hippel-Lindau (VHL) syndrome.

Synonyms: Adenoma of endolymphatic sac, adenoma of temporal bone or mastoid, adenocarcinoma of

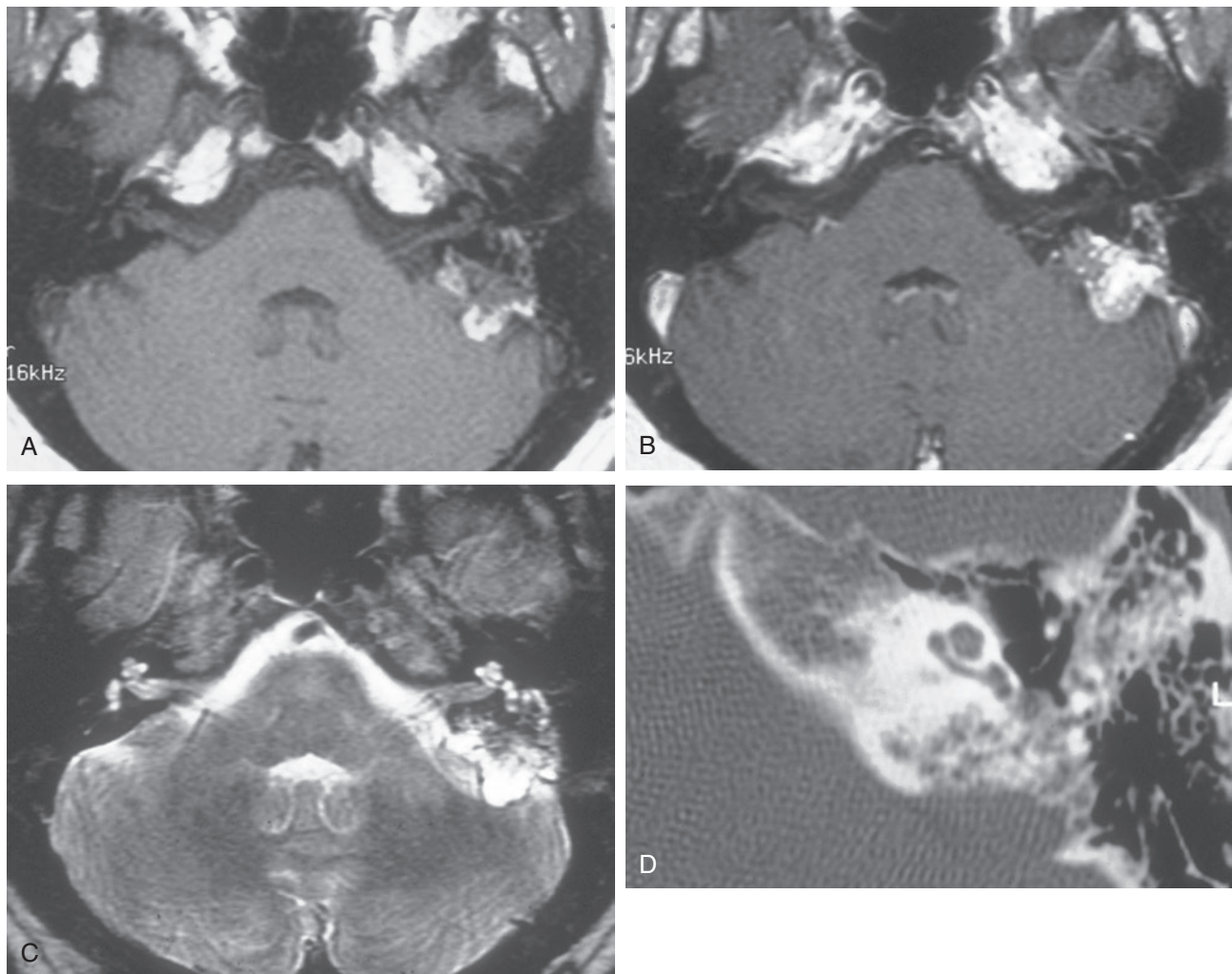


Fig. 24-44. Endolymphatic sac papillary tumor.

A and **B**, Pre- and post-contrast-enhanced T1-weighted images. **C**, T2-weighted image. The tumor has focal heterogeneous signal intensity on both T1-weighted and T2-weighted images caused by blood products and calcification. It shows heterogeneous enhancement after contrast administration. **D**, CT image in bone algorithm shows a destructive lesion with irregular, moth-eaten bone margins extending to the medial mastoid. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 20-179, p 1372.)

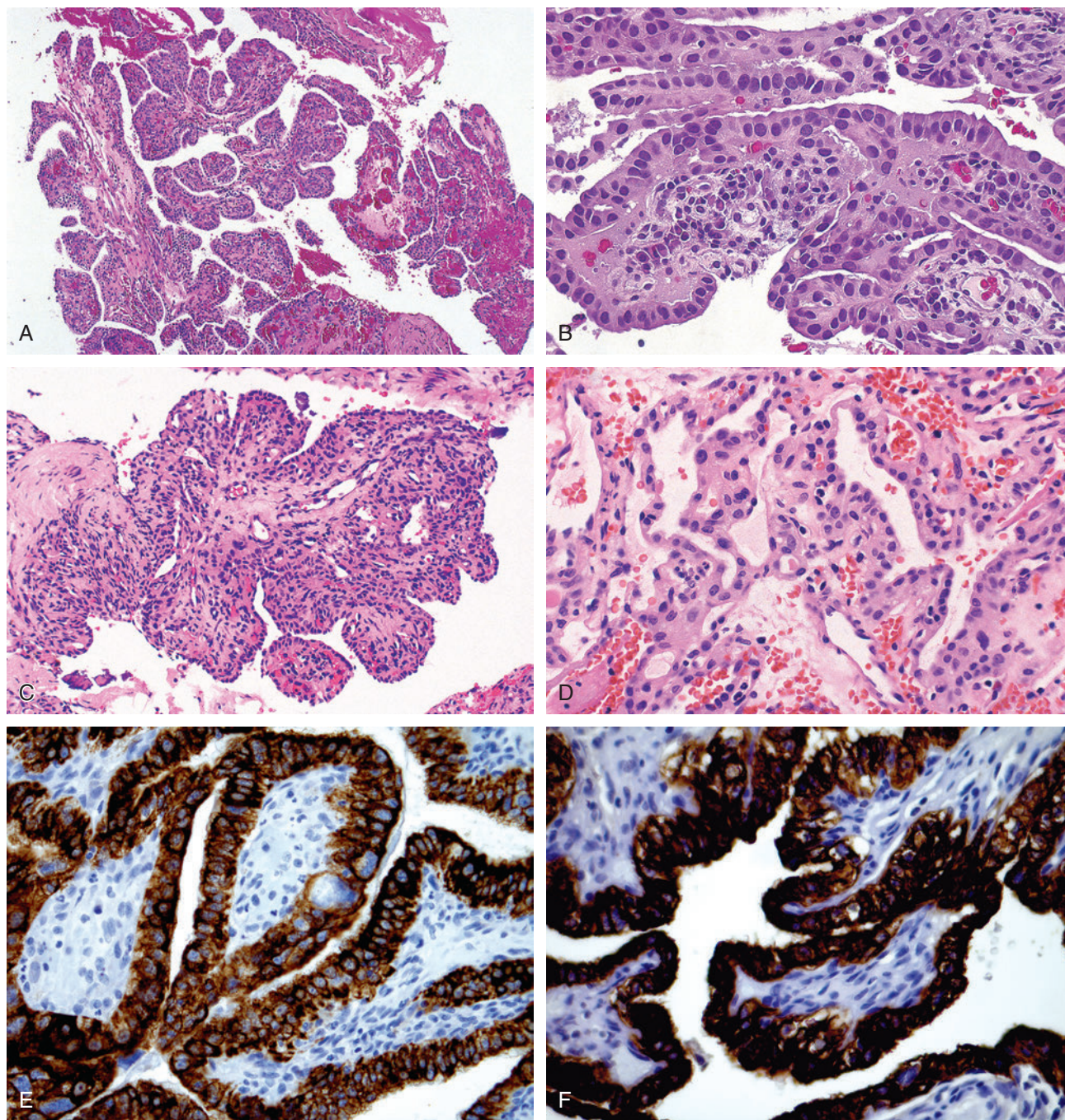


Fig. 24-45. Endolymphatic sac papillary tumor.

A, Endolymphatic sac papillary tumor characterized by a papillary growth pattern. **B**, The epithelial component is distinct, composed of a single layer of cuboidal to columnar-appearing cells with delineated cell borders. **C**, In this example, despite the papillary architecture, the epithelial component is not as readily identifiable. **D**, Even at higher magnification, the epithelium is indistinct and the overall process may be mistaken for granulation tissue. The epithelial component is diffusely immunoreactive for cytokeratins, including **(E)** CAM5.2 and **(F)** CK7.

temporal bone or mastoid, low-grade adenocarcinoma of probable endolymphatic sac origin, papillary adenoma of temporal bone, aggressive papillary tumor of temporal bone, aggressive papillary middle ear tumor, and Heffner tumor

NOTE: Owing to its aggressive behavior this neoplasm was initially considered to be low-grade adenocarcinoma. Although the majority of ELSPTs have an indolent biologic course, raising the possibility that these neoplasms may be benign or at worst of

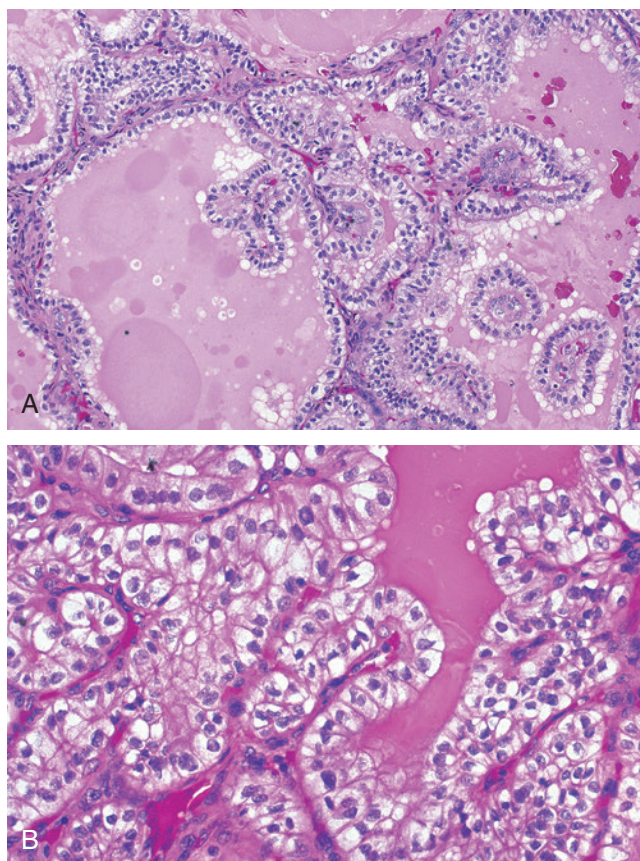


Fig. 24-46. Endolymphatic sac papillary tumor.

A, This inner ear tumor localized to the petrous apex shows the appearance of a thyroid lesion, including variably sized cystic spaces containing eosinophilic (colloid-like) material. **B**, At higher magnification, the presence of a papillary architecture, colloid-like material, and variability in the nuclear size and shape with dispersed to clear-appearing nuclear chromatin and an occasional intranuclear inclusion mimics the histology of a papillary thyroid carcinoma. Thyroglobulin and thyroid transcription factor 1 (TTF-1) staining were negative (not shown).

indeterminant malignant potential, the documented reports of metastatic ELSPT would support its classification as an adenocarcinoma.

Clinical

- No gender predilection; occurs over a wide age range from the second through eighth decades of life
- Most common symptom is unilateral hearing loss ranging from 6 months to 18 years in duration:
 - Hearing loss is most frequently sensorineural rather than conductive, but mixed types of hearing loss also occur.
- Other symptoms include tinnitus, vertigo, ataxia, and cranial nerve deficits.

- CT scan and MRI:
 - Lytic temporal bone lesion measuring from 4 to 6 cm
 - Center of the lesions most often seen at or near the posterior-medial face of the petrous bone.
 - Extension of tumor to the posterior cranial cavity leads to suggestions that the tumor originated from the cerebello-pontine angle; extension results in cerebellar involvement and evidence of compression and/or shifting of the fourth ventricle, brainstem, or pineal gland.
 - Angiographic studies show a vascular or hyper-vascular lesion.
- Endolymphatic sac origin for these tumors supported by:
 - Early clinical manifestations of vestibular disease, including sensorineural hearing loss, tinnitus, and episodic vertigo
 - Radiographic features showing the tumor to grow in the region of the posterior-medial petrous ridge, a site where the endolymphatic sac is located
 - Intraoperative identification of an *in situ* tumor (originating from within the endolymphatic sac)
 - Morphologic similarities and shared immunohistochemical and ultrastructural features of the tumor with the normal endolymphatic sac epithelium
 - Histologic studies of the epithelium of normal human mature endolymphatic ducts and sacs in archival temporal bone sections showed hyperplastic tubular outgrowths, usually situated in the intraosseous portion of the endolymphatic sac:
 - Such appearances imply that the epithelium of the endolymphatic ducts and sacs has the potential of producing a malignant papillary glandular neoplasm.
- Diagnosis is based on clinical, radiographic, and pathologic correlation.
- Diagnosis of ELSPT should prompt the clinician to exclude the possibility that the patient has von Hippel-Lindau (VHL) syndrome:
 - VHL germline mutation with an autosomal-dominant inheritance pattern usually identified
 - Tumor suppressor gene for VHL has been identified at chromosome 3p25-p26
 - Patients with VHL have a predisposition to the development of numerous CNS and abdominal organ tumors (Box 24-3).
 - Approximately 1 in 35,000 to 40,000 people have VHL, of whom 10% to 15% have ELSPT.

Pathology

Histology

- Histopathologic appearance of ELSPT is variable.
- Most show papillary and focally cystic growth:

BOX 24-3 Neoplasms Associated with von Hippel-Lindau Syndrome

- Retinal angiomas
 - Cerebellar and spinal hemangioblastomas
 - Endolymphatic sac papillary tumor
 - Renal cysts and cystadenomas
 - Pancreas: microcystic adenoma; endocrine tumors
 - Pheochromocytoma
 - Epididymal cyst and cystadenoma
- Papillary structures are generally not complex in their growth.
 - Neoplastic cells vary in appearance from flattened or attenuated appearing cells to columnar appearing cells and are most often only a single row of cells.
 - Occasionally, surface epithelial cells may have the appearance suggesting a double layer of cells (epithelial and myoepithelial); however, the “outer” row of cells, in all probability, represent a stromal element as they have not been shown to be immunoreactive with epithelial markers.
 - Epithelial cells have uniform nuclei that are usually situated either in the center of the cells or toward the luminal aspect and have a pale eosinophilic to clear appearing cytoplasm; the latter may predominate in any given tumor.
 - Cell borders may be seen but, not infrequently, the neoplastic cells lack a distinct cell membrane.
 - Due to the absence of a distinct cell membrane around the neoplastic cells, a sharp demarcation separating the neoplastic cells from the subjacent granulation tissue is not present.
 - This appearance may create diagnostic confusion so that the neoplastic proliferation is not appreciated, and the entire process may be viewed erroneously as reactive.
 - This interpretation is further enhanced by the presence in the stroma of a mixed inflammatory cell infiltrate, fibrosis, vascular proliferation, fresh hemorrhage and/or hemosiderin (within the neoplastic cells or within macrophages), cholesterol granulomas and dystrophic calcification; the latter does not include laminated calcific concretions (psammoma bodies)
 - In some cases, there are hypercellular areas with crowded, variably sized cystic glandular spaces that contain eosinophilic (colloid-like) material remarkably similar to thyroid tissue.
 - In all cases, pleomorphism is minimal, and mitotic activity and necrosis are rarely present.
 - A granulation tissue reaction is seen in association with the neoplastic cells and includes small vascular spaces lying in close proximity to the surface epithelium and/or within the stroma of the papillary fronds.

- Histochemistry:
 - Intracytoplasmic diastase-sensitive, periodic acid-Schiff (PAS)–positive material can be seen.
 - Colloid-like luminal material stains strongly with periodic acid Schiff (PAS) with and without diastase digestion.
 - Intracytoplasmic and intraluminal mucin staining is rarely positive.
 - Iron stains are positive.
- Immunohistochemistry:
 - Diffusely cytokeratin positive (AE1/AE3, CAM5.2, CK7)
 - Variable reactivity with epithelial membrane antigen (EMA), S-100 protein, vimentin, neuron specific enolase (NSE), glial fibrillary acidic protein (GFAP), Ber-EP4, synaptophysin, and Leu-7
 - Thyroglobulin, thyroid transcription factor 1 (TTF1), PAX8 negative
- Electron microscopy:
 - ELSPT shows the presence of intercellular junctional complexes, microvilli, basement membrane material, rough endoplasmic reticulum, and intracytoplasmic glycogen and secretory granules.
- Cytogenetics and molecular biology:
 - Germline mutations of the *VHL* tumor suppressor gene are usually detected in patients with ELSPT; however, sporadic cases unrelated to *VHL* occur.

Differential Diagnosis

- Nonneoplastic reactive or inflammatory processes
- Choroid plexus papilloma (CPP):
 - CPPs are intracranial (i.e., intraventricular) tumors
 - Histologic features of CPPs are different from those of ELSPT:
 - CPPs have a complex papillary pattern in which the neoplastic cells are arranged in an orderly layer of columnar epithelial cells situated on delicate fibrovascular stalks.
 - Neoplastic cells of CPPs have a distinct, well-formed continuous basement membrane separating them from the surrounding stromal tissue.
 - Prominent stromal calcification (psammomatoid bodies) and xanthomatous change may be present in CPPs.
 - Immunohistochemical stains assist in differentiating ELSPT from CPP:
 - Cytokeratin positive (similar to ELSPT)
 - Consistent S100 protein and vimentin
 - Focally glial fibrillary acidic protein positive

- Middle ear adenoma:
 - Clinical, radiographic, and pathologic features that are unique to ELSPT should allow for its distinction from middle ear adenoma.
 - Same would apply for the other common neoplasms of the middle ear and temporal bone
- Ceruminous gland adenocarcinoma
- Metastatic adenocarcinoma, particularly papillary carcinoma of the thyroid and renal cell carcinoma:
 - The absence of thyroglobulin, TTF1, and PAX8 reactivity would differentiate ELSPT from metastatic papillary thyroid carcinoma.
 - Metastatic renal cell carcinoma shows immunoreactivity for renal cell carcinoma antibody CD10, PAX2, PAX8, and CAIX, which are not found in ELSPT.
- These tumors are primarily of mesenchymal origin, including matrix-forming such as osteosarcoma and chondrosarcoma.
- Osteosarcomas of the skull:
 - Are uncommon, with approximately 1% to 2% of all osteosarcomas occurring in this location
 - Often arise in the setting of Paget disease of bone, fibrous dysplasia, or secondary to radiotherapy
 - Osteosarcomas of the skull are aggressive tumors with a tendency to metastasize to the lungs and brain and with 5-year survivals of less than 15%.
- Chondrosarcomas of the temporal bone are:
 - Rare
 - Petrous apex and posteromedial aspect of the temporal bone are perhaps the most common sites of occurrence.
 - Are not necessarily lethal tumors as with reported 76% disease-free survival over periods ranging up to 8 years

Treatment and Prognosis

- Radical surgery including mastoidectomy and temporal bone resection that may necessitate sacrifice of cranial nerves is the preferred treatment and is potentially curative.
- Local recurrence will result following inadequate surgical removal; operative morbidity may be high.
- Despite being low grade and slowly growing, these neoplasms are capable of widespread infiltration and destruction and may be lethal.
- Rarely may metastasize
- Prognosis is dependent on the extent of disease and the adequacy of resection:
 - Earlier detection when the tumors are relatively small and confined may decrease the operative-associated morbidity and be curative.
- In 25% of the cases reported, prior temporal bone resection was performed indicative of the initial occurrence of this neoplasm.
- Proposed grading system for ELSPT includes:
 - Grade I: confined to the temporal bone, middle ear, and external auditory meatus
 - Grade II: extends into the posterior fossa:
 - More than half of all ELSPTs are grade II at presentation
 - Grade III: involves the posterior and middle cranial fossae
 - Grade IV: extends to the clivus or sphenoid wing:
 - Very rare and occurs in only 2% to 4% of patients with ESPT

OTHER MALIGNANT TUMORS OF THE MIDDLE EAR AND TEMPORAL BONE

- Although uncommon, a number of other malignant tumors can originate in the middle ear or temporal bone.

- Other malignancies of the middle ear and temporal bones include hematolymphoid, including malignant lymphomas (non-Hodgkin and Hodgkin), leukemia, and plasma cell dyscrasias; middle ear and temporal bone involvement by a malignant hematolymphoid neoplasm often is secondary to primary disease elsewhere.

METASTATIC TUMORS TO THE MIDDLE EAR AND TEMPORAL BONE (SECONDARY TUMORS)

(Fig. 24-47)

- Metastatic tumors secondarily involving the middle ear and temporal bone originate from virtually every site.
- More common malignant tumors to metastasize to this region originate from the breast, head and neck, lungs, and prostate gland.
- Other tumors that may metastasize to this region include malignant melanoma, thyroid carcinomas, and renal cell carcinoma.
- Immunohistochemical staining is often required to confirm the diagnosis of a metastasis to the ear and temporal bone:
 - Breast: Mammaglobin, BRST-2, GATA3 positive
 - Lung: Napsin A, TTF-1, CK7 positive
 - Prostate: PSA, PAP, prostatein positive
 - Melanoma: S100 protein, HMB45, melan A, tyrosinase, MITF1, SOX10 positive
 - Thyroid: Thyroglobulin, TTF1, PAX8 positive
 - Kidney: CD10, RCC, PAX2, PAX8, CAIX positive
- Although metastases to the temporal bone often occur late in the disease course, metastatic

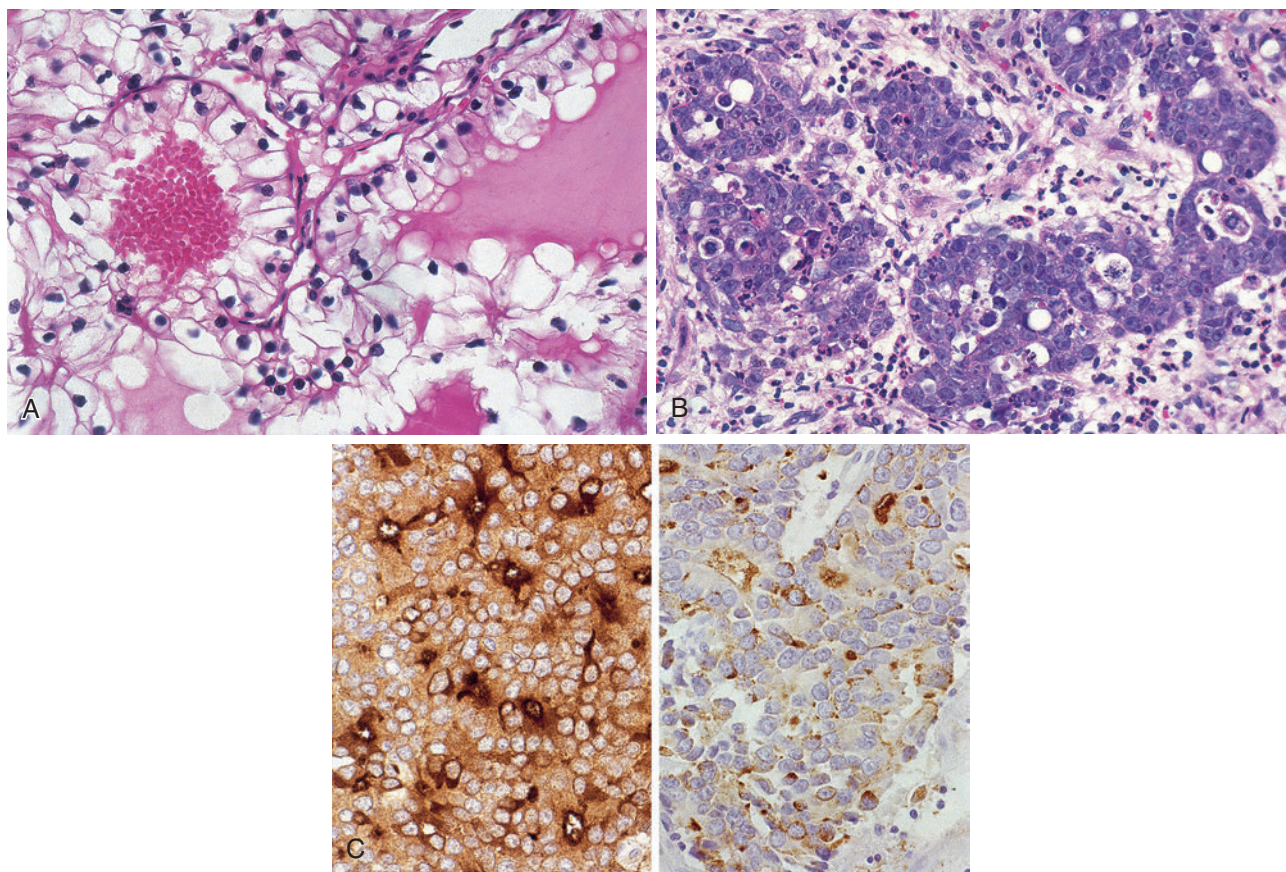


Fig. 24-47. Metastatic tumors to the ear/temporal bone.

A, Metastatic renal cell carcinoma to the temporal bone showing characteristic cells with clear cytoplasm, distinct cell borders, intraluminal red blood cells, and fibrovascular stroma separating neoplastic nests; the lesional cells were reactive for RCC, CD10, PAX2, PAX8, and CAIX (not shown). **B**, Metastatic prostate adenocarcinoma with gland formation and neoplastic cells showing prominent nucleoli and associated inflammatory cell infiltrate and individual cell necrosis. The overall histology is unusual for any primary middle ear or temporal bone malignant tumor prompting consideration for a metastasis. **C**, Immunohistochemical stains show reactivity for prostate specific antigen (*left*) and prostatic acid phosphatase (*right*), confirming the diagnosis of metastatic prostatic adenocarcinoma. In both cases, there was no known history of a primary renal carcinoma and prostate carcinoma and only following the presence and identification of these metastases was a primary cancer of the kidney and prostate gland discovered.

involvement of the temporal bone may represent the initial presentation of a distant malignant disease.

- Metastatic disease to the temporal bone occurs via hematogenous spread but may also occur by direct extension from a nearby primary tumor (e.g., squamous cell carcinoma), meningeal carcinomatosis or

leptomeningeal extension from an intracranial primary neoplasm.

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Immunohistochemistry of Middle Ear Neoplasms (Table 25-1)

TABLE 25-1 Immunohistochemical Reactivity of Middle Ear Neoplasms

	CK	EMA	p63	CG	SYN	S100	NSE	GFAP	VIM	DES	Myog
MEA	+	+	–	–	–	–	–	–	–	–	–
MEA/NE	+	+	–	+	+	V	+	–	–	–	–
JTP	–	–	–	+	+	++ [‡]	+	–	–	–	–
MEN	± [*]	+	–	–	–	–	–	–	+	–	–
AN	–	–	–	–	–	+ (N/C)	+	–	–	–	–
ESPT	++ [†]	+		v	v	v	v	v	–	–	–
RMS	– [§]	–	– [¶]	–	–	–	–	–	+	+	+ (N)

AN, Acoustic neuroma; CG, chromogranin; CK, cytokeratin; DES, desmin; EMA, epithelial membrane antigen; ESPT, endolymphatic sac papillary tumor; GFAP, glial fibrillary acidic protein; JTP, jugulotympanic paraganglioma; MEA, middle ear adenoma; MEN, meningioma; Myog, myogenin; (N), nuclear staining; (N/C), nuclear and cytoplasmic; NE, neuroendocrine features; NSE, neuron-specific enolase; RMS, rhabdomyosarcoma; SYN, synaptophysin; VIM, vimentin.

+, Positive; –, negative; +/-, variably positive.

*Cytokeratins can be positive (as a whole may be positive in 20% of cases; may approach 40% positivity in epithelial variants).

[†]AE1/AE3, CAM5.2, CK7.

[‡]Positive in the peripherally situated sustentacular cells; SOX10 (nuclear) reactivity may be present, as well.

[§]May be positive in up to 50% of alveolar rhabdomyosarcomas.

[¶]May be focally positive.

Non-Neoplastic Diseases of the Thyroid Gland

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE THYROID GLAND

See [Box 27-1](#).

BOX 27-1 Classification of Non-Neoplastic Lesions of the Thyroid Gland

Developmental

- Heterotopia/ectopia of thyroid tissues
- Lingual thyroid
- Thyroglossal duct cyst
- Lateral aberrant thyroid, parasitic nodule, and mechanical implantation
- Mediastinal thyroid and other sites of thyroid tissue
- Intranodal thyroid inclusions
- Struma ovarii and associated lesions
- Follicular epithelial metaplasia: squamous; oncocytic
- Others

“Inclusions” in the Thyroid Gland

- Intrathyroidal parathyroid tissue, thymic tissue, salivary gland tissue
- Intrathyroidal epithelial (branchial cleft-like) cysts
- Ultimobranchial apparatus rests
- Intrathyroidal fat, muscle, and cartilage
- Pigment and crystals in the thyroid
 - Iron; lipofuscin; crystals
 - Black thyroid (minocycline)

Nonautoimmune Thyroiditides (Inflammatory, Infectious, and Noninfectious)

- Acute inflammatory conditions
- Infectious thyroiditis
- Granulomatous thyroiditis (subacute thyroiditis; de Quervain)
- Multifocal granulomatous thyroiditis (palpation thyroiditis)
- Invasive fibrous thyroiditis (Reidel disease)
- Radiation thyroiditis
- Drug-induced thyroiditis
- Infectious granulomatous thyroiditis
- Sarcoidosis of the thyroid gland

Autoimmune Thyroiditis

- Chronic (focal) lymphocytic thyroiditis
- Chronic lymphocytic (Hashimoto) thyroiditis
- Others
- Autoimmune hyperthyroidism (diffuse hyperplasia or Graves disease)

Goiters

- Nodular goiter
- Congenital inborn disorders (dyshormonogenetic goiter)
- Amyloid goiter

DEVELOPMENTAL ANOMALIES

Heterotopia or Ectopic Thyroid Tissue ([Figs. 27-1 through 27-3](#))

Definitions: Heterotopia is the presence of otherwise normal-appearing tissue in an abnormal location. Ectopic thyroid tissue is the presence of thyroid in any location other than its normal anatomic position.

Synonyms: Aberrant thyroid rests; choristoma

- Normal thyroid tissue can be found within the soft tissue structures (fat and muscle) of cervical neck:
 - Reflects developmental abnormality and should not be mistaken for malignancy:
 - Thyroid tissue in skeletal muscle often located at or around the isthmus portion of the gland
 - Absence of tissue response such as fibrosis (desmoplasia) and/or the presence of architectural or cytomorphic changes indicative of a neoplasm (i.e., papillary carcinoma) are of assistance in differentiating normal (ectopic) thyroid tissue from neoplastic thyroid tissue.
 - Presence of thyroid tissue within lymph nodes especially located lateral to the jugular vein and carotid artery represents metastatic (papillary) carcinoma; exception would be thyroid tissue in a midline lymph node that may represent thyroid inclusions, but strict criteria must be applied to accept such thyroid tissue as inclusions and not metastatic tumor (see below).

Clinical

- Heterotopic thyroid tissue may be seen in any location from the tongue (foramen cecum at the base of the tongue) to the suprasternal notch (site of the normal gland):
 - May represent failure of descent from foramen cecum (median anlage) or, less likely, differentiation of thyroid tissue in abnormal locations
- Excluding thyroglossal duct cysts, presence of heterotopic thyroid tissue is rare and almost exclusively seen in suprahyoid locations usually located in or close to midline:
 - Most common heterotopic focus for thyroid tissue is base of tongue, referred to as lingual thyroid (see below)

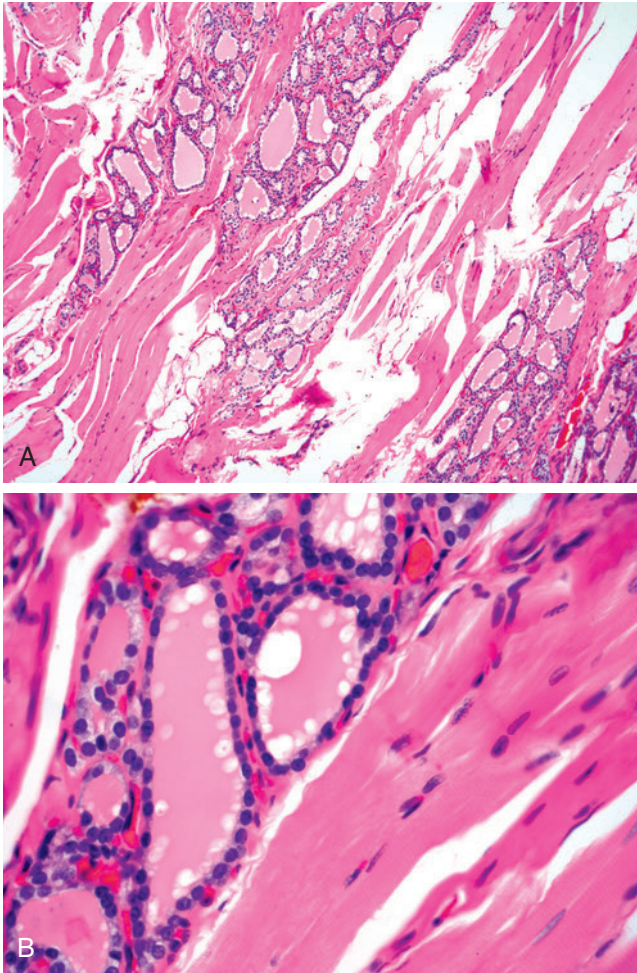


Fig. 27-1. Thyroid tissue in skeletal muscle.

Thyroid follicles can be found within the soft tissue structures of cervical neck, including skeletal muscle and fat, reflecting a developmental abnormality, and should not be mistaken for malignancy. Thyroid tissue in skeletal muscle is often located at or around the isthmus of the gland. The absence of tissue response such as fibrosis (desmoplasia) and/or the presence of architectural or cytomorphic changes indicative of a neoplasm (i.e., papillary thyroid carcinoma) assist in differentiating normal (ectopic) thyroid tissue from neoplastic thyroid tissue.

- Other sites include (cranial to caudal direction):
 - Sella turcica
 - Submandibular region
 - Larynx
 - Trachea
 - Mediastinum (superior > posterior)
 - Aortic arch, pericardium, and heart
 - Esophagus
- More distant sites of heterotopic thyroid tissue include:
 - Duodenal wall
 - Hepatobiliary (liver, porta hepatis, gallbladder, common bile duct)

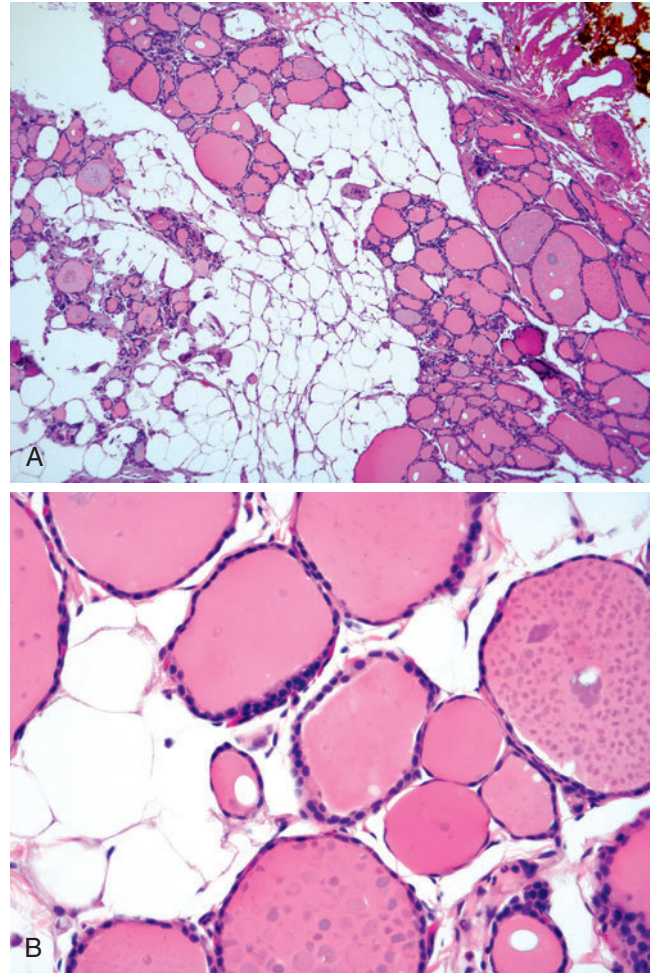


Fig. 27-2. Thyroid tissue in fat.

Similar to thyroid tissue in skeletal muscle (see previous image) thyroid follicles can be found within the cervical neck fat often located at or around the isthmus of the gland. The absence of desmoplasia and/or the presence of features that may be diagnostic for papillary thyroid carcinoma assist in differentiating normal (ectopic) thyroid tissue from neoplastic thyroid tissue.

- Pancreas
- Adrenal gland
- Retroperitoneum
- Vagina and inguinal region
- Ovarian thyroid tissue is referred to as struma ovarii (see below).
- Rarely, multiple ectopic thyroid tissue may be present in separate sites in same patient.
- Diseases that affect thyroid gland proper may also affect ectopic thyroid tissues, including:
 - Inflammatory diseases (e.g., Hashimoto thyroiditis, Graves disease, others)
 - Goiter
 - Neoplasms

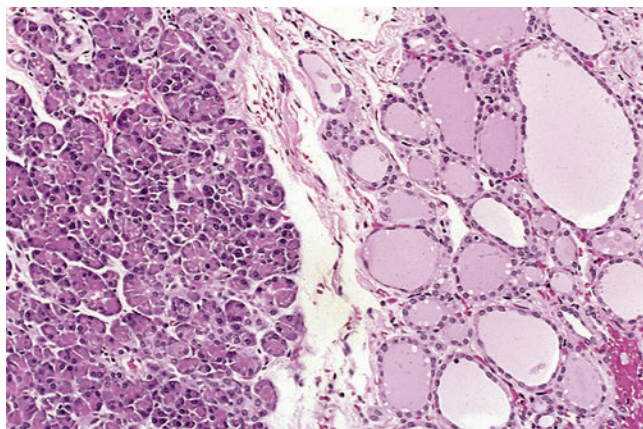


Fig. 27-3. Thyroid ectopia.

Ectopic thyroid tissue in the pancreas.

- Imaging with ^{123}I may establish the diagnosis noninvasively.
- Etiology:
 - None known
 - Rarely, familial thyroid heterotopia may occur.

Pathology

- Histologically, heterotopic thyroid tissue includes presence of normal-appearing, colloid-filled thyroid follicles:
 - Cytomorphologic findings include round to oval nuclei with coarse nuclear chromatin lacking constellation of nuclear features diagnostic for thyroid papillary carcinoma.
 - C-cells are absent.
- Immunohistochemistry:
 - Unnecessary for identification but cells will be:
 - Reactive for thyroglobulin, thyroid transcription factor 1, PAX8, CD56
 - Nonreactive for calcitonin, neuroendocrine markers (e.g., synaptophysin, chromogranin)
- Cytogenetics and molecular genetics:
 - Few reports evaluating molecular alterations in thyroid ectopia were without molecular alterations associated with malignant tumors of follicular cell derivation (*BRAFV600E*, *N-RAS*, *H-RAS*, *K-RAS*).

Differential Diagnosis

- Any thyroid tissue found lateral to large neck vessels (i.e., carotid artery, jugular vein) should be considered metastatic tumor rather than ectopia:
 - Especially true for foci of thyroid follicles in lymph nodes:
 - Represent metastatic papillary thyroid carcinoma even in absence of diagnostic nuclear features

- Different types of malignant neoplasms may be seen uncommonly associated with heterotopic tissues, including papillary carcinoma and follicular carcinoma:
 - In such circumstances, evaluation indicated to exclude origin from thyroid gland proper
 - In presence of malignant follicular-derived neoplasm within thyroid gland proper, presence of thyroid carcinoma in “ectopic” site represents metastatic disease.
 - Only in absence of malignant follicular-derived neoplasm within thyroid gland proper can presence of thyroid carcinoma in “ectopic” site be considered as originating from the ectopic site.
- Presence of thyroid follicles in midline or paramidline lymph nodes may represent thyroid inclusions or metastatic papillary carcinoma (see [Thyroid Tissue in Lymph Nodes](#) later in this chapter).

Treatment and Prognosis

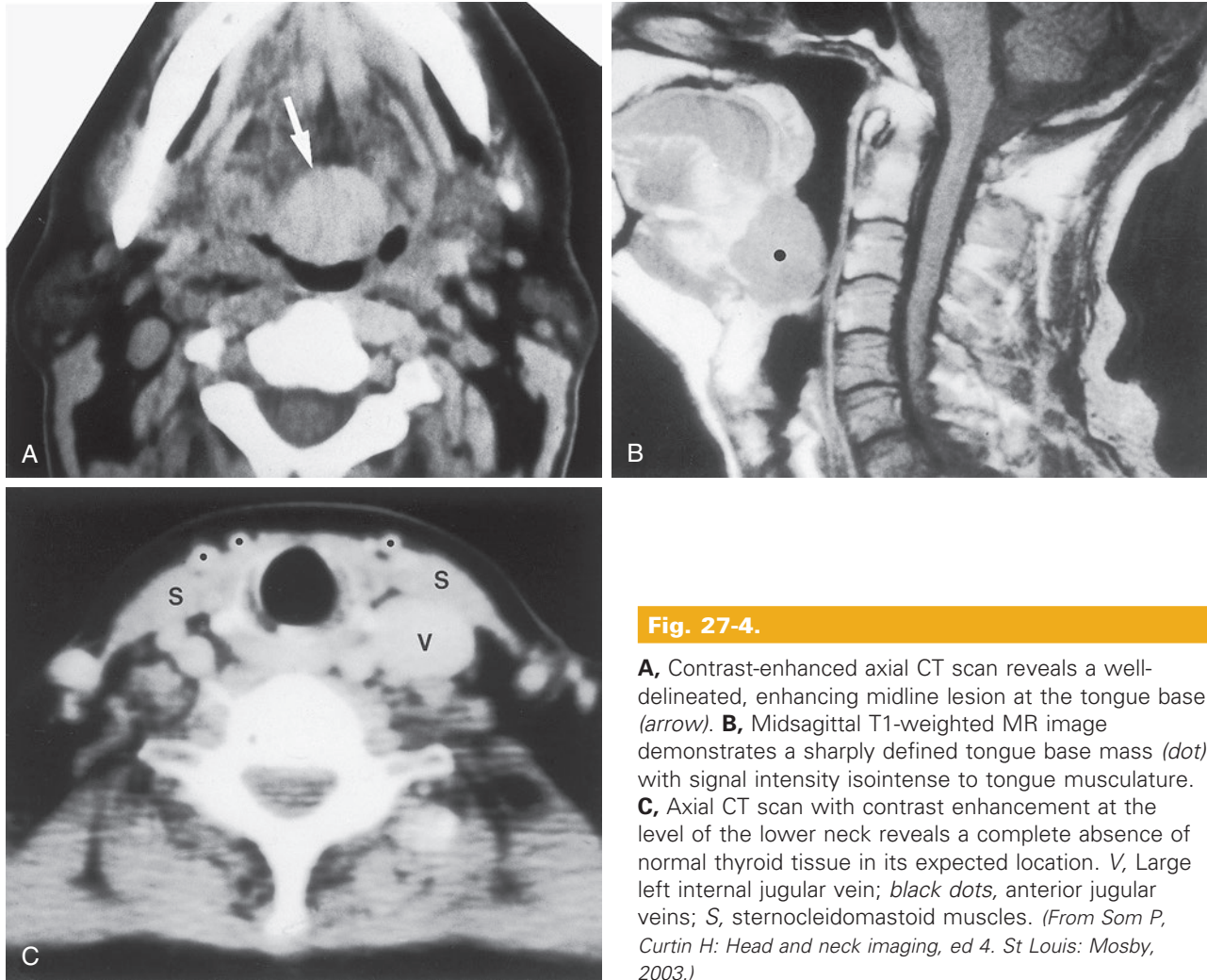
- In general, heterotopic thyroid tissue is benign.
- Complete or partial agenesis of thyroid gland is extremely rare.

Lingual Thyroid (Figs. 27-4 and 27-5)

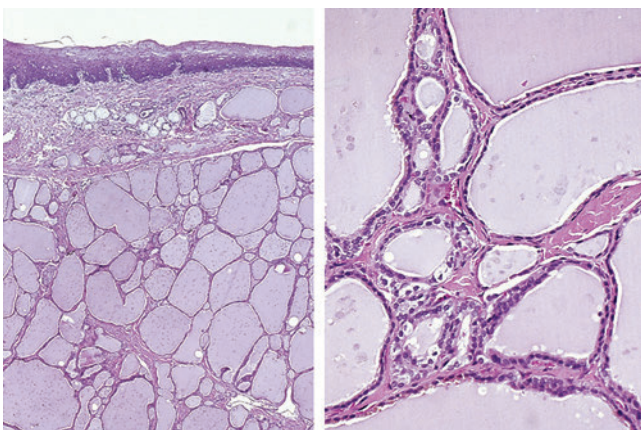
Definition: Developmental anomaly in which there is abnormal descent of thyroid gland with localization to base of tongue.

Clinical

- Thyroid tissue restricted to lingual region is rare, occurring in 1 in 100,000 persons.
- Affects women more than men (3:1 to 7:1); most often diagnosed in adolescence but may occur over a wide age range from birth to the seventh decade of life
- Most frequently seen along the midline of base of the tongue between the foramen cecum and the epiglottis; rarely, body of the tongue (sublingual) may be affected.
- Majority of patients who are symptomatic are women; contributing factors are thought to be related to puberty, pregnancy, and menopause.
- Most common symptom is dysphagia.
 - Lingual thyroid may grow large, resulting in dyspnea, orthopnea, and severe respiratory distress.
 - Other symptoms may include bleeding, voice changes, a foreign body sensation, snoring, and sleep apnea.
- Clinical presentation:
 - 70% of patients with symptomatic lingual thyroid are hypothyroid.

**Fig. 27-4.**

A, Contrast-enhanced axial CT scan reveals a well-delineated, enhancing midline lesion at the tongue base (*arrow*). **B**, Midsagittal T1-weighted MR image demonstrates a sharply defined tongue base mass (*dot*) with signal intensity isointense to tongue musculature. **C**, Axial CT scan with contrast enhancement at the level of the lower neck reveals a complete absence of normal thyroid tissue in its expected location. V, Large left internal jugular vein; *black dots*, anterior jugular veins; S, sternocleidomastoid muscles. (From Som P, Curtin H: *Head and neck imaging*, ed 4. St Louis: Mosby, 2003.)

**Fig. 27-5. Lingual thyroid.**

Left, The lingual squamous epithelium overlies a submucosa that focally retains its seromucous glands but is predominantly replaced by unencapsulated benign thyroid tissue. *Right*, The thyroid follicular epithelium is essentially normal in appearance.

- 10% suffer from cretinism.
- Hyperthyroidism exceptionally rare finding
- In greater than 75% of patients, cervical thyroid tissue is absent (total migration failure) and lingual thyroid represents only thyroid tissue present:
 - In such situations surgical removal of lingual thyroid results in hypothyroidism.
- Appropriate preoperative clinical work-up for lingual thyroid includes:
 - Routine blood work, including thyroid function tests thyrotropin, thyroxine, and thyroid hormone binding ratio
 - Scintigraphy with technetium or radioiodine studies, computerized tomography, or magnetic resonance imaging to:
 - Determine whether normally placed thyroid tissue is present or absent
 - Determine whether there are other ectopic foci of thyroid tissue (thyroid follicles may be found in hyoid region)

- Determine functional activity of lingual thyroid tissue
- Incisional biopsies must be performed with caution because this may cause sloughing of gland, infection, necrosis, or hemorrhage.
- Radiology:
 - Tc-99m pertechnetate scanning is an efficient diagnostic tool that yields high-quality images in this clinical setting.
 - Computed tomography shows a mass at the base of the tongue with a greater density than the tongue.
 - On MR imaging, a well-defined mass of low-intermediate T2 signal in the midline base of the tongue, neither with invasive tendency nor with a cervical thyroid gland in the normal site, strongly indicates a lingual thyroid.

Pathology

Gross

- Submucosal varying in appearance from smooth to lobulated to nodular mass, with a red color, soft to firm consistency, and ranging in size from 2 to 3 cm:
 - Overlying mucosa may be intact or ulcerated.

Histology

- Thyroid tissue is:
 - Submucosal and unencapsulated
 - May be nodular and hypercellular
 - Thyroid follicular epithelium is essentially normal in appearance (i.e., without evidence of papillary carcinoma).
 - May extend into skeletal muscle
- Immunohistochemistry:
 - Unnecessary for identification but cells will be:
 - Reactive for thyroglobulin, thyroid transcription factor 1, PAX8, CD56
 - Nonreactive for calcitonin, neuroendocrine markers (e.g., synaptophysin, chromogranin)

Differential Diagnosis

- Lymphoepithelial cyst of oral cavity
- Cribiform adenocarcinoma of minor salivary glands of oral cavity (See Section 7):
 - May show histologic similarities to papillary thyroid carcinoma
 - Absence of immunoreactivity for thyroglobulin and TTF-1
- Low-grade nasopharyngeal papillary adenocarcinoma (See Section 3):
 - May show histologic similarities to papillary thyroid carcinoma
 - Lesional cells are:
 - TTF-1 positive (nuclear staining)
 - Thyroglobulin negative

Treatment and Prognosis

- Therapy varies:
 - Asymptomatic euthyroid patients with ectopic thyroid do not usually require therapy but are kept under observation.
 - For symptomatic patients, surgical excision (intraorally or pharyngotomy) is preferred treatment:
 - Transoral robotic surgery (TORS) has provided minimally invasive approach to completely and safely excise ectopic lingual thyroid.
 - In patients without normally situated cervical thyroid tissue or other ectopic foci of thyroid tissue, auto-transplantation of thyroid tissue into the neck muscles can be done.
 - Other modes of therapy include:
 - Shrinking the mass by using thyroid hormones or use radioactive iodine (^{131}I) to ablate the lingual thyroid
 - Use of radioactive iodine results in destruction of other thyroid tissue and may also cause sloughing of the gland and hemorrhage.
 - In case of absence of orthotopic thyroid tissue, long-term thyroid hormone replacement recommended
- Prognosis is good:
 - Surgical resection of lingual thyroid glands achieves significant improvement in patient symptoms with low rates of recurrence.
 - Complications of surgery are uncommon and may include:
 - Postoperative bleeding and epiglottic perforation, airway obstruction secondary to angioedema
- Malignant neoplasms may arise from lingual thyroid:
 - Papillary thyroid carcinoma is the most common type.
 - May be associated with cervical nodal metastasis
 - Treatment best managed with surgical excision of all thyroid tissue followed by radioactive iodine ablation
 - In such circumstances, evaluation indicated to exclude origin from thyroid gland proper
 - In presence of malignant follicular-derived neoplasm within thyroid gland proper, presence of thyroid carcinoma in “ectopic” site represents metastatic disease.
 - Only in absence of malignant follicular-derived neoplasm within thyroid gland proper can presence of thyroid carcinoma in “ectopic” site be considered as originating from the ectopic site.

Thyroglossal Duct Cyst (TDC)

(Figs. 27-6 through 27-11)

Definition: Persistence and cystic dilatation of thyroglossal duct in midline of the neck.

Clinical

- No gender predilection; occurs over a wide age range but the majority of patients present before the fourth decade of life
- Majority of cases occur in the midline of the neck above the thyroid isthmus but below level of the hyoid bone:



Fig. 27-6. Thyroglossal duct cyst.

Thyroglossal duct cyst appearing as a midline neck mass at the level of the hyoid bone.

- Thyroglossal duct cysts are nearly always connected to hyoid bone.
- Uncommonly, TDCs may occur lateral to midline but do not occur in the lateral portion of the neck (i.e., lateral to jugular vein).
- Clinical presentation of an uninfected TDC usually that of asymptomatic midline neck mass:
 - Mass typically moves upward on swallowing.
 - Inflamed or infected TDCs may be associated with tenderness and pain.
 - Extrinsic airway compression in neonates with apnea, cyanosis, and respiratory compromise may uncommonly occur.
- Radiology:
 - Midline round or elongated cystic lesion
 - Expansion and/or destruction of the cartilaginous structure of the hyoid bone may be seen.
 - Seldom contains enough thyroid follicular tissue to be seen on scintiscan
 - Presence of nodular soft tissue excrescences in a midline cystic neck mass on CT scan may suggest the possibility of a papillary carcinoma arising in a thyroglossal duct cyst.

Pathology

Fine-Needle Aspiration Biopsy (FNAB)

- Smears from thyroglossal cysts are low in cellularity, and inflammatory cells are more numerous than epithelial cells.
- Squamous or respiratory epithelium may be identified.

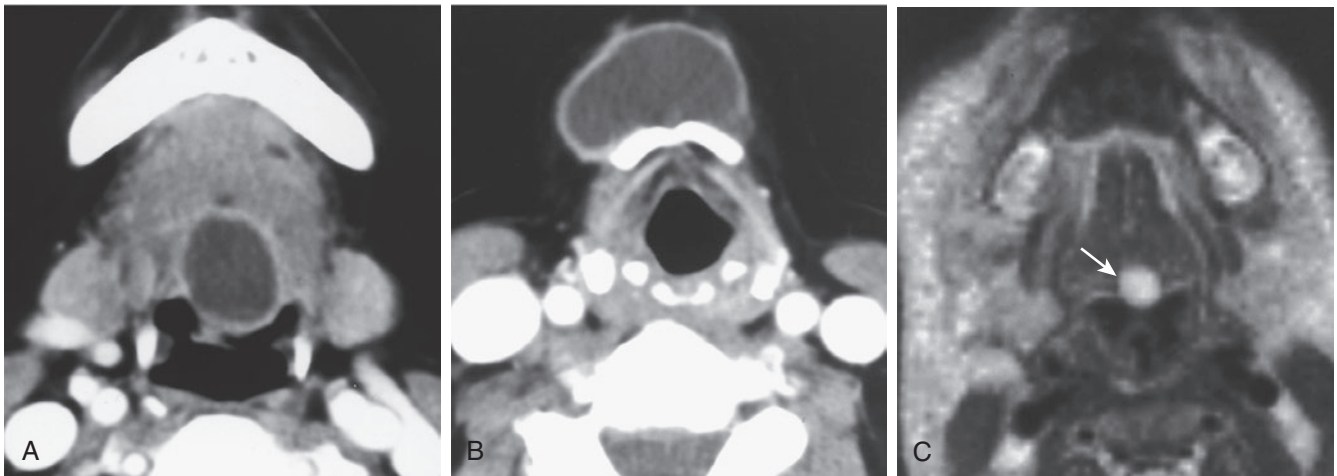


Fig. 27-7. Thyroglossal duct cyst.

Thyroglossal duct cysts. **A** and **B**, Contrast-enhanced, axial, CT images demonstrate a well-circumscribed, rim-enhancing cystic mass along the path of the thyroglossal duct from the foramen cecum/base of tongue (**A**) to the infrahyoid neck (**B**). **C**, Axial, T2-weighted, MR image from another patient, a neonate, demonstrates a small hyperintense lesion in the midline of the tongue base at the expected location of the foramen cecum (arrow). (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 28-126, page 1726.)

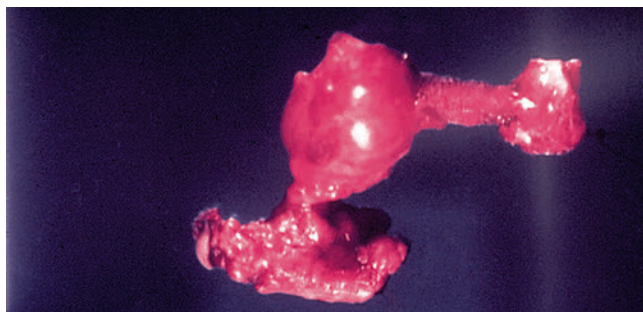


Fig. 27-8. Thyroglossal duct cyst.

Thyroglossal duct cyst resection specimen (Sistrunk procedure) includes an en bloc removal of the cyst, the middle third of the hyoid bone, and the suprahyoid tract.

- Inflammatory cells, especially mature lymphocytes, are frequently present.

Gross

- Smooth walled cystic structures usually measure less than 2 cm.
- Cystic content includes clear mucinous fluid; infected cysts contain purulent material.

Histology

- Epithelial-lined cystic proliferation within (hyoid) bone
- In noninflamed cysts, the cysts lining is respiratory (columnar) epithelium but may also include squamous epithelium.
- In presence of inflammation, cyst lining undergoes metaplastic change and is lined by squamous epithelium.
- Presence of thyroid tissue in cyst wall varies and may be dependent on the extent of specimen sampling:
 - In general, thyroid tissue can be found in more than 60% of the cases.
 - Absence of thyroid tissue does not exclude diagnosis.
- Thyroid tissue may be normal, hyperplastic, and nodular or neoplastic (see below).

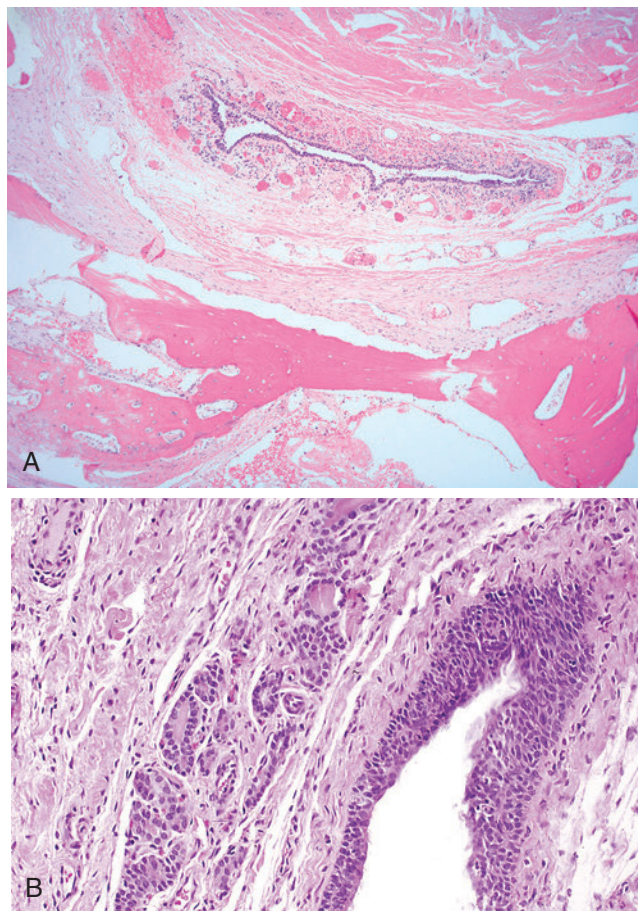
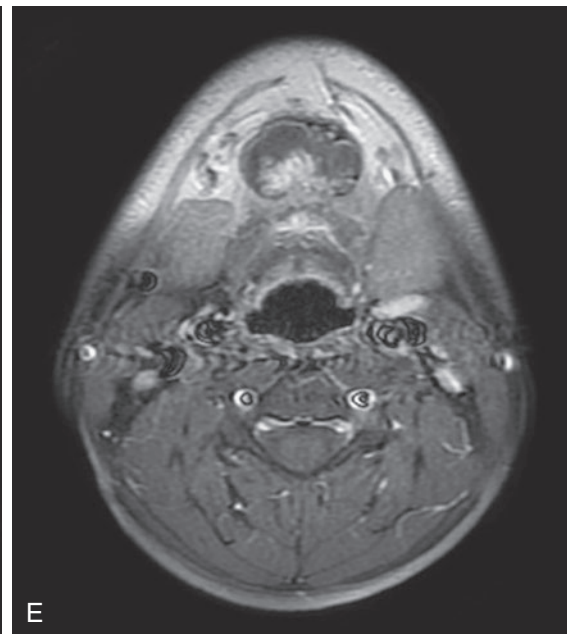
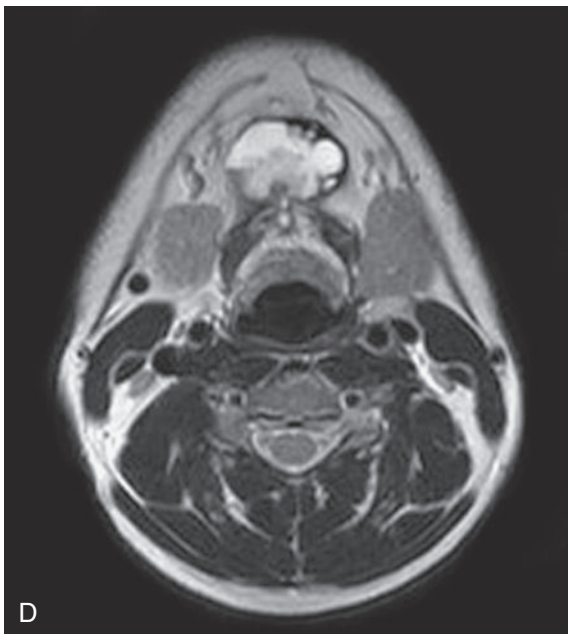
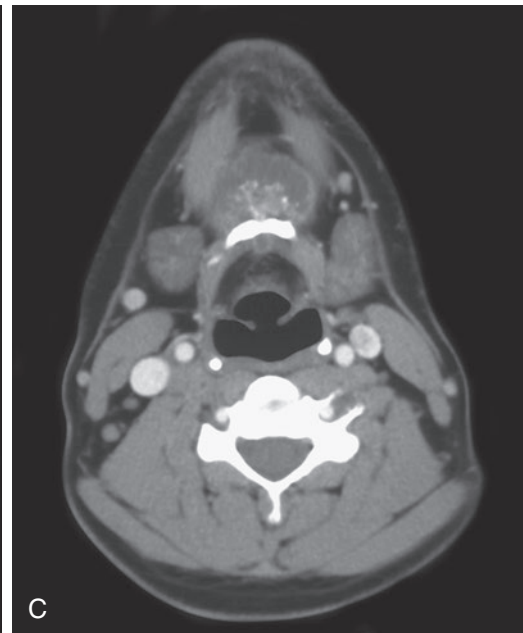
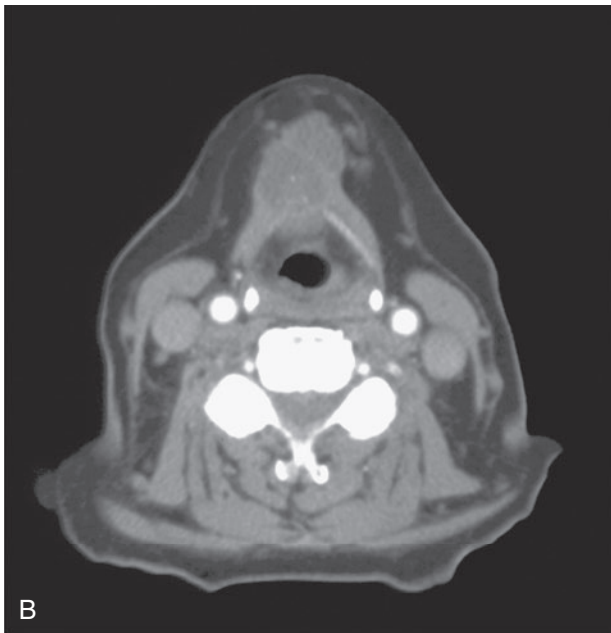
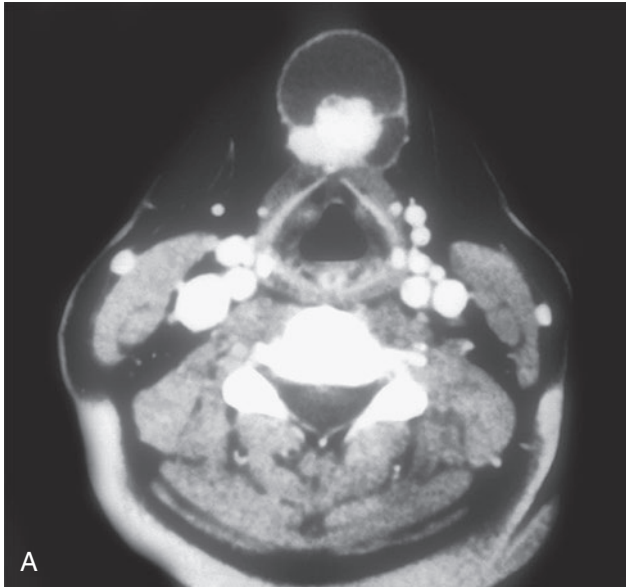


Fig. 27-9. Thyroglossal duct cyst.

A, Low magnification showing the presence of an epithelial lined cyst within (hyoid) bone. **B**, At higher magnification the cyst is variably lined by squamous epithelium and ciliated respiratory epithelium (mid lower); note the presence of benign thyroid tissue (colloid-filled follicles) within the cyst wall. The presence of thyroid tissue in cyst wall varies and may be dependent on the extent of specimen sampling. The absence of thyroid tissue does not exclude diagnosis.

Fig. 27-10. Papillary thyroid carcinoma in thyroglossal duct cyst.

A, Axial contrast-enhanced CT scan shows a midline cyst just caudal to the level of the hyoid bone. Within the cyst is an enhancing nodule and there is some infiltration of the adjacent strap muscles. This was a papillary thyroid carcinoma within a thyroglossal duct cyst. At surgery, there was extension of the tumor into the strap muscles. **B**, Axial CT scan shows a lobulated, midline, cystic mass involving the strap muscles and bulging back into the larynx. Small calcifications are present within the mass. **C**, Axial CT scan of another patient shows a cystic midline mass attached to the hyoid bone with speckled calcifications within it. Axial T2-weighted (**D**) and T1-weighted, fat-suppressed, contrast-enhanced (**E**) images of this patient show the calcified region within the mass has a low-to-intermediate T2-weighted signal intensity and it enhances. At surgery this was a papillary thyroid carcinoma within a thyroglossal duct cyst with extension of the tumor into the strap muscles. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 37-45, page 2264.)



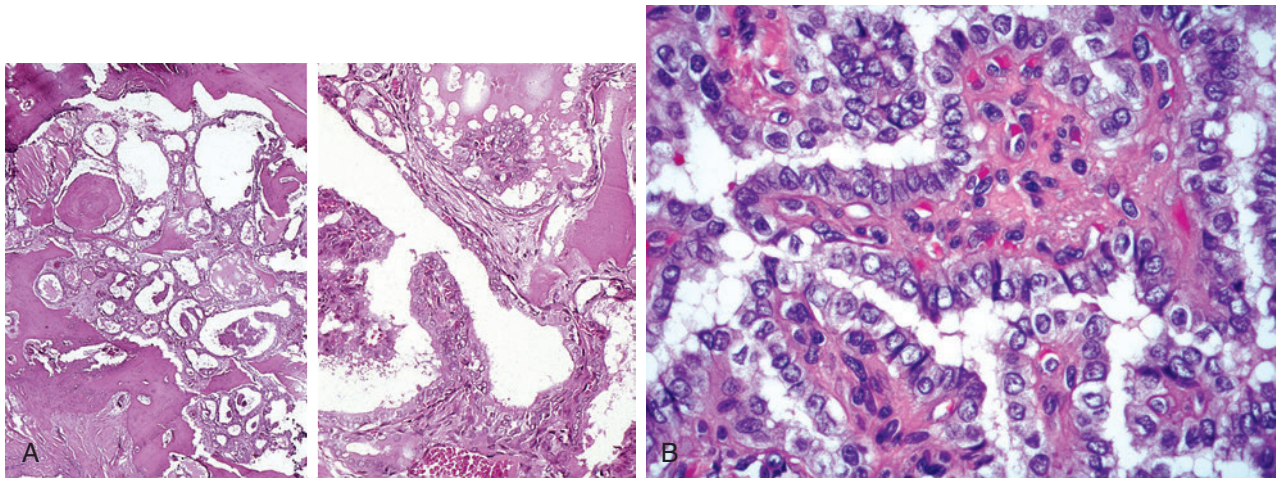


Fig. 27-11. Papillary thyroid carcinoma in thyroglossal duct cyst.

Papillary thyroid carcinoma arising in thyroglossal duct cyst. **A**, *Left panel*, Proliferation within the hyoid bone that includes colloid-filled follicles. *Right panel*, Papillary fronds with fibrovascular core. **B**, At higher magnification nuclear features diagnostic for papillary thyroid carcinoma are present.

- Secondary retrogressive changes may be present, including:
 - Fibrosis
 - Chronic inflammatory cell infiltrate
 - Squamous metaplasia that may be focal or extensive

Differential Diagnosis

- Thymic cyst
- Metastatic (cystic) papillary thyroid carcinoma
- Laryngocele
- Branchial cleft cyst
- Squamous cell carcinoma:
 - Presence of extensive squamous metaplasia may raise concern for possible presence of squamous cell carcinoma but metaplastic foci typically bland-appearing lacking cytomorphic features of carcinoma

Treatment and Prognosis

- Surgery is preferred treatment:
 - Sistrunk procedure includes en bloc surgical resection of cyst, middle third of the hyoid bone, and suprahyoid tract up to base of tongue (foramen cecum).
- Adequate surgery results in cure with low to no recurrences:
 - Reported recurrence rates range from 0% to 11%.
 - Extended surgical procedures prevent recurrence.
- Benign and malignant neoplasms may occur in the setting of a thyroglossal duct cyst:
 - Benign tumors include follicular adenoma.

- Development of a carcinoma in a thyroglossal duct cyst is rare:
 - Most carcinomas that develop in this setting are papillary carcinomas.
 - Rare examples of follicular carcinoma (oncocytic, nononcocytic types), undifferentiated (anaplastic) thyroid carcinoma, squamous (epidermoid) carcinoma, and adenosquamous carcinoma
 - Squamous (epidermoid) carcinoma and adenosquamous carcinoma in all probability arise from cyst lining rather than from thyroid cell component.
- C-cell-related lesions, including medullary thyroid carcinoma, do not occur in thyroglossal duct cysts due to the different embryologic derivation of the C-cells.
- Papillary thyroid carcinoma arising in the setting of a thyroglossal duct cyst:
 - Occur more commonly in women than men
 - Occur over a wide age range (first through eighth decades of life)
 - Are of usual morphologic type:
 - Variant types may include follicular variant, tall cell variant.
 - Similar (excellent) prognosis to that of papillary thyroid carcinoma arising in thyroid gland proper
 - May recur or metastasize and rarely may be lethal
 - Detailed evaluation of thyroid gland proper indicated
 - No clear consensus exists regarding optimal management, which may include:

- Sistrunk procedure
- Sistrunk procedure with total thyroidectomy
- Sistrunk procedure with total thyroidectomy and neck dissection
- Following total thyroidectomy:
 - Approximately one third may have concomitant papillary thyroid carcinoma in thyroid gland proper:
 - Often represent incidental papillary microcarcinomas
 - Nodal cervical metastasis may be present.
 - Such findings suggest that ultrasonography and, if warranted, fine-needle aspiration biopsy should be performed, and in presence of suspected lesion in thyroid gland proper and/or lymph node, Sistrunk procedure with total thyroidectomy, and neck dissection should be performed.
- In cases of lateral aberrant thyroid with associated lymphocytic thyroiditis, presence of a prominent lymphoid infiltrate gives the overall impression that the tissue is from a lymph node potentially leading to mistaken diagnosis of metastatic carcinoma:
 - Nodal tissue has subcapsular sinuses, whereas thyroid tissue with lymphocytic thyroiditis does not.
- Aberrant thyroid tissue shows histopathologic changes similar to those seen in thyroid gland proper (e.g., lymphocytic thyroiditis, goitrous changes).
- BRAF V600E mutation analysis reported in limited number of aberrant thyroid tissue was negative.
- Mechanical implantation of thyroid tissue (normal or hyperplastic) refers to presence of thyroid tissue in the neck due to surgical intervention or trauma:
 - Unattached to thyroid gland may be the result of prior surgery or accidental trauma
 - In such instances, there usually is a prominent fibrotic reaction and/or suture material seen in association with the thyroid tissue.

Parasitic Nodule

Definition: Refers to occurrence of thyroid nodule in the neck in which there is no connection to thyroid gland due to ablation of this connection or lack of identification of connection to the main gland:

- Usually an expression of nodular hyperplasia (adenomatoid nodules) or nodular chronic lymphocytic (Hashimoto) thyroiditis
- Less often expression of diffuse hyperplasia (i.e., Graves disease)

Synonyms: Sequestered thyroid nodule or accessory nodule

- Lateral aberrant thyroid: former term used for thyroid tissue lateral to jugular vein:
 - Most of such cases, especially in lymph nodes, represent metastatic papillary thyroid carcinoma.
 - Many of such previously termed cases represent parasitic nodules.
- “Aberrant” tissue may be connected to the thyroid by a thin fibrous strand that may or may not be appreciated by the surgeon or the pathologist, or there may not be a discernible attachment to thyroid gland proper.
- May occur in the mediastinum as part of mediastinal nodular hyperplasia (goiter)
- Stipulations for diagnosis of parasitic nodule include:
 - Aberrant thyroid tissue should be located in same fascial plane as thyroid gland.
 - Thyroid tissue not identified in relationship to a lymph node:
 - If thyroid tissue is seen within lymph node parenchyma, then it should be considered as metastatic carcinoma.
 - Presence of subcapsular sinuses assists in identifying given structure as being a lymph node.

Thyroid Tissue in Lymph Nodes

(Figs. 27-12 and 27-13)

- Controversial issue whether benign thyroid inclusions in lymph nodes truly exist or whether all thyroid tissue located within a lymph node, irrespective of the nodal site or the degree of tumor differentiation, represents metastatic carcinoma from a primary thyroid tumor
- In theory, it is conceivable that benign thyroid inclusions in lymph nodes may occur similar to nevus cell inclusions or salivary gland inclusions within lymph nodes; however, to consider a possible diagnosis of benign thyroid inclusion, strict criteria must be met, including:
 - Lymph node is located in midline, near midline, or medial to jugular vein.
 - Thyroid tissue is limited in extent (only a few follicles) located in nodal capsule and not found in subcapsular sinus(es), does not replace nodal parenchymal tissue, and/or is not found in multiple lymph nodes.
 - Inclusions are cytologically bland without histologic evidence to support diagnosis of metastatic papillary thyroid carcinoma.
 - Absence of psammoma bodies
 - Primary thyroid carcinoma is not present; however, this does not entirely exclude an occult primary tumor with metastatic (nodal) disease.
- Even if the above criteria are met, a diagnosis of benign thyroid inclusions in lymph nodes should be made with caution as, in all likelihood, these foci

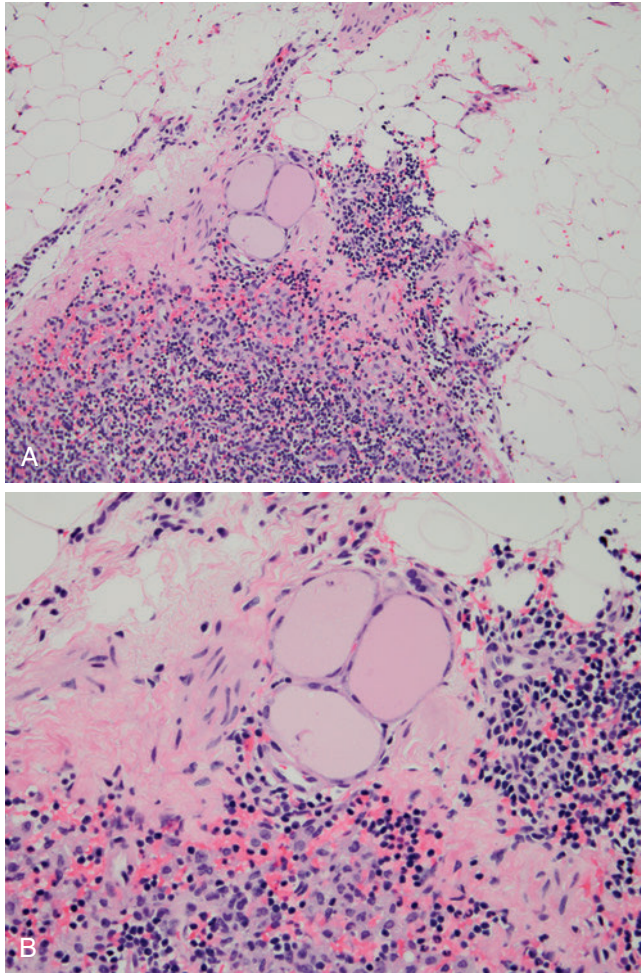


Fig. 27-12. Benign nodal thyroid inclusions.

(Benign) thyroid inclusions in a midline lymph node.

A, Very few colloid-filled follicles are identified in the nodal capsule and not in subcapsular sinus(es) and/or in nodal parenchyma. **B,** At higher magnification the follicular cells are cytologically bland without histologic evidence to support diagnosis of metastatic papillary thyroid carcinoma.

represent metastatic papillary thyroid carcinoma (even in absence of cytomorphologic evidence of thyroid papillary carcinoma):

- A diagnosis of metastatic carcinoma likely would result in thyroidectomy (lobectomy or total thyroidectomy).
- Primary carcinoma often located in ipsilateral thyroid lobe but metastatic carcinoma in central compartment nodes may arise from anywhere in thyroid gland.
- Primary carcinoma may be small and clinically undetectable.
- Histologic identification of primary thyroid carcinoma may require exhaustive sectioning and histologic evaluation of resected thyroid gland, including:

- Multiple levels of paraffin blocks
- In absence of identifying primary carcinoma, “flipping” paraffin blocks and cutting multiple levels may be necessary
- Even following exhaustive search primary carcinoma may not be detected, which does not exclude the primary residing in thyroid gland proper nor “rule in” benign thyroid inclusions.
- Diagnosis of metastatic papillary thyroid carcinoma can be made if:
 - Thyroid tissue is located in a lymph node that is lateral to jugular vein and/or there is cytomorphologic evidence (i.e., nuclear features) diagnostic for papillary thyroid carcinoma irrespective of location of lymph node(s).
- Diagnostic confusion may occur in setting of parasitic nodule (see above) with chronic lymphocytic (Hashimoto) thyroiditis:
 - In this setting, prominent lymphocytic thyroiditis, which may include germinal centers, could simulate the appearance of a lymph node so that thyroid tissue is considered as metastatic to a “lymph node.”
 - In contrast to lymph nodes, this tissue does not have subcapsular spaces, and thyroid follicular epithelium has changes associated with chronic lymphocytic (Hashimoto) thyroiditis, including cytoplasmic oxyphilia with enlarged nuclei lacking the constellation of cytomorphologic (nuclear) features of papillary thyroid carcinoma.
 - Immunohistochemistry:
 - In absence of known primary cancer, immunoreactivity for thyroglobulin confirms thyroid origin and differentiates metastatic thyroid carcinoma from carcinomas that may show histologic similarities to thyroid tumors, including salivary gland tumors (e.g., acinic cell carcinoma, mammary analogue secretory carcinoma, others) and non-head and neck cancers (e.g., lung, others).
 - Unlike thyroglobulin, TTF1 is not uniquely limited to lesions of thyroid gland origin.
 - Papillary thyroid carcinoma (and to a much lesser extent other thyroid type carcinomas) may originate in ovarian teratoma (i.e., struma ovarii), but such occurrences are rare and even rarer to metastasize to the head and neck (see below).
- Limited diagnostic utility in differentiating benign thyroid inclusions from metastatic papillary thyroid carcinoma:
 - Benign inclusions and metastatic carcinoma are immunoreactive for thyroglobulin, TTF-1, PAX8

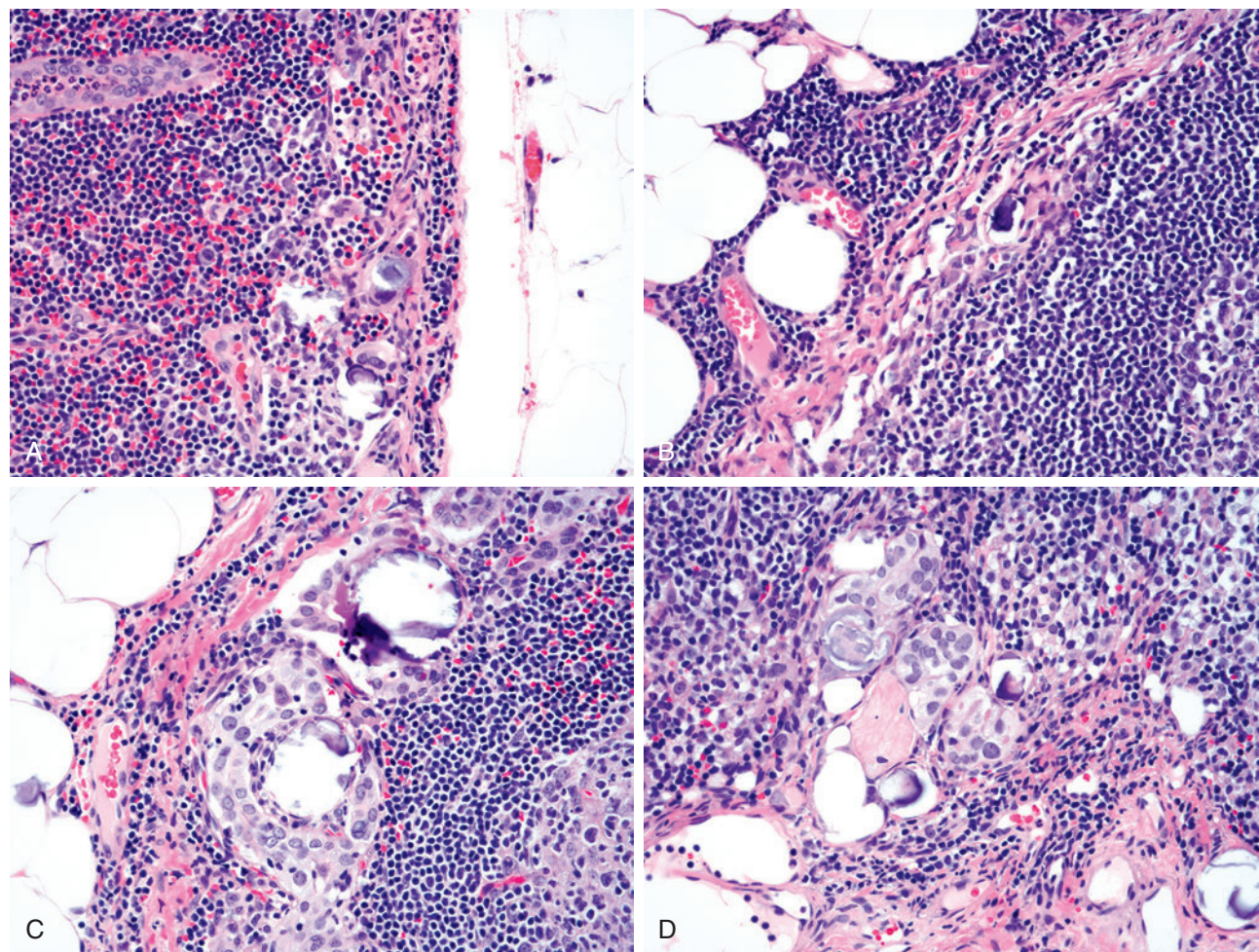


Fig. 27-13. Metastatic papillary thyroid carcinoma.

A and **B**, Isolated “naked” psammoma bodies in the subcapsular sinuses of involved lymph nodes. **C** and **D**, In other lymph nodes, viable foci of metastatic papillary thyroid carcinoma including psammoma bodies were identified. In the presence of isolated psammoma bodies in lymph nodes chances are high that viable papillary carcinoma will be identified in the same or other resected lymph nodes. The primary focus of the metastatic carcinoma was found in the ipsilateral thyroid lobe (not shown).

- There may be some utility to using HBME1 (and CK19, galectin 3) in trying to differentiate benign inclusions (should be HBME1 negative) from metastatic papillary thyroid carcinoma (should show strong membranous HBME1 staining), but such staining is not sensitive or specific (see more detailed discussion in Chapter 28 under Papillary Thyroid Carcinoma).
- *BRAF* and/or *RET/PTC* mutational analysis could assist in discriminating thyroid follicular epithelium in association with chronic lymphocytic thyroiditis (*BRAF* or *RET/PTC* negative) from foci of papillary thyroid carcinoma (*BRAF* or *RET/PTC* positive).
- “Naked” psammoma bodies in lymph nodes:
 - Psammoma bodies are round calcific concretions showing concentric laminations.
 - Not entirely specific for papillary thyroid carcinoma but are exceptionally rare in benign thyroid diseases and in other thyroid carcinomas:
 - Represent important diagnostic clue to presence of papillary thyroid carcinoma
 - Found in approximately 50% of papillary thyroid carcinomas
 - Particularly common in tumors with classic papillary architecture and considered essentially pathognomonic for papillary thyroid carcinoma
 - Often seen in association with lesional cells showing typical nuclear features for papillary thyroid carcinoma but may be identified as

isolated finding in thyroid parenchyma, in areas of inflammation, and/or in fibrotic areas without associated lesional cells that may be referred to as “naked” psammoma bodies

- If present in lymph nodes chances are high that papillary carcinoma is present in lymph node with primary focus of carcinoma in (ipsilateral) thyroid lobe
 - Primary carcinoma may be very small and difficult to detect clinically and histologically.
- Should be noted that presence of psammoma bodies is not limited to thyroid cancer and can be seen in association with other primary malignancies, including salivary gland tumors (e.g., acinic cell carcinoma, mammary analogue secretory carcinoma, polymorphous low-grade adenocarcinoma, cribriform adenocarcinoma of minor salivary glands, others), as well as primary non-head and neck malignant tumors (e.g., lung, ovary, thymus, others)
- Generally considered rare for a primary salivary gland carcinoma to metastasize as a clinically occult primary carcinoma
- Although presence of “naked” psammoma bodies in lymph nodes is highly correlated to metastatic papillary thyroid carcinoma, simply because there are accompanying psammoma bodies in lymph nodes does not necessarily equate to a diagnosis of metastatic (primary) thyroid carcinoma:
 - Histologic evidence in support of a thyroid origin and/or immunohistochemical confirmation (i.e., thyroglobulin) required
- When thyroid gland enters the thoracic inlet, reduced pressure on inspiration may accelerate the migration:
 - Clinically, inferior part of gland cannot be determined due to its location behind the manubrium.
- Goiters with intrathoracic extension usually lead to development of earlier and more severe symptoms:
 - Compression of trachea, esophagus, and great vessels more likely to occur in confined space or tracheal inlet
 - Exacerbation of symptoms may occur at night when patient is supine or lies on one side or other, or by certain positions that increase tracheal compression.
 - Occlusion of thoracic outlet may occur when arms extended over head
 - Referred to as Pemberton sign
 - Results in obstruction of venous return from head and neck region in visible venous distension over neck and plethoric changes in color of facial skin that may be associated with difficulty breathing and/or rarely syncope
- Intrathoracic extension occurs primarily into anterior mediastinum:
 - Approximately 10% located in posterior mediastinum
- Radiology:
 - On chest x-ray, an anterior mediastinal mass may be seen; thyroid scans (^{123}I) may show functional activity as well as the inferior extension of the thyroid gland.
 - Computed tomography and magnetic resonance imaging are extremely useful tools in the diagnosis of mediastinal goiters; features of a mediastinal mass seen on computed tomography (CT) that favor or suggest a thyroid origin (substernal goiter) include:
 - Anatomic continuity with the cervical thyroid
 - CT density greater than muscle
 - A rise in CT density and prolonged enhancement following contrast injection (≥ 2 minutes)
 - Multiple areas of calcification and proximity of the mass to the trachea
 - Tc-99m pertechnetate scintigraphy with and without oral administration of potassium perchlorate (KCLO₄) administration is an accurate and cost-effective imaging method to diagnose retrosternal goiter:
- Most mediastinal goiters are benign (adenomatoid nodules):
 - Thyroid malignancies can be seen in a mediastinal thyroid tissue and include:
 - Papillary carcinoma (microcarcinoma, classic type, follicular variant, others), follicular

Mediastinal Thyroid (Substernal Goiter)

Definition: Presence of goitrous thyroid extending from thyroid gland proper into the mediastinum (substernal or retrosternal):

- Most widely used definition is one in which >50% of total bulk of thyroid gland extends into mediastinum.
- Additional consideration for substernal goiter is one that descends below plane of thoracic inlet.

Clinical

- Clinical parameters, including treatment of substernal goiter, are similar to those goiters (adenomatoid nodules) situated within the normally located thyroid (see later in this chapter).
- As multinodular goiter enlarges, it has a tendency to move inferiorly due to fascial planes favoring this migration.

carcinoma, and undifferentiated (anaplastic) carcinoma

- Mediastinal goiters generally do not respond to thyroid suppression and require surgical removal:
 - Further, due to the risk of sudden enlargement with possibility of airway compression or obstruction, intrathoracic goiters should be surgically removed.

OVARIAN THYROID TISSUE

Definition: Thyroid tissue differentiation occurring in setting of an ovarian teratoma.

Struma Ovarii

(Figs. 27-14 through 27-16)

Definition: Ovarian teratomas in which thyroid tissue is predominant (at least 50%) or sole tissue component.

Clinical

- Presence of thyroid tissue within an ovarian teratoma varies and may be a function of adequate sampling:
 - Benign thyroid tissue occurs in from 5% to 15% of mature ovarian teratomas.
- May occur in a wide range of ages including from second to ninth decades of life
- Clinical presentation (of an ovarian teratoma, in general) is that of an abdominal mass and acute abdominal pain; rarely, may initially be detected as an ovarian mass complicating pregnancy.
- Functional abnormalities may occur and include:
 - Hyperthyroidism
 - Rarely struma ovarii may coexist with Graves disease.
 - Patients may present with ascites that, in the presence of an ovarian mass, may be suspicious for ovarian carcinoma.
 - Ascites and hydrothorax (“pseudo-Meig syndrome”) may occur and may be associated with raised serum CA 125 levels.
- Bilaterality may occur in 5% to 10% of cases.
- Radiology:
 - CT shows cystic components with slightly high density.
 - MRI findings include the presence of multilocular cystic mass with a variable signal intensity within loculi.
 - Loculi or small cysts within septations may show low signal intensity on T1-weighted images and very low signal intensity on T2-weighted images.
 - Gd-DTPA enhanced T1-weighted images may show the presence of thick septations and locally

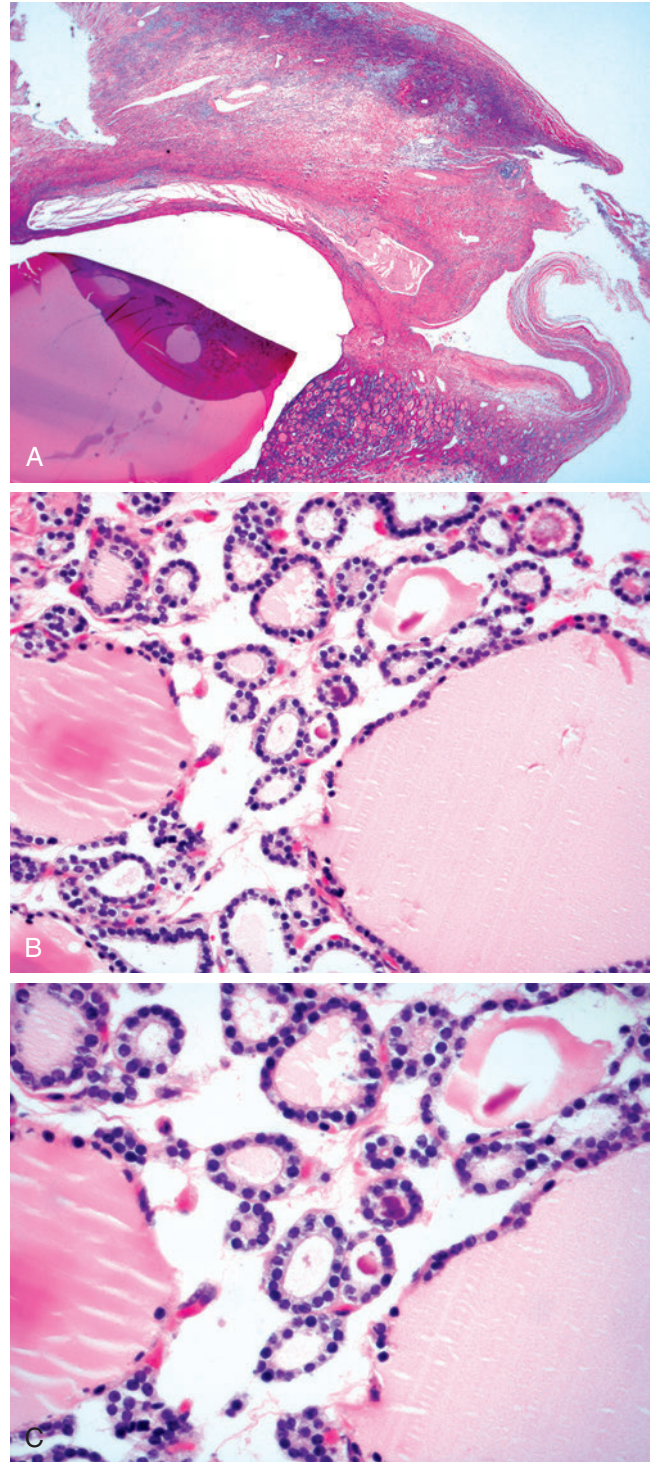


Fig. 27-14. Struma ovarii.

A, Low magnification showing the presence of ovarian parenchyma (*top*) and presence of thyroid parenchyma (*bottom right*) composed of colloid-filled follicles.

B and **C**, Thyroid parenchyma composed of a benign follicular epithelial cell proliferation with features of an adenomatoid nodule.

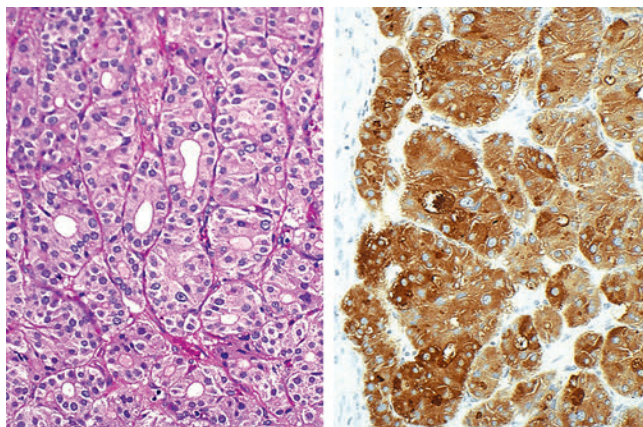


Fig. 27-15. Proliferative struma ovarii.

Left, Follicular growth pattern with minimal to absent colloid. *Right*, The presence of thyroglobulin immunoreactivity is confirmatory of thyroid follicular epithelial cell tissue.

thickened wall with marked enhancement (corresponding microscopically to thyroid tissue).

Pathology

Gross

- Often resembles nodular goiter, appearing as multiple glistening brown nodules

Histology

- Thyroid tissue may be one of many tissue types of the teratoma representing only a minor component of ovarian teratoma; however, in those instances in which the thyroid tissue predominates (at least 50%) or is the sole component of the teratoma, the designation of struma ovarii is applied.
- Histology of struma ovarii most often is that normal-appearing thyroid follicular tissue or as a multinodular goiter with colloid-filled variably sized follicles lined by flattened follicular epithelial cells:
 - Papillary hyperplasia of follicular epithelium can be seen.
 - Secondary degenerative changes such as fibrosis, cyst formation, and hemorrhage can occur.
- Discrete mass lesions composed of densely cellular thyroid follicles (without evidence of malignancy) may be seen and have been termed proliferative struma ovarii.
- Clear cell and signet ring cell cytoplasmic changes can occur.
- Changes of lymphocytic thyroiditis may occur.
- Immunohistochemistry:
 - Thyroglobulin reactivity:
 - Positive in struma ovarii, as well as in thyroid follicular neoplasms (benign and malignant) that occur in this setting

- Thyroid transcription factor 1 (TTF-1) expressed in follicular epithelial cells, as well as in respiratory epithelium, if present
- Calcitonin, chromogranin, and synaptophysin negative
- Cytogenetics and molecular genetics:
 - Various molecular alterations identified in malignant struma ovarii (see below), including:
 - *RET/PTC*
 - *BRAF*
 - *RAS*
 - *PAX8-PPAR γ*

Thyroid Neoplasms in Struma Ovarii

- Thyroid neoplasms arising in setting of struma ovarii are rare:
 - In theory, any neoplasm affecting the thyroid follicular epithelium proper can occur in setting of struma ovarii.
 - Most common type of thyroid neoplasm to occur in this setting is papillary thyroid carcinoma:
 - May be referred to as malignant struma
 - Most are conventional type and follicular variant; less commonly other variants reported, including tall cell variant
 - Diagnosis is based on finding architectural, but more importantly, on the cytomorphic features of papillary carcinoma.
 - Invasive growth (vascular or stromal) is not required for a diagnosis of papillary carcinoma.
 - Follicular carcinoma may occur in the setting of struma ovarii:
 - In contrast to diagnosis of papillary carcinoma in this setting, a diagnosis of follicular carcinoma is based on presence of capsular or vascular invasion and absence of cytomorphic features of papillary thyroid carcinoma.

Differential Diagnosis

- Metastasis to ovary from a primary thyroid carcinoma:
 - Extraordinarily rare occurrence
 - Synchronous or metachronous papillary thyroid carcinoma within struma ovarii (malignant struma) and thyroid gland reported:
 - Rare case reports
 - Differences in microscopic features, immunohistochemical staining (HBME1, CK19, galectin-3), and molecular genetics (*BRAF V600E*, *RAS*, *RET/PTC*) reported

Treatment and Prognosis

- Treatment for ovarian teratoma including struma ovarii is surgical excision:

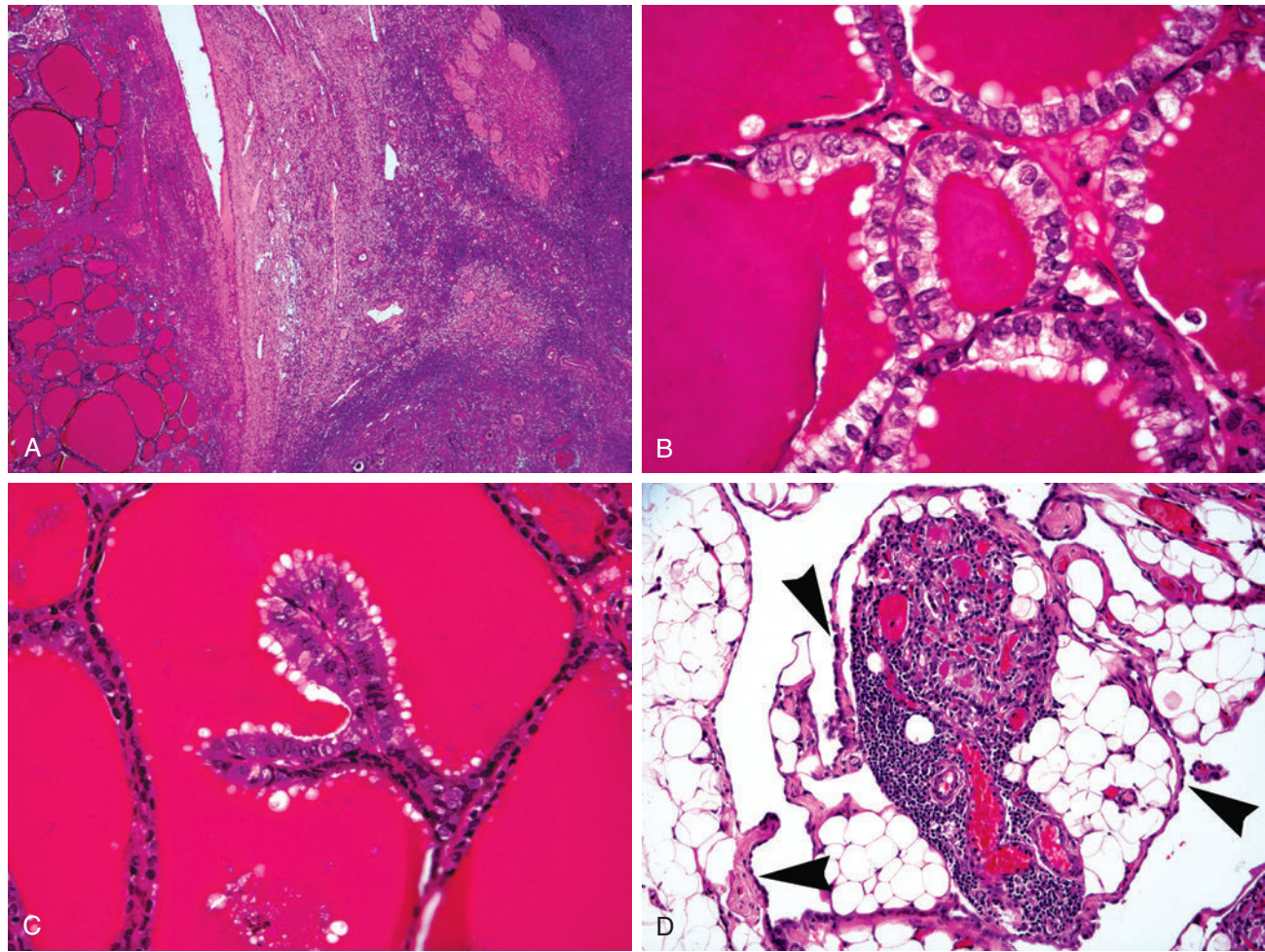


Fig. 27-16. Malignant struma.

Papillary thyroid carcinoma in struma ovarii (malignant struma). **A**, Low magnification showing the presence of colloid-filled thyroid follicles (*left*) in ovarian parenchyma (*right*). **B**, Most of the lesion showed a follicular growth pattern in which the follicles are lined by cells showing nuclear features diagnostic for papillary thyroid carcinoma. **C**, Focal papillary architecture was identified. **D**, Metastatic papillary thyroid carcinoma to a mesenteric lymph node; mesothelial cells are readily identified (*arrowheads*).

- Unilateral salpingo-oophorectomy or total abdominal hysterectomy and salpingo-oophorectomy (unilateral or bilateral)
- Surgical removal is curative.
- In setting of benign struma ovarii, if there is a normally situated (cervical) thyroid gland without abnormalities, then surgical intervention relative to the normally situated thyroid gland not indicated
- Treatment for malignant struma ovarii is surgical excision:
 - Unilateral salpingo-oophorectomy or total abdominal hysterectomy and salpingo-oophorectomy (unilateral or bilateral)
 - Total thyroidectomy also performed:
 - Required to treat with radioactive iodine
- Metastatic disease from papillary carcinoma in struma ovarii may occur and include such sites as:
 - Contralateral ovary, peritoneum, regional lymph nodes, liver, and brain
- Overall prognosis associated with malignant thyroid tumors in struma ovarii has been good:
 - 89% 10-year survival
 - 84% 25-year survival
 - Recurrence may occur within months or decades following initial resection.
 - Although unusual, fatalities secondary to widespread metastatic disease have occurred:
 - May occur years following initial diagnosis
 - Long-term follow-up indicated
- Clinical features predictive of biologic malignancy in struma ovarii include:

- Presence of adhesions, peritoneal fluid ($>$ or $=$ 1 L), or a serosal rent
- Pathologic factors predictive of a poorer prognosis in struma ovarii include:
 - Large size ($>$ or $=$ 10 cm), strumal component more than 80%, extensive papillary carcinoma, especially with solid areas, necrosis, and increased mitotic activity (≥ 5 mitoses per 10 high-power fields)
- So-called benign strumatosus has been used for presence of benign thyroid follicular epithelium within the peritoneum:
 - These foci should be considered as representing metastatic thyroid carcinoma.
- Rare instances of non-Hodgkin malignant lymphomas have been reported in struma ovarii.

Strumal Carcinoid (Fig. 27-17)

Definition: Ovarian tumor that includes presence of thyroid tissue admixed with carcinoid tumor:

- In this setting, other teratomatous elements are usually absent.

Clinical

- Majority of women with strumal carcinoids are postmenopausal, but this tumor may occur over a wide age range from the third through eighth decades of life.
- Clinical presentation is similar to that of any ovarian teratoma presenting as an enlarging abdominal mass or identified as an incidental finding on routine gynecologic (or urologic) evaluation.

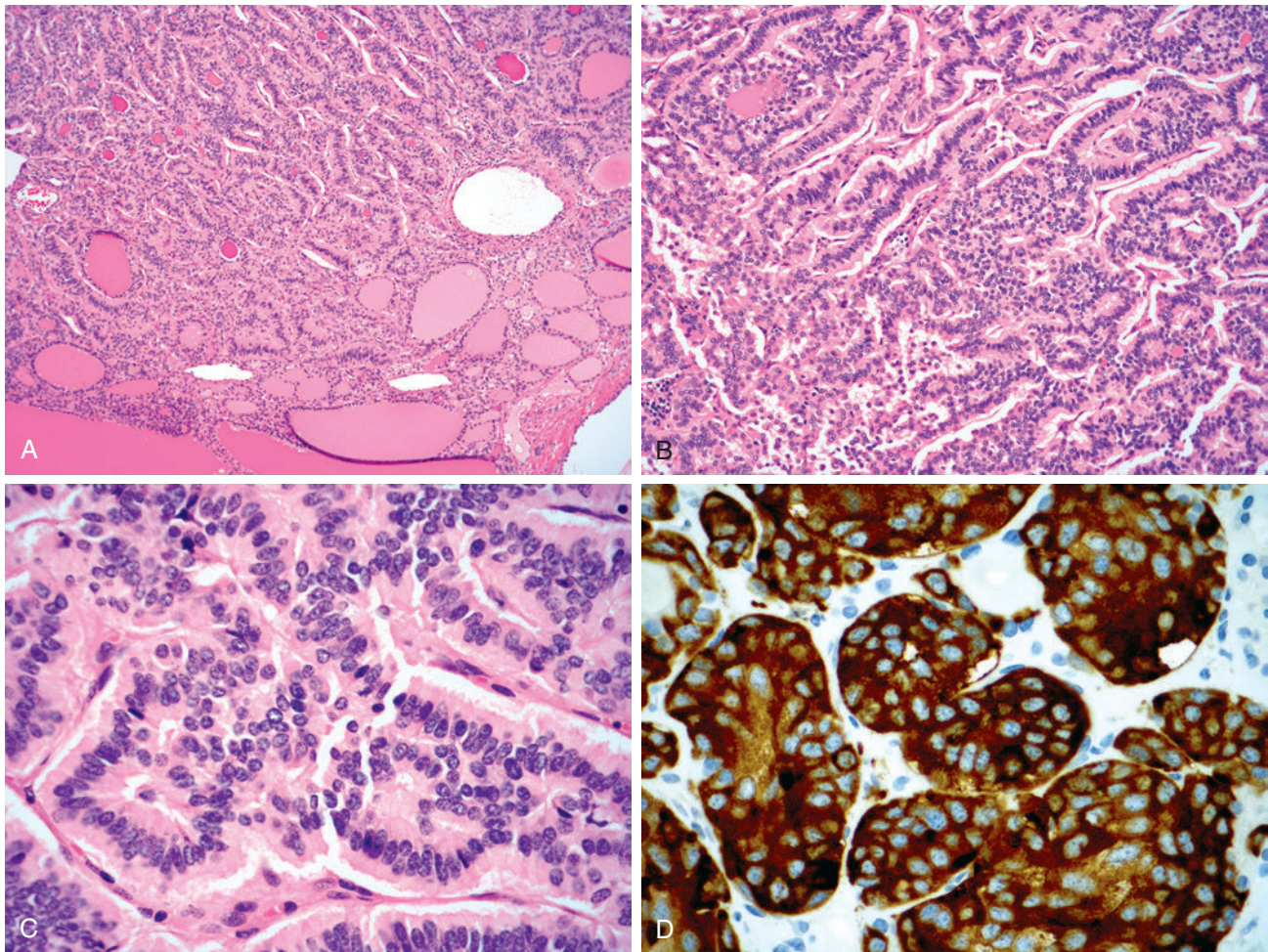


Fig. 27-17. Strumal carcinoid.

A and B, Thyroid tissue within the ovary (not shown) included foci with trabecular and organoid growth. **C,** At higher magnification the lesional cells are composed of round to oval nuclei with dispersed (stippled) appearing nuclear chromatin. **D,** Lesional cells are immunoreactive for synaptophysin.

- Other (uncommon) clinical presentations may include:
 - Constipation, pain on defecation, virilization, hirsutism, symptoms related to function of the thyroid component, and association with multiple endocrine neoplasia 2A:
 - Peptide YY found in association with symptoms of constipation
 - Extremely rare occurrence of carcinoid syndrome has been reported.
 - Similarly rare occurrence of carcinoid heart disease has been reported.
 - Rarely reported in association with struma ovarii and malignant transformation, including follicular variant of papillary thyroid carcinoma, mucinous cystadenomacarcinoma, and strumal carcinoid
- Histogenesis of strumal carcinoid remains controversial:
 - Most likely, histologic elements of this tumor arise from a common progenitor cell such as gives rise to the ovarian teratoma (i.e., endodermal germ cell)
 - No evidence to support C-cell origin for carcinoid component
- Calcitonin only rarely identified
- Neurohormonal peptides that can be present include pancreatic polypeptide, glucagon, somatostatin, vasoactive intestinal polypeptide, and substance P.
- Thyroglobulin and TTF-1 negative in carcinoid component but thyroglobulin and TTF-1 reactive in noncarcinoid thyroid follicular component of strumal carcinoid
- Prostatic acid phosphatase (PAP) may be present in carcinoid component:
 - Similar findings as identified in rectal (hindgut) carcinoids
- Electron microscopy:
 - Neurosecretory granules can be seen.

Differential Diagnosis

- Atypical carcinoid:
 - Extraordinarily rare examples reported
 - As compared to (typical) strumal carcinoid tumor shows greater degree of nuclear pleomorphism, higher mitotic rate, and focal necrosis
 - May metastasize including to bone

Treatment and Prognosis

- Treatment is surgical removal.
 - May include:
 - Unilateral salpingo-oophorectomy in younger-age patients
 - Bilateral oophorectomy and hysterectomy in older-age patients
- Prognosis:
 - Considered excellent following surgical removal even in presence of metastatic tumor
 - Fatalities have been reported.

Pathology

Histology

- Characterized by presence of normal thyroid follicular tissue admixed with carcinoid tumor:
 - Diagnosis is made as long as both components are present and is not based on whether one or the other predominates.
- Carcinoid component:
 - Trabecular growth
 - Composed of cells with small round to oval nuclei with dispersed (“salt and pepper”) chromatin
 - Rarely, acellular eosinophilic extracellular material representing stromal amyloid deposition is present.
 - Rarely, carcinoid component may be of mucinous type (mucus-secreting cells).
- Follicular epithelial component composed of colloid-filled follicles lined by flat to columnar cells with round to oval nuclei and coarse nuclear chromatin:
 - Birefringent calcium oxalate monohydrate crystals are identified in the colloid material.
- Teratomatous elements, including cutaneous and respiratory epithelium, can be identified.
- A dense fibrous stroma is present.
- Histochemistry:
 - Carcinoid component will be argentaffin and argyrophilic positive.
- Immunohistochemistry:
 - Synaptophysin, chromogranin, NSE, and serotonin positive in carcinoid component

METAPLASIA OF THYROID FOLLICULAR EPITHELIUM

Definition: A benign process in which there is a phenotypic alteration from one cell type to another cell type.

Squamous Metaplasia

(Figs. 27-18 and 27-19)

- Benign process in which the normal follicular epithelium changes to one with squamous cell features
- Can occur in a wide variety of settings (Box 27-2)
- Clinical features in which squamous metaplasia occurs based on the pathologic process in which it appears
- Most often, squamous metaplasia of thyroid follicular epithelium seen in setting of lymphocytic thyroiditis and in adenomatoid nodules with retrogressive changes, the latter occurring spontaneously or

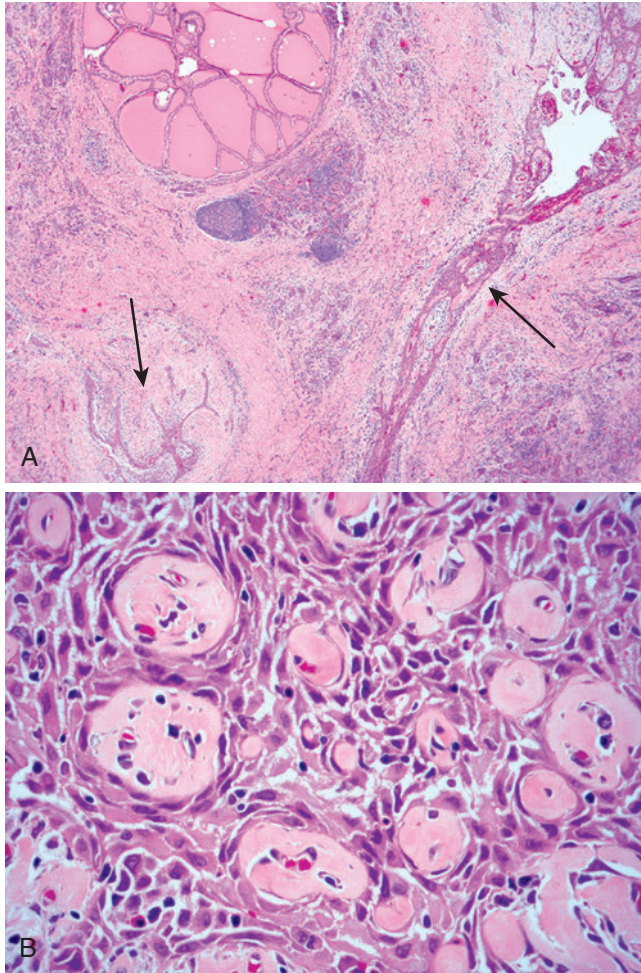


Fig. 27-18. Squamous metaplasia in the thyroid gland.

A, Foci of squamous metaplasia (*arrows*) seen in association with a small adenomatoid nodule (*top*) and background of chronic lymphocytic thyroiditis. **B,** At higher magnification the metaplastic foci include individual cell keratinization and intercellular bridges.

secondary to traumatic event such as a prior fine-needle aspiration biopsy

- Not infrequently may be seen in association with papillary thyroid carcinoma (with or without lymphocytic thyroiditis)
- Alternative theory to squamous metaplasia of follicular epithelial cells is origin from solid cell nests of ultimobranchial derivation:
 - Bulk of evidence favors follicular epithelial cell origin for presence of squamous cells in thyroid gland.

Pathology

- Histology of squamous metaplasia includes:
 - Bland appearance in which nests of cells are round to oval (including “morule” formation) without infiltrative growth

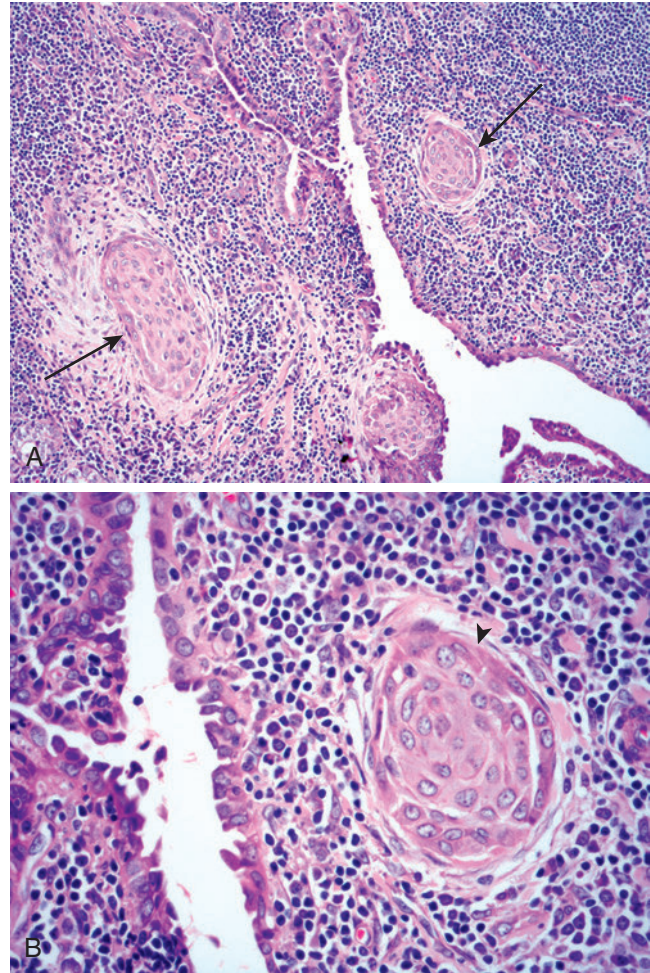


Fig. 27-19. Squamous metaplasia occurring in association with papillary thyroid carcinoma.

A, Foci of squamous metaplasia (*arrows*) are seen in association with cystic papillary thyroid carcinoma and background of chronic lymphocytic thyroiditis.

B, Squamous metaplasia (*arrowhead*) has bland cytomorphic appearance in which nests of cells are round to oval (“morule” formation) without infiltrative growth. The metaplastic focus is located adjacent to a cystic epithelial proliferation (*left*) lined by cells showing nuclear features diagnostic for papillary thyroid carcinoma.

- Keratinization and intracellular bridges can be seen.
- Basaloid cells may be present.
- Cytologic atypia absent, including:
 - Lack of significant pleomorphism and atypia
 - Low nuclear-to-cytoplasmic ratio
 - Mitotic figures can be seen but are limited in number and atypical mitoses not present.
- Absence of associated mucous cells
- Extent of squamous metaplasia may be:
 - Focal (more common)
 - Extensive (less common)

BOX 27-2 Thyroid Lesions That May Have Associated Squamous Metaplasia**Non-Neoplastic**

- Nodular goiter (adenomatoid nodules) with or without retrogressive changes
- Chronic (focal) lymphocytic thyroiditis
- Hashimoto thyroiditis and variants
- Following fine-needle aspiration biopsy or incisional biopsy
- Developmental:
 - Solid cell nests (squamous foci)
 - Thymic rests (Hassall corpuscles)

Neoplasms

- Papillary thyroid carcinoma
- Diffuse sclerosing variant of papillary thyroid carcinoma
- Primary squamous cell carcinoma
- Primary mucoepidermoid carcinoma
- Metastatic squamous cell carcinoma to the thyroid
- Teratoma

- Immunohistochemistry:
 - Cytokeratin (AE1/AE3) positive
 - Variable reactivity for thyroglobulin, TTF-1 may be negative
 - p63 positivity can be seen with predominant positivity at periphery of cell nests.
 - Calcitonin, chromogranin, carcinoembryonic antigen (CEA), and high molecular weight keratin (e.g., 34βE12) negative
- Mutational analysis:
 - *BRAF* and *RAS* negative

Differential Diagnosis

- Primary thyroid squamous cell carcinoma and mucoepidermoid carcinoma (MEC) (see Chapter 28):
 - Both thought to arise from squamous metaplasia of thyroid follicular epithelial cells
 - Majority of cases of squamous metaplasia lack the cytologic atypia and/or infiltrative growth of squamous cell carcinoma.
 - Absence of admixture of epidermoid cells, mucous cells, and intermediate cells allows differentiation from MEC.

Treatment and Prognosis

- Predicated on setting in which the squamous metaplasia occurs

Oncocytic (Oxyphilic) Metaplasia
(Figs. 27-20 and 27-21)

Definition: Oncocytic (oxyphilic) metaplasia is derived from the Greek word meaning “swollen” and results from an increase in mitochondrial content of a cell.

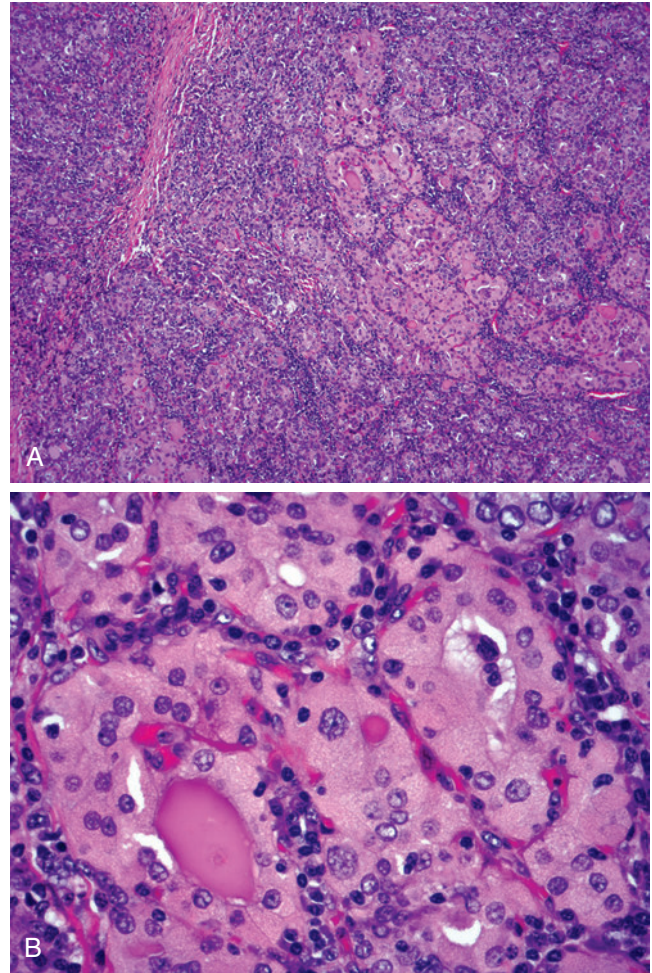


Fig. 27-20. Oncocytic (oxyphilic) metaplasia.

A, Chronic lymphocytic (Hashimoto) thyroiditis with follicular epithelial cells showing oncocytic metaplasia. **B,** At higher magnification oncocytic metaplasia is characterized by the cells with brightly eosinophilic and granular cytoplasm. The oncocytic cytoplasmic changes are associated with nuclear enlargement and pleomorphism, some degree of nuclear clearing, and the presence of prominent eosinophilic nucleoli. Despite the nuclear enlargement, the nuclei remain round with coarse chromatin pattern lacking features of papillary thyroid carcinoma.

- By light microscopy, an oncocytic cell is one that has prominent granular eosinophilic-appearing cytoplasm.
- Oncocytic change not limited to the thyroid but occurs in many nonendocrine organs (e.g., salivary glands, others) as well as in other endocrine organs (pituitary gland, parathyroid gland, adrenal glands).

Synonyms: Hürthle cell is a designation restricted to oncocytic cells in thyroid gland; in all other

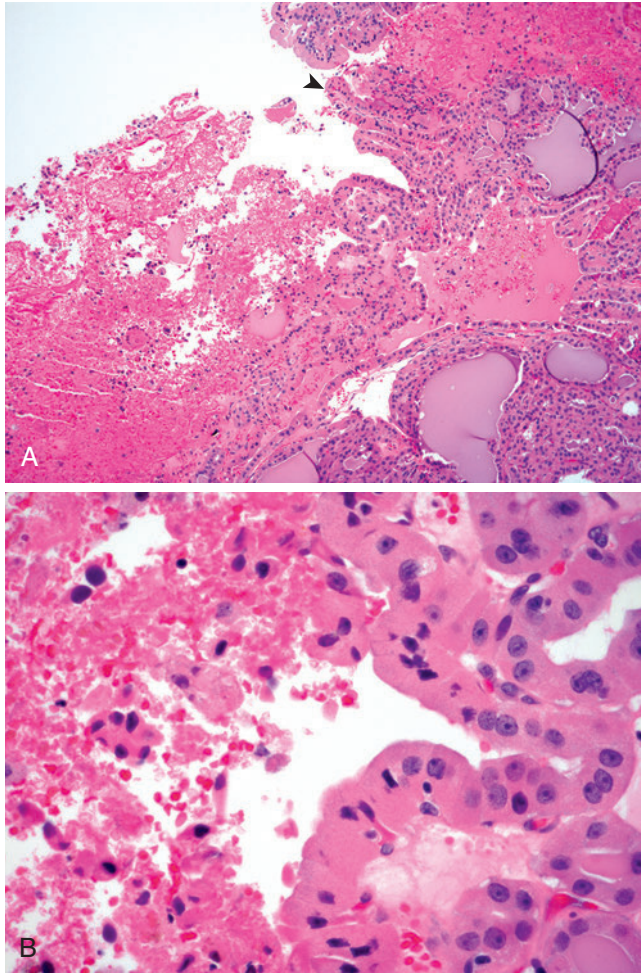


Fig. 27-21. Cellular adenomatoid nodule with oncocytic (oxyphilic) metaplasia.

A, Oncocytic cells are prone to retrogressive changes as may occur following a fine-needle aspiration biopsy that may include papillary architecture (*arrowhead*), necrosis, and hemorrhage. **B**, Follicular cells with oncocytic metaplasia characterized by the cells with brightly eosinophilic and granular cytoplasm adjacent to areas of necrosis and hemorrhage.

(extrathyroidal) sites, use of the terms oncocyte or oxyphilic cell interchangeable

- Several points regarding the presence of oncocytic cells include:
 - Hürthle originally described cell now thought to represent the parafollicular cell or C-cell of ultimobranchial derivation and not oncocyte
 - Askanazy originally described oncocytic cell in thyroid gland.
- Use of designation oncocytic cell, oxyphilic cell, or Hürthle cell in relationship to thyroid lesions is purely descriptive and indicative of a type of change in a cell and NOT indicative (in and of itself) of a

BOX 27-3 Thyroid Lesions That May Have Oncocytic Cell Changes

Non-Neoplastic Lesions

- Nodular goiter (adenomatoid nodules)
- Autoimmune thyroiditis
 - Chronic lymphocytic (Hashimoto) thyroiditis
 - Graves disease
- Post-radiation
- Aging

Neoplasms

- Follicular adenoma, oncocytic variant
- Follicular carcinoma, oncocytic variant
- Papillary thyroid carcinoma, oncocytic variant
- Medullary thyroid carcinoma, oncocytic

specific diagnosis or of any specified biologic behavior:

- Too often, clinicians are under the assumption that a “Hürthle cell neoplasm” is malignant and is synonymous with a follicular carcinoma.
 - Erroneous assumption, oncocytic cell changes can be seen in non-neoplastic and neoplastic (benign and malignant) thyroid lesions ([Box 27-3](#))
 - May occur in solid cell nests (oncocytic solid cell nests)

Pathology

- Histologically, an oncocytic cell characterized by presence of an abundant eosinophilic granular-appearing cytoplasm
- Oncocytic cytoplasmic changes:
 - Associated with enlargement of the cell nucleus:
 - This alteration in nuclear size may lead to an erroneous diagnosis of papillary thyroid carcinoma.
 - Diagnostic confusion may be minimized by:
 - Evaluating the setting in which changes are occurring (e.g., presence of a prominent lymphocytic cell infiltrate as seen in chronic lymphocytic thyroiditis)
 - Evaluating for other changes that may support a diagnosis of papillary thyroid carcinoma, in particular constellation of nuclear changes that in addition to nuclear enlargement includes nuclear variation in size and shape, clear to very fine-appearing nuclear chromatin, margination of chromatin along nuclear membrane, nuclear crowding and overlapping, nuclear grooves, and nuclear pseudoinclusions
 - In addition to enlarged nuclei, cytoplasmic oncocytic change is often associated with prominent central-located eosinophilic nucleoli

- Retrogressive changes:
 - Oncocytic cells perhaps due to oxygen-sensitive nature of mitochondria may be easily traumatized, leading to marked degenerative changes following such events as fine-needle aspiration or core biopsy:
 - Degenerative changes may include pseudopapillary or papillary growth, infarction, necrosis, and hemorrhage.
- Clear cell changes in follicular epithelial cells represent a degenerative process and may be associated and perhaps arise from oncocytic metaplasia.
- Special stains for mitochondria include:
 - Phosphotungstic acid hematoxylin (PTAH): red granular appearance
 - Novelli stain: dark purple appearance
- Immunohistochemistry:
 - Cytokeratin and vimentin positive
 - Weakly thyroglobulin reactive; TTF1 positive
 - Synaptophysin, chromogranin, and calcitonin negative
- Electron microscopy:
 - Cytoplasm filled with mitochondria showing abnormalities in size, shape, and content
- No specific treatment:
 - Treatment and prognosis are predicated on the setting in which the oxyphilic cell changes are seen.

“INCLUSIONS” IN THYROID GLAND

- Embryologic development of the thyroid gland in association with the branchial and pharyngeal pouches allows for incorporation of other branchial and pharyngeal pouch-derived endodermal and mesodermal structures within the thyroid gland.

Intrathyroidal Parathyroid Tissue, Thymic Tissue, Salivary Gland Tissue (Fig. 27-22)

- Branchial and pharyngeal pouch endodermal structures found within thyroid gland include:
 - Parathyroid tissue, thymic tissue, and salivary gland tissue
- Presence of these heterotopic tissues is generally an incidental finding and not cause for surgical removal of thyroid gland.
- Heterotopic parathyroid tissues found within substance of thyroid gland (intrathyroidal) and not outside the thyroid gland (beyond the capsule)
 - Finding parathyroid tissue outside gland reflects inadvertent surgical removal of parathyroid gland(s) at time of thyroid gland resection.

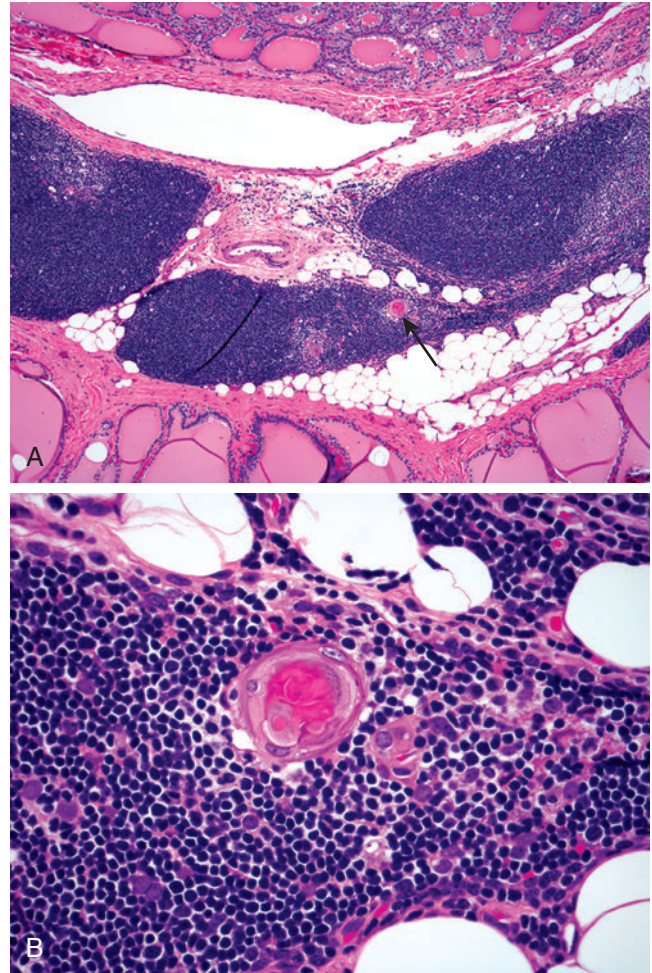


Fig. 27-22. Intrathyroidal thymic tissue.

A, Clusters of predominantly lymphoid cells (*arrows*) within the thyroid gland. **B**, At higher magnification Hassall corpuscles were identified confirming the presence of thymic tissue.

- Incidental parathyroidectomy not uncommon (13.8%) after thyroidectomy and usually not associated with postoperative biochemical hypocalcemia
- In theory, any pathologic process that affects these tissues in their normal anatomic locations may occur when they are found within thyroid tissue; however, in general, histologic appearance of heterotopic tissues is within normal limits and pathologic changes of these tissues (i.e. hyperplasia, neoplasia) are rare:
 - Intrathyroidal hyperfunctioning parathyroid glands can occur.
 - Hyperparathyroidism related to these intrathyroidal parathyroid glands most often due to a parathyroid adenoma and, less often, due to an intrathyroidal parathyroid carcinoma or hyperplasia

- Intrathyroidal thymic-related neoplasms and salivary gland tumors are rare.
- Assessment for patients with hyperparathyroidism may include preoperative noninvasive imaging studies, including neck ultrasound, nuclear medicine scan (technetium-99m-pertechnetate uptake), neck and mediastinal computed tomography scan, and neck and mediastinal magnetic resonance imaging that may localize parathyroid lesions within thyroid gland.
- At times, it may be difficult to histologically differentiate thyroid tissue from parathyroid tissues:
 - Overlapping histomorphologic features of thyroid and parathyroid tissues may include:
 - Clear cell or oncocytic cytoplasmic changes
 - Presence of follicle formation with luminal colloid-like material
 - Features of parathyroid tissue that may be of assistance in differentiating it from thyroid follicular cells include:
 - Overall smaller cell size
 - Hyperchromatic nuclei
 - Sharp cell borders
 - Clear cytoplasm
 - Mixture of different cell types (chief cells, oncocytic cells, clear cells)
 - More pronounced nesting and/or trabecular growth pattern
 - More delicate vascular pattern
 - Presence of parathyroid hormone, parafibromin, synaptophysin, and chromogranin with absence of thyroglobulin immunoreactivity
- Histologic identification of thymic tissue (presence of Hassall corpuscles) and salivary gland parenchyma usually not problematic

Intrathyroidal Branchial Cleft-Like (Epithelial/Lymphoepithelial) Cysts (Figs. 27-23 and 27-24)

- Considered uncommon
- Predominantly occur in adults
- Majority of these cysts are incidentally found in thyroid glands removed for other reasons; occasionally, cysts may attain large sizes presenting as thyroid mass.
- Clinically detectable cysts may appear as a “cold” nodule on thyroid scan and rarely as a “hot” nodule.
- Radiographic (sonographic) imaging may suggest thyroid neoplasm.
- Histogenesis:
 - Due to histologic similarities to branchial cleft cysts, these intrathyroidal cystic structures have been postulated as being of branchial cleft derivation; however, histogenesis not known.

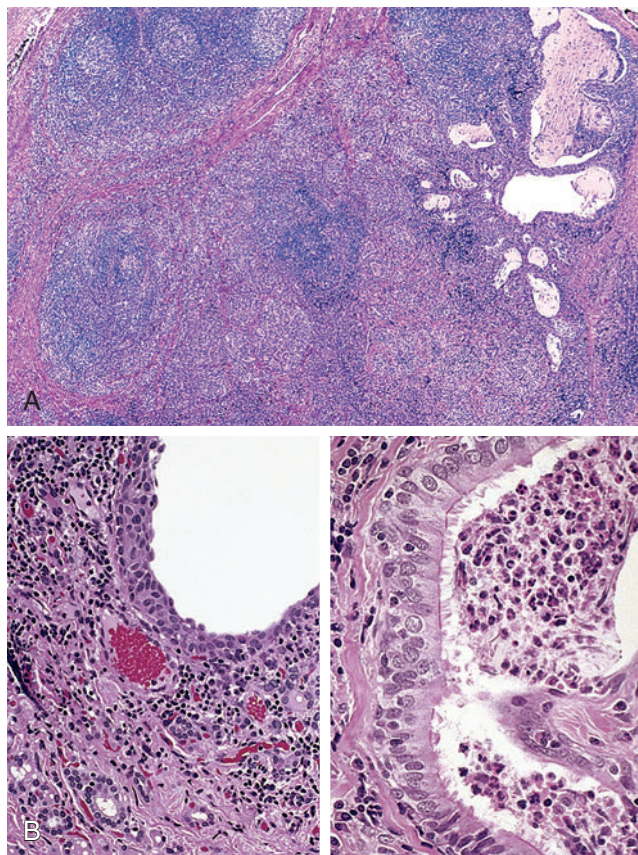


Fig. 27-23. Intrathyroidal branchial cleft-like (epithelial or lymphoepithelial) cysts.

A, Scattered cystic structures are seen (*upper right*) in a background of changes of chronic lymphocytic (Hashimoto) thyroiditis. **B**, The cysts are usually lined by squamous epithelium (*left*) but may include ciliated respiratory epithelium (*right*). These findings were identified in a lateral thyroid lobe rather than in more central (isthmic) portions of the gland, making thyroglossal duct origin less likely.

- Among the considerations is that these intrathyroidal cysts:
 - Part of spectrum of changes associated with chronic lymphocytic (Hashimoto) thyroiditis representing secondary changes (i.e., squamous metaplastic foci with cystic change)
 - In support of a metaplastic alteration with associated cyst formation (which we favor) is the fact that:
 - Chronic lymphocytic (Hashimoto) thyroiditis invariably present in thyroid gland in which the intrathyroidal cysts are seen
 - Identical cysts present as incidental findings in cases of lymphocytic thyroiditis.
 - Cystic lesions often are multifocal and bilateral.

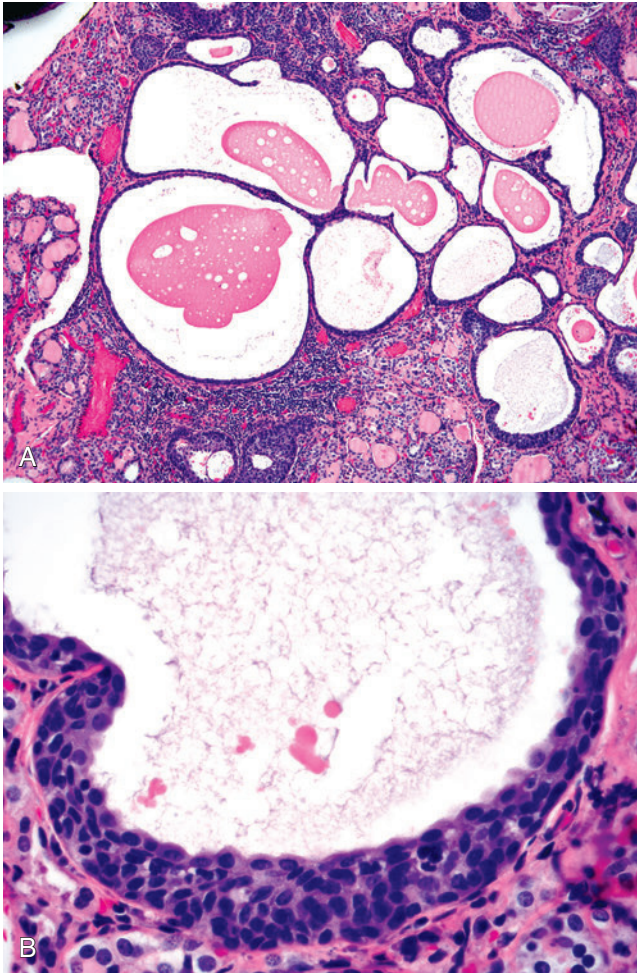


Fig. 27-24. Intrathyroidal branchial cleft-like (epithelial or lymphoepithelial) cysts.

A. In this example many more variably sized cysts are identified, some containing amorphous eosinophilic appearing (colloid-like) material. **B.** At higher magnification the cysts were entirely lined by squamous epithelium.

- Acquired representing cystic degenerative changes of a pre-existing lesion (nodule or neoplasm)
- Originate from developmental rests in thyroid such as solid cell nests (SCN), which represent vestiges of branchial cleft-derived ultimobranchial apparatus
 - In support of this consideration is identification of other branchial cleft-derived structures (e.g., parathyroid glands, thymus) in the thyroid gland
- Histologically:
 - Cystic lesions vary in size from small and indistinct to large and dominant.
 - Dense fibrous capsule may separate cystic lesion from surrounding thyroid tissue.

- Cysts predominantly lined by squamous epithelium consisting of one or multiple layers of cells
- Columnar cell (respiratory-type) epithelium can be seen (with or without cilia):
 - May contain goblet cells that stain for mucin
 - Intermixed with squamous epithelium
- Dense lymphocytic cell infiltrate seen deep to cystic epithelial lining and may include lymphoid aggregates with reactive germinal centers
- Cysts almost invariably occur in association with chronic lymphocytic thyroiditis (Hashimoto thyroiditis or nonspecific chronic thyroiditis).
- Immunohistochemistry
 - Cystic epithelial lining:
 - Reactive with cytokeratins and carcinoembryonic antigen (CEA)
 - Nonreactive for thyroglobulin, calcitonin, or chromogranin
- Cysts are of limited biologic concern.

Solid Cell Nests (SCN) (Figs. 27-25 and 27-26)

Synonyms: Solid ultimobranchial apparatus nests; cystic SNC

- Although the subject of debate, SCN probably are cellular remnants of ultimobranchial apparatus.
- SCN generally incidentally found in thyroid glands removed for other reasons
- When found, SCN localize to lateral lobes (posterolateral and posteromedial aspects) reflecting the migration of ultimobranchial apparatus-derived thyroid cells exclusively to lateral thyroid lobes:
 - SCN as well as C-cell hyperplasia and medullary thyroid carcinoma are not found and do not occur in the isthmus portion of thyroid gland.
- SCN are not uncommon and can be found in more than 25% of resected thyroid glands:
 - Identification of SCN is a function of tissue sampling
- SCN are generally of no biologic concern.

Pathology

- Most measure 0.1 mm on average but may attain larger sizes.
- Appear as small, discrete cell nests, cords, or clusters interspersed among thyroid follicles
- Thought to be composed of two cell types, main cells and C-cells:
 - Predominant (main) cells composed of epithelial cells with:
 - Round to oval-shaped cells with elongated to round-appearing nuclei, finely granular nuclear chromatin, and acidophilic cytoplasm

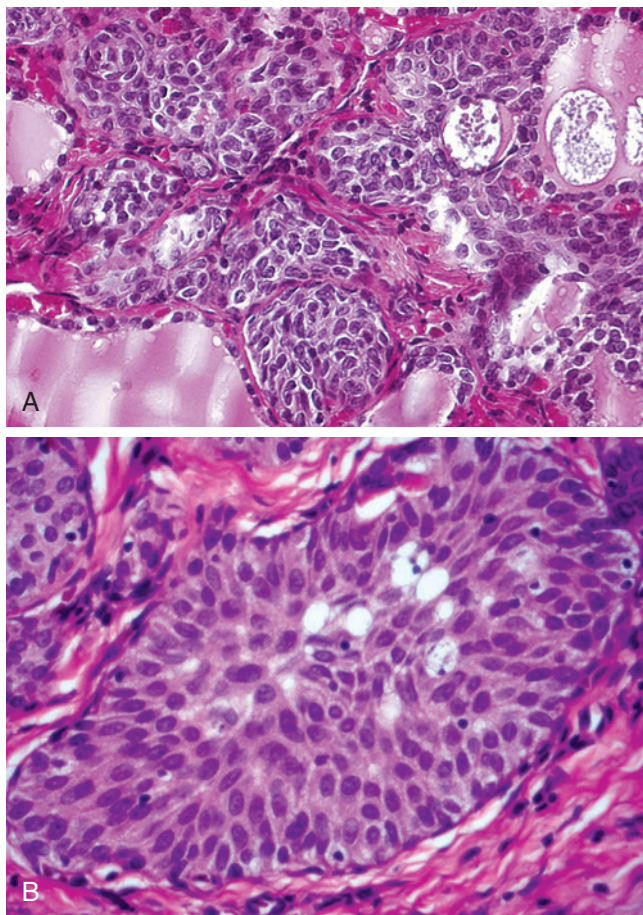


Fig. 27-25. Solid cell nests.

A, B, Solid cell nests in the normal thyroid gland composed small cell nests comprised of epithelial cells with a squamoid (epidermoid) appearance. Neither keratinization (horny pearl formation or individual cell) nor intercellular bridges are found.

- Nuclear grooves may be present.
- Squamoid (epidermoid) differentiation may be present.
 - Keratinization (horny pearl formation or individual cell) and intercellular bridges are not found.
- Cystic change may be present:
 - Referred to as cystic SCN
 - Lined by flattened multilayered epithelium most often with squamoid features and less commonly by ciliated columnar epithelium
 - Dense eosinophilic intraluminal material may be present.
- Rarely, oncocytic cytoplasmic change reported (oncocytic solid cell nests):
 - Acquire mitochondrial alterations similar to those seen in follicular cells and C-cells
- Second less prominent C-cells composed of cells with clear-appearing cytoplasm and round nuclei

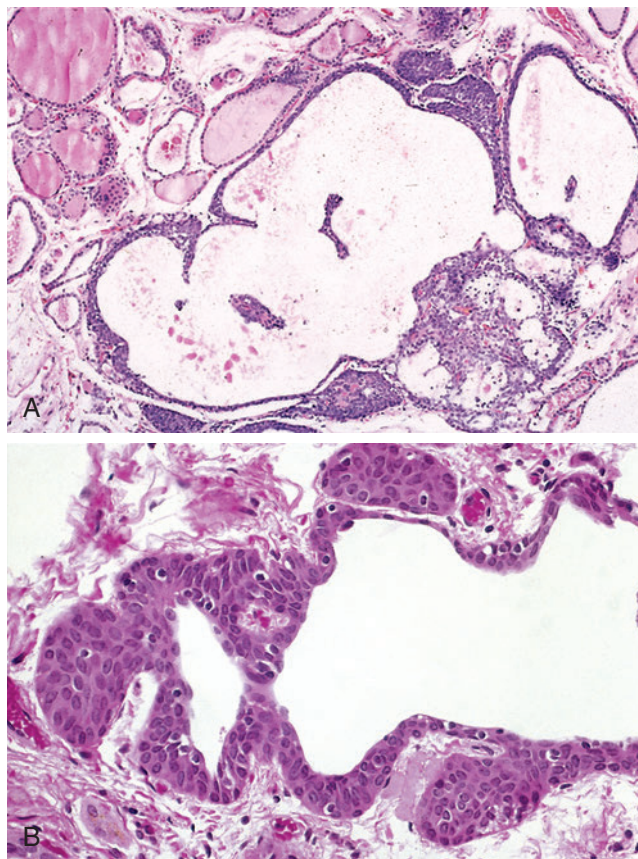


Fig. 27-26. Cystic solid cell nests in the normal thyroid gland.

A, Predominantly cystic and focally solid foci within the thyroid gland. **B,** At higher magnification the cystic and solid areas are composed of epidermoid-appearing cells.

- May merge with thyroid follicle to create so-called mixed follicle
- Mucicarminophilic material can be found:
 - Presence of mucosubstances in SCN thought to be degenerative changes of epidermoid cells, possibly representing true endodermal-derived C-cell conglomerates
- Immunohistochemistry:
 - Main cells are:
 - Cytokeratins (AE1/AE3, CAM5.2, CK903 (34βE12), CK7, CK19) positive
 - CK20 negative
 - Strongly express p63, as well as carcinoembryonic antigen
 - Galectin 3 positive
 - Typically negative for thyroglobulin, TTF-1, HBME1, calcitonin, and parathyroid hormone
 - C-cells are:
 - Positive for calcitonin, chromogranin, synaptophysin

- Positive for cytokeratins (AE1/AE3, CAM5.2, and CK 7)
- Thyroglobulin negative
- Focal immunoreactivity for TTF-1 can be found.
- p63 negative
- These findings demonstrate a dual cell population in solid cell nests with main cells of the solid cell nests displaying a basal/stem cell phenotype (p63 and basal cytokeratin positivity) and C-cells showing features of parafoveolar differentiation.
- Cytogenetics and molecular genetics:
 - Single case of SNC hyperplasia reported to demonstrate *BRAF*(V600E) mutation and *BRAF*(G593D) mutation
 - Supporting histogenetic link between main cells of SNC and papillary thyroid carcinoma
 - Suggesting solid cell nest hyperplasia as precursor lesion of papillary thyroid carcinoma

Differential Diagnosis

- Papillary thyroid carcinoma
- Medullary thyroid carcinoma

MESENCHYMAL-DERIVED “INCLUSIONS” IN THE THYROID GLAND

- Similar to heterotopic endodermal structures found in thyroid gland, heterotopic mesodermal-derived structures such as fat, muscle, and cartilage can also be identified within thyroid gland.

Fat in the Thyroid Gland (Figs. 27-27 through 27-29)

Synonyms: Hamartomatous adiposity; adenolipomatosis; adipose metaplasia

- Rarely, mature adipose tissue can be found within thyroid gland under normal conditions.
- Mature adipose tissue in thyroid gland can also be found in association with numerous pathologic conditions or lesions, including:
 - Adenomatoid nodules, amyloid goiter, lymphocytic thyroiditis, thyroid atrophy, follicular adenoma (adenolipoma), papillary carcinoma, follicular carcinoma, and rarely, diffuse hyperplasia and dysmorphogenetic goiter
- Presence of (non-neoplastic) mature adipose tissue in thyroid gland is an incidental finding found in excision of gland for other reasons.
- Amount and distribution of mature fat varies from a few adipocytes in a limited portion of gland to substantial collections in multifocal sites and/or diffuse infiltration.

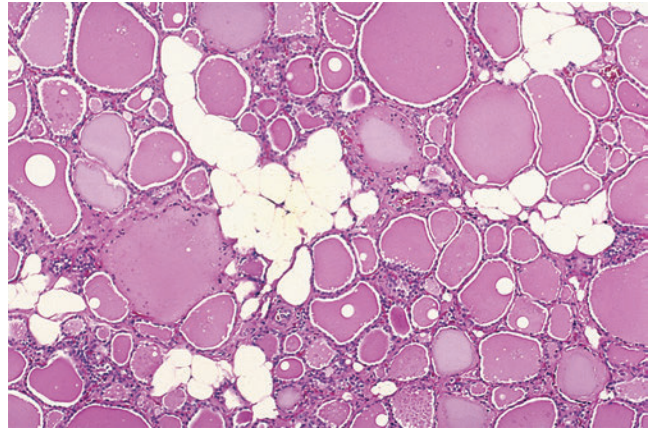


Fig. 27-27. Fat in the thyroid gland.

Mature adipose tissue in normal thyroid parenchyma.

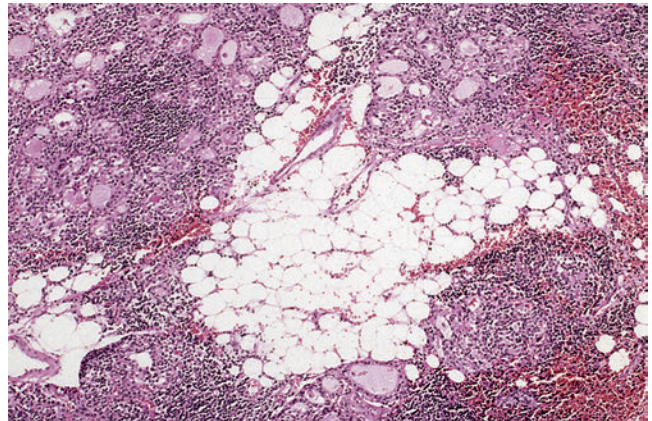


Fig. 27-28. Fat in Hashimoto thyroiditis.

Mature adipose tissue in the setting of chronic lymphocytic (Hashimoto) thyroiditis.

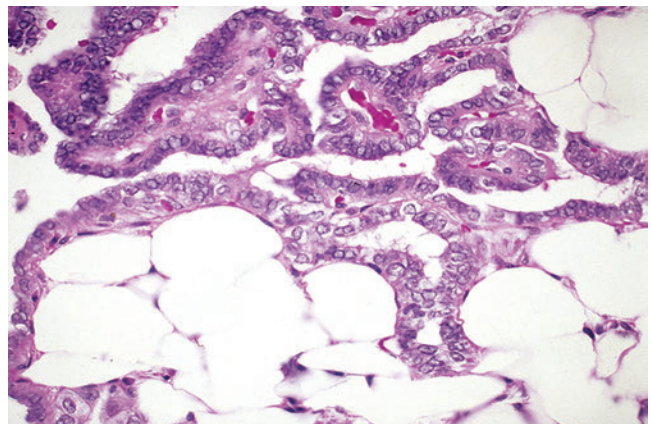


Fig. 27-29. Fat in papillary thyroid carcinoma.

Mature adipose tissue in papillary thyroid carcinoma.

- Adipose tissue is intimately admixed with thyroid tissue and does not appear as a separate, solid mass lesion such as would appear in an adipose neoplasm.
- Mature adipocytes appear as fairly uniform cells with some variation in size and shape that are characterized by presence of clear to vacuolated cytoplasm compressing and eccentrically displacing cell nucleus; nuclei are hyperchromatic without pleomorphism.
- Rarely, foci of extramedullary hematopoiesis may be seen within adipose tissue.
- Mechanism by which mature adipose tissue is found in thyroid gland is not known
 - Some possible explanations include:
 - Embryologic rests
 - Metaplasia from stromal fibroblasts
 - Senile involution
 - True neoplastic component
- Benign and malignant lipogenic tumors of the thyroid gland are extraordinarily uncommon.

Muscle in the Thyroid Gland

(Fig. 27-30)

- Similar to adipose tissue in thyroid glands, presence of skeletal muscle is an incidental finding and may be seen in thyroid gland under normal conditions as well as in variety of pathologic conditions.
- Presence of (non-neoplastic) skeletal muscle in thyroid gland is an incidental finding found in excision of gland for other reasons.

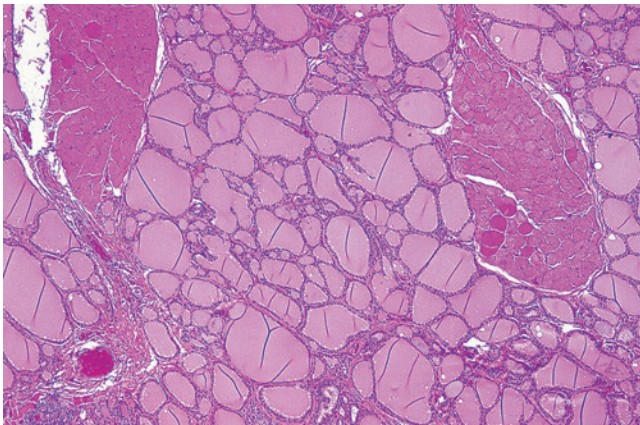


Fig. 27-30. Mature skeletal muscle in the thyroid gland.

Skeletal muscle in the thyroid gland (or vice versa) is typically found in the isthmic portion of thyroid gland or in the pyramidal lobe. The skeletal muscle is intimately admixed with thyroid tissue and does not appear as a separate, solid mass lesion such as would appear in a myogenic neoplasm.

- Skeletal muscle typically found in association with isthmic portion of thyroid gland or pyramidal lobe
- Skeletal muscle is intimately admixed with thyroid tissue and does not appear as a separate, solid mass lesion such as would appear in a myogenic neoplasm.
- Thyroid tissue in skeletal muscle is cytologically benign without findings diagnostic for malignancy.
- Benign and malignant myogenic tumors of the thyroid gland are extraordinarily uncommon.

Cartilage in the Thyroid Gland

(Fig. 27-31)

- As with fat and skeletal muscle, mature cartilage can be found in the thyroid gland (adenochondroma); when found it is as an incidental finding found in glands removed for other reasons.

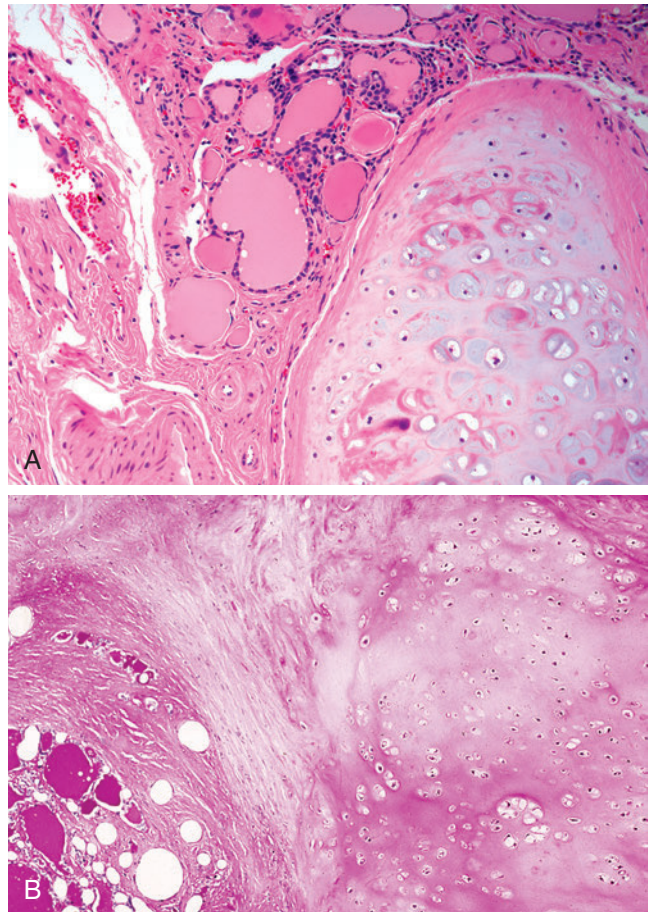


Fig. 27-31. Cartilage in the thyroid gland.

A, Incidentally identified mature cartilage found in a thyroid gland removed for multinodular goiter. **B**, Chondroid focus occurring as a degenerative phenomenon in the setting of adenomatoid nodules.

- Cartilage in thyroid gland may also occur as a metaplastic process seen in association with some pathologic conditions (e.g., adenomatoid nodules).
- Benign and malignant cartilaginous tumors of the thyroid gland are extraordinarily uncommon.

Pigment and Crystals in the Thyroid Gland

Iron

- Following hemorrhage with release of iron from red blood cells, resorption takes place and iron is converted to hemosiderin, which is stored in cell cytoplasm of phagocytizing cells (macrophages) as well as in thyroid follicular cells.
- In thyroid gland, hemosiderin can be found in virtually all pathologic conditions and represents an incidental finding.
- Reflects secondary phenomenon due to hemorrhage and can follow trauma (e.g., post–fine-needle aspiration biopsy, core biopsy) identified in adenomatoid nodules or various neoplasms
- Hemosiderin may be found in macrophages, within the stromal tissues, or within the follicular epithelial cells:
 - Hemosiderin is readily apparent in hematoxylin- and eosin-stained slides and appears as intracytoplasmic coarse brown to yellow pigment.
 - If necessary, iron stains (Prussian blue, Mallory) can be used to identify iron and distinguish it from other pigments.
- Rarely, iron can be stored in the thyroid as a component of a disorder of iron metabolism rather than a secondary phenomenon due to hemorrhage.
- Most cases of iron deposition not associated with thyroid dysfunction:
 - Uncommonly, secondary hypothyroidism may develop.

Lipofuscin

- Lipofuscin pigment represents degenerative (aging) phenomenon in which there is intracytoplasmic accumulation of small yellow to light brown granular-appearing pigment.
- In thyroid gland, lipofuscin pigment can be seen within follicular epithelial cells.
- True nature of lipofuscin has yet to be determined, but it has been shown to react with:
 - Lipid (Sudan IV) and lipofuscin stains
 - Shows diastase-sensitive, periodic acid-Schiff positive intracytoplasmic material
 - Shows lysosomes by electron microscopy
 - Contains the presence of histidine and tryptophan
 - Iron staining is absent.

- Lipofuscin deposition in thyroid gland is an incidental finding, more often seen in thyroid glands from older individuals.
- There is no evidence to indicate that presence of lipofuscin within any cell, including thyroid follicular cells, causes dysfunction or functional compromise of that cell.

Minocycline-Associated Changes (Black Thyroid) (Fig. 27-32)

- Minocycline, a tetracycline derivative, administered to adults for treatment of various reasons (infections, acne) may cause black pigmentation and discoloration of various sites, including skin and thyroid gland.
 - Thyroid involvement referred to as black thyroid

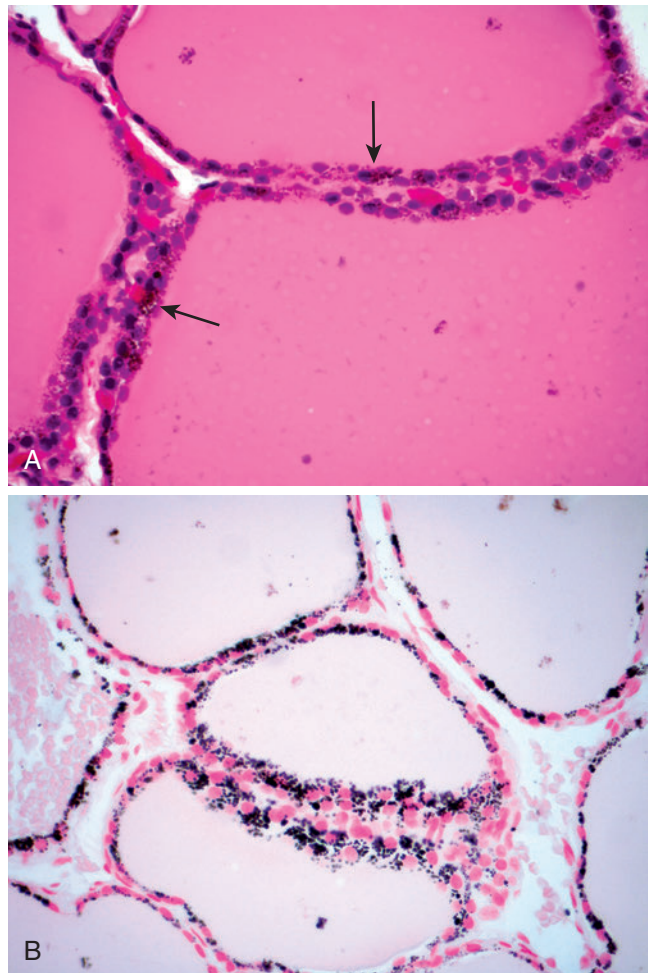


Fig. 27-32. Minocycline pigment (black thyroid).

A, The pigment appears as granular and black to brown on hematoxylin and eosin stain (arrows). **B**, The intracytoplasmic pigment is positive by argaffin (Fontana) staining.

- Presence of minocycline-related pigmentation of thyroid gland is, by and large, not associated with glandular enlargement (hyperplasia) nor functional abnormalities of gland.
 - Rarely, hypothyroidism may be seen in minocycline pigmentation of thyroid gland.
 - Rarely, follicular adenoma, follicular carcinoma, and papillary thyroid carcinoma may be associated with minocycline-induced black thyroid.
- Minocycline pigment appears within cytoplasm of follicular epithelial cells as granular and black to brown:
 - Pigment can also be seen within follicle lumina as large black to brown deposits admixed with colloid.
- Minocycline shares histochemical, electron microscopic, and elemental analysis features with lipofuscin, including:
 - Positive staining with periodic acid-Schiff (PAS), lipid, and lipofuscin stains
 - Presence of lysosomes and autofluorescence
 - Argentaffin stains (Fontana) may be positive.
 - Iron staining negative
 - Increase in vimentin staining in follicular epithelium compared with normal control thyroid glands
 - Thyroglobulin and ubiquitin staining in follicular epithelium is reduced compared with control thyroid tissues.
- True “makeup” of minocycline pigment is still not fully known; possibilities include:
 - Degradation products of drug combined with lipofuscin
 - Oxidation degradation of the drug
 - Drug interaction and alteration of tyrosine metabolism
 - Lysosomal dysfunction
- Localization of pigment may vary from case to case such that in presence of adenomatoid nodules or an adenoma pigment can be seen:
 - In pathologic component of gland and not surrounding uninvolved thyroid
 - In uninvolved thyroid but not in pathologic component of gland
 - In pathologic component of gland and surrounding uninvolved thyroid parenchyma
- Antidepressant agents may be associated with red pigmentation of thyroid gland felt to be due to lysosomal accumulation of drug.

Crystals in the Thyroid Gland

(Fig. 27-33)

- Intracoloidal crystals are not infrequently found in thyroid gland under normal conditions as well as in a pathologic condition.

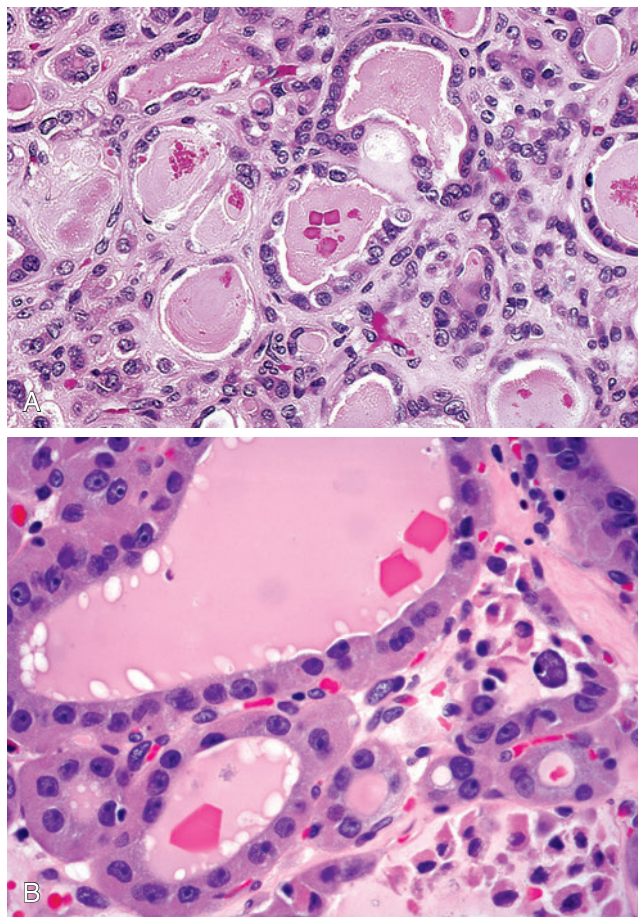


Fig. 27-33. Crystals in the thyroid gland.

A, B, Follicular adenoma with intracoloidal crystals of varying size and geometric shapes.

- Finding of intracoloidal crystals not associated with any specific diagnosis and may be found in virtually all thyroid abnormalities:
 - Highest prevalence of crystals occurs in association with benign diseases and is most commonly seen in nodular goiters followed by follicular adenomas.
 - Crystals may be found in association with malignant tumors (e.g., papillary carcinomas, follicular carcinomas), but prevalence is low.
 - Low prevalence of crystals seen in association with Graves disease, lymphocytic thyroiditis, and subacute thyroiditis
- Frequency of finding crystals within thyroid gland appears to increase with age.
- Intrathyroidal crystals are exclusively found within colloid and do not appear within cytoplasm of the follicular epithelial cells or in stromal tissues.
- Crystals may be found by fine-needle aspiration, but occurrence of crystals in thyroid fine-needle cytology is lower than that in histologic specimens.

- Crystals are readily apparent by light microscopy; polarization enhances their detection.
- Crystals vary in size and shape and appear in a variety of geometric shapes.
- Chemical analysis of crystals indicates that they are composed of calcium oxalate.
- Finding intracoloidal crystals may be a function of increasing age and/or disease state.
- A separate population of patients who have increased frequency of intracoloidal crystals are those undergoing hemodialysis for chronic renal failure.
- Occurrence of crystals in normal human thyroid is associated with a low-functional state of the thyroid follicles.

HYPOTHYROIDISM AND HYPERTHYROIDISM

General Considerations: Hypothyroidism

Definition: Disorder in which thyroid gland is unable to synthesize and secrete sufficient amounts of thyroid hormone to meet requirement of brain and peripheral tissues.

Primary hypothyroidism: Thyroid failure that results from disease of thyroid gland, including clinical and pathologic state that results from decreased production and subnormal amount of circulating thyroid hormone; accounts for 99% of all cases of hypothyroidism.

Secondary hypothyroidism: Result of decreased thyroid stimulation by thyroid-stimulating hormone (TSH) due to pituitary disease.

Tertiary hypothyroidism: Result of decreased thyroid stimulation by thyroid-stimulating hormone (TSH) due to a decrease in pituitary stimulation resulting from a deficiency in thyrotropin releasing hormone (TRH).

Central or hypothyrotropic hypothyroidism: Synonyms for secondary and tertiary hypothyroidism.

Primary Hypothyroidism

Clinical

- Most common clinical disorder of thyroid function
- Most often caused by disorder of thyroid gland leading to decrease in thyroidal production and secretion of thyroxine (T_4) and triiodothyronine (T_3) invariably accompanied by increased thyrotropin (TSH) secretion
- May result from diseases or treatments that destroy thyroid tissue or interfere with thyroid hormone biosynthesis
- Causes of hypothyroidism are listed in [Box 27-4](#):
 - Worldwide, iodine deficiency most common cause of hypothyroidism

BOX 27-4 Causes of Hypothyroidism

Primary Hypothyroidism

- Chronic autoimmune thyroiditis (atrophic and goitrous forms)
- Radiation treatment (^{131}I therapy, external radiotherapy to head and neck for nonthyroid malignant disease)
- Surgery (total or subtotal thyroidectomy)
- Iodine deficiency
- Drug-induced (antithyroidal medications: lithium, iodine, and iodine-containing drugs and radiographic contrast material)
- Infiltrative diseases of thyroid (amyloidosis, scleroderma)
- Defective thyroid hormone biosynthesis
- Congenital defects in thyroid hormone biosynthesis
- Developmental abnormalities (thyroid dysgenesis)

Central Hypothyroidism (Secondary and Tertiary Hypothyroidism)

- Pituitary disease (neoplasms, infarcts, trauma)
- Hypothalamic disease (neoplasms, infectious disease, trauma)

Transient Hypothyroidism

- Silent (painless) thyroiditis (including postpartum thyroiditis)
- Subacute thyroiditis
- After withdrawal of thyroid hormone therapy in euthyroid patients

- In areas where iodine intake is adequate, most common causes are chronic autoimmune thyroiditis and radiation-induced hypothyroidism secondary to radioactive iodine treatment of hyperthyroidism.
- Equal gender predilection; may occur in all age groups but more commonly affects adults
- May be clinically overt or subclinical; subclinical hypothyroidism is defined as elevated serum TSH and normal thyroxine (T_4) and T_3 concentrations.
- Clinical manifestations independent of cause:
 - Overt hypothyroidism defined as:
 - High serum TSH concentrations and low serum free T_4 concentrations
 - Many but not all patients have symptoms and signs of hypothyroidism but clinical spectrum of severity may be broad even in overt hypothyroidism such that some patients may have very subtle manifestations of disease (few signs and symptoms), whereas others may have more extreme manifestations (myxedema coma).
 - Subclinical hypothyroidism defined as:
 - High serum TSH concentrations (usually <10 mU/L) and normal serum free T_4 concentrations
 - Patients typically have few or no symptoms and signs of hypothyroidism.

- Clinical symptoms and signs of hypothyroidism include (in no particular order):
 - Fatigue, lethargy, sleepiness, mental impairment, depression, cold intolerance, slow movements, slow speech, hoarseness, bradycardia, dry skin, decreased perspiration, nonpitting edema, anemia, decreased appetite, constipation, weight gain, arthralgia, hyporeflexia, paresthesia, menstrual abnormalities (typically menorrhagia), and infertility
- Three types of clinical evidence suggest hypothyroidism:
 - Symptoms and signs consistent with thyroid hormone deficiency
 - Evidence of diseases, previous treatment, or exposure known to cause thyroid or pituitary failure
 - Presence of disorders associated with increased risk of chronic autoimmune thyroiditis
- Myxedema:
 - Severe hypothyroidism sometimes referred to as myxedema but myxedema is not synonymous with hypothyroidism
 - Represents accumulation of glycosaminoglycans in soft tissues (subcutaneous and other interstitial sites), resulting in nonpitting edema of hypothyroid patients
 - Most common in severe (long-standing) primary hypothyroidism
- Factors potentially influencing clinical features of hypothyroidism include:
 - Patient age:
 - In children and adults effects are potentially reversible.
 - In infants, hypothyroidism may result in irreversible mental and physical retardation (see below, endemic cretinism) unless treatment is initiated early.
 - Presence of other diseases:
 - If there is not generalized destruction of thyroid gland, compensatory increase in TSH secretion may maintain thyroid secretion at near normal levels so that the clinical manifestations of hypothyroidism may remain subclinical for years.
 - Rate at which hypothyroidism develops:
 - Those patients with rapid onset of hypothyroidism have more symptoms than those patients who develop it gradually.
- Laboratory testing:
 - Low serum free thyroxine (T_4) levels and elevated serum thyroid-stimulating hormone (TSH) levels confirm presence of hypothyroidism.
 - Serum triiodothyronine (T_3) concentrations also decline but not frankly low until thyroidal T_3 -secretion and hepatic T_4 -to- T_3 conversion.

- Generalized myxedema:
 - Develops in patients with long-standing, severe generalized thyroid deficiency
 - Clinical features result from glycosaminoglycan accumulation in soft tissues resulting in a full face, nonpitting periorbital and cutaneous edema (most marked around the hands), which does not resorb during recumbency (unlike cardiogenic edema).
 - The soft tissue fluid accumulation is composed of a mixture of mucopolysaccharides, hyaluronic acid, and chondroitin sulfate.
 - Fluid may accumulate in virtually every part of the body, some of these sites in which fluid accumulation occurs due to thyroid deficiency and result in clinical signs and symptoms

Select Clinical Manifestations of Hypothyroidism

- Cardiovascular (myxedema heart):
 - Most common cardiovascular abnormality of hypothyroidism is pericardial effusion
 - Other changes relate to cardiac papillary muscle contractile abnormalities, electrical abnormalities resulting in sinus bradycardia as seen by electrocardiographic changes such as prolonged QT intervals, flattening and inversion of T waves, and in children the so-called mosque sign with a dome-shaped T wave and partially obliterated ST segment.
 - Radiographic findings include cardiomegaly.
 - Incidence of atherosclerotic cardiovascular disease is increased in hypothyroid patients.
- Pulmonary:
 - Direct pulmonary effects, including altered pulmonary function tests, depressed ventilatory drives, pleural effusions, decreased surfactant production in the neonate
 - Indirect pulmonary effects, including phrenic nerve paralysis, congestive heart failure causing pulmonary edema, obesity causing atelectasis, others
- Neurologic manifestations
 - Psychiatric disturbances most prominently depression
 - Adults with acquired hypothyroidism have propensity to develop entrapment neuropathies (e.g., carpal tunnel syndrome).
 - Mental retardation and cretinism well-recognized complications of endemic iodine deficiency and untreated overt congenital hypothyroidism
 - Myxedema coma:
 - Rare syndrome represents severe life-threatening hypothyroidism.
 - Most frequently occurs in elderly women with long-standing hypothyroidism

- More likely to occur in winter months possibly associated with extreme cold
- Other possible precipitating factors include infection, drugs (anesthetics, sedatives, tranquilizers, narcotics, lithium), trauma, cerebrovascular accidents, congestive heart failure.
- Cardinal features include hypothermia and unconsciousness.
- High mortality rates in untreated patients
- Should be viewed as a medical emergency
- Rapid diagnosis with immediate initiation of appropriate therapy is key in preventing death; therapy includes ventilatory support, control of water and electrolyte imbalances, temperature control, administration of hydrocortisone therapy in the presence of coexisting adrenal insufficiency, and initiation of thyroid hormone therapy.
- Renal:
 - Alterations in renal hemodynamics and kidney function resulting in generalized fluid retention
 - Extravascular accumulation of protein-rich fluid (albumin and other proteins) results in weight gain but there is a decrease in the plasma volume and a fall in cardiac output.
- Upper aerodigestive tract:
 - Airway obstruction due to goiter, enlarged tongue, pharyngeal muscle dysfunction
 - Uncommonly myxoid polyps of larynx occur in hypothyroid patients.
- Other manifestations of hypothyroidism include:
 - Infectious complications:
 - Increased susceptibility to infections of respiratory tract, urinary tract, and skin reported in hypothyroid patients
 - Hematologic:
 - Anemia is common in hypothyroidism (seen in up to 30% to 40% of patients).
 - Anemia most often normo- or macrocytic and normochromic and represents a normal physiologic response:
 - Thyroid hormone has a stimulatory effect on erythropoiesis via erythropoietin.
 - Deficiency in thyroid hormone leads to decrease in erythropoiesis due to slowing of metabolic rate, decrease in oxygen requirement, and decrease in erythropoietin levels.
 - Small percentage of hypothyroid patients (2% to 15%) have microcytic anemia.
 - Little significant effects on white blood cells and platelets occur.
- Myxedematous endemic cretinism:
 - Occurs in areas of endemic goiter and severe iodine deficiency
 - Represents most serious complication of endemic goiter
- In severe endemic goiter, irreversible abnormalities of intellect and physical development occur in a high number of patients.
- Clinically includes:
 - Mental deficiency with defects in hearing and speech
 - Disorders of standing and gait
 - Hypothyroidism and stunted growth
- Iodine deficiency is fundamental in cause of endemic cretinism and if severe enough, may be the only factor causing cretinism.
 - Other factors may include natural-occurring goitrogens, thyroid autoimmunity, trace element deficiency (selenium, manganese), congenital infections and perinatal anoxia.
- No specific therapy
- Rehabilitation is similar to patients with cerebral palsy.
- Prevention is by efficient iodine prophylaxis.
- Treatment of hypothyroidism
 - May be as simple as replacing thyroxine (T_4) using levothyroxine (LT_4)
 - Considered preferred treatment for hypothyroidism
 - Most patients treated with LT_4 as single agent
 - In some instances, hypothyroidism does not result from destruction of gland but due to another cause (Box 27-4) not be remedied by levothyroxine (LT_4) replacement.
 - In these instances, identification and treatment of underlying cause is paramount in controlling effects of hypothyroidism.

Thyrotoxicosis and Hyperthyroidism

Definitions:

Thyrotoxicosis: Clinical syndrome of hypermetabolism and hyperactivity that results when serum concentrations of free thyroxine (T_4), free triiodothyronine (T_3), or both are elevated.

Hyperthyroidism: Sustained increases in thyroid hormone biosynthesis and secretion by thyroid gland.

- Hyperthyroidism and thyrotoxicosis are not synonymous:

- Although many patients with thyrotoxicosis have hyperthyroidism, others do not, such as those patients in whom thyrotoxicosis is caused by release of excess hormone from thyroid in absence of increased synthesis, such as thyroiditis or exogenous thyroid hormone administration.

Clinical

- Hyperthyroidism less common than hypothyroidism
- Causes of thyrotoxicosis (with and without hyperthyroidism) listed in Box 27-5.

BOX 27-5 Causes of Thyrotoxicosis**Associated with Hyperthyroidism (Elevated Thyroid RAIU)**

- Graves disease
- Toxic nodular or multinodular goiter
- Solitary hyperfunctioning (toxic) adenoma
- Inappropriate TSH hypersecretion
- Gestational trophoblastic disease (hydatidiform mole; choriocarcinoma)
- Hyperemesis gravidarum
- Familial gestational hyperthyroidism

Associated with Low Thyroid RAIU

- Postpartum and sporadic silent thyroiditis
- Painful subacute thyroiditis (de Quervain, granulomatous)
- Acute infectious thyroiditis (bacterial, fungal, others)
- High-dose radiotherapy
- Surgical manipulation
- Infarction of adenoma
- Excess exogenous thyroid hormone
- Metastatic thyroid cancer
- Iodine-induced hyperthyroidism
- Struma ovarii

RAIU, Radioactive iodine uptake.

- Most common cause of spontaneous thyrotoxicosis is Graves disease, ranging from 60% to 90% in different regions of the world; most of remaining cases caused by:
 - Toxic nodular goiter
 - Autonomously functioning solitary thyroid adenoma
 - Several types of thyroiditis
- Clinical manifestations independent of cause:
 - Many patients with thyrotoxicosis have overt clinical and biochemical disease.
 - Thyrotoxicosis may be subclinical (subclinical thyrotoxicosis) defined as:
 - Normal serum free T_4 and T_3 concentrations and low serum thyrotropin (TSH) concentrations
 - Patients usually have no symptoms and signs of thyrotoxicosis but if present are usually mild and nonspecific.
- Biochemical confirmation of thyrotoxicosis can be determined on basis of:
 - Elevated levels of serum total and free thyroxine (T_4) and triiodothyronine (T_3) concentrations and decreased serum thyroid-stimulating hormone (TSH) levels
 - Biochemical confirmation of thyrotoxicosis does not include cause of disease.
- Factors that may determine manifestations of thyrotoxicosis include:
 - Age of patient:
 - Compared to younger patients, older patients have:
 - Fewer symptoms and signs of sympathetic activation (e.g., anxiety, hyperactivity, tremor)
 - More symptoms and signs of cardiovascular dysfunction (e.g., congestive heart failure, atrial fibrillation) and more likely to lose weight
 - Elderly patients with thyrotoxicosis may present with predominant involvement of one organ system and without the classic signs and symptoms of thyrotoxicosis referred to as apathetic thyrotoxicosis.
 - Presence or absence of a concomitant disease
- Clinical signs and symptoms of thyrotoxicosis include:
 - Nervousness, fatigue, weakness, heat intolerance, increased perspiration, hyperactivity, tachycardia, arrhythmias, palpitation, systolic hypertension, increased appetite, loss of weight, warm and moist skin, hyperreflexia, tremor, muscle weakness, and menstrual disturbances
- Signs associated with specific causes of thyrotoxicosis include:
 - Thyroid pain and tenderness with presence of a goiter (diffuse or nodular)
 - Ophthalmopathy and localized myxedema seen in Graves disease
- Laboratory findings:
 - Elevated serum total and free thyroxine (T_4) and triiodothyronine (T_3) concentrations
 - Most patients have high serum concentrations of both hormones.
 - Some patients have isolated increases in either thyroxine (T_4) or triiodothyronine (T_3).
 - Although serum thyroid hormone measurements are useful for detecting and monitoring thyrotoxicosis there are limitations:
 - There are other causes of elevated thyroxine (T_4) and triiodothyronine (T_3) concentrations (Box 27-6).
 - Some thyrotoxic patients have serum thyroxine (T_4) and triiodothyronine (T_3) concentrations within upper portion of normal range.
 - Other tests include measurement of thyroid radiiodine uptake (RAIU) and scan, thyroid ultrasound, and measurements of thyroid peroxidase, thyroglobulin, and TSH receptor (TSHR) antibodies.
 - RAIU most useful because it distinguishes between thyrotoxicosis caused by hyperthyroidism (elevated RAIU) and thyrotoxicosis caused by thyroiditis, exogenous thyroid hormone administration, and other etiologies (low RAIU)
- Significant systemic manifestations of thyrotoxicosis include:

BOX 27-6 Causes of Elevated Serum Thyroxine Concentrations

- Thyrotoxicosis
- Increased serum protein binding
- Increased serum thyroxine-binding globulin concentration:
 - Inherited
 - Estrogen (pregnancy, exogenous, tumoral production)
 - Hepatitis
 - HIV infection
 - Drugs (methadone, heroin, clofibrate, 5-fluorouracil)
- Familial dysalbuminemic hyperthyroxinemia
- Increased serum transthyretin binding and concentrations
 - Inherited
 - Pancreatic carcinoma, hepatoma
- Psychiatric and medical illness
- Drugs
 - Propranolol
 - Amiodarone
 - Radiographic contrast agents used for cholecystography
- Anti-T₄ immunoglobulins

- Cardiovascular:
 - Heart is major target organ for thyroid hormone action
 - Among many clinical manifestations of thyrotoxicosis, cardiovascular complications have highest potential for life-threatening consequences:
 - Increase in cardiovascular deaths demonstrated in patients with thyrotoxicosis
- Hemodynamic changes:
 - Increased systolic (increased stroke volume and rapid heart rate) and diastolic (shortened circulation time and decreased cardiac indices) functions
 - Despite presence of increased cardiac contractility and high output state caused by thyrotoxicosis, cardiac failure may (paradoxically) occur with decreased cardiac function, resulting in evidence of congestive heart failure, including pitting edema and pulmonary congestion.
 - Electrocardiographic changes include sinus tachycardia, atrial fibrillation
 - Increased metabolic demand may lead to:
 - Increased cardiac oxygen demand and risk of ischemia
 - Increased risk of atrial arrhythmias particularly fibrillation
 - Promotes development of congestive heart failure in susceptible individuals
 - Mitral valve prolapse is common abnormality found in Graves disease (pathophysiologic mechanisms for mitral valve prolapse in Graves disease are not known).
- Exertional dyspnea even without evidence of heart failure
- Muscular:
 - Generalized myopathy (weakness) and atrophy:
 - Most commonly involves pelvic girdle and shoulder muscles
 - Exophthalmic ophthalmoplegia (localized paralysis of ocular muscles) characterized by lid lag, lid retraction, and exophthalmos
 - Myasthenia gravis:
 - Coexistence of myasthenia gravis and thyrotoxicosis is uncommon (<1% of patients).
 - Incidence of thyrotoxicosis as a complication of myasthenia gravis is not as uncommon, occurring in up to 6% of myasthenia gravis patients.
 - Thyrotoxic periodic paralysis:
 - Characterized by attacks of flaccid paralysis (all extremities and trunk) with areflexia and abolition of electrical excitability may be a rare complication of thyrotoxicosis
 - Result of intracellular shift of potassium in genetically and clinically susceptible patient
- Neurologic (CNS):
 - Neuropsychiatric disorders:
 - Nervousness, irritability, tremulousness, anxiety disorders, depression, mania, and schizophreniform disorders may occur.
 - Discrete neurologic syndromes:
 - Chorea (rapid, nonrepetitive, random movement of extremities or less commonly facial muscle or trunk) is an unusual manifestation of thyrotoxicosis.
 - Resolves following successful treatment of thyroid condition
 - Severe acute systemic states with delirium, coma, and convulsions (thyrotoxicosis storm)
- Treatment of thyrotoxicosis:
 - Directed at cause of hyperthyroid state
 - Emphasis of treatment is on Graves disease because it is most common cause of thyrotoxicosis.
 - However, an underlying cause may not be readily established, rendering control of disease difficult.
 - Potential treatment modalities include:
 - Antithyroid drugs in an attempt to make the patient euthyroid: thionamides (e.g., propylthiouracil, methimazole); iodide; potassium perchlorate; lithium
 - Radioactive iodine
 - Surgery:
 - Subtotal thyroidectomy oldest form of therapy for thyrotoxicosis:

- Defined as removal of most of thyroid gland leaving few grams of posterior portion of each lobe
 - Presently performed in United States only under special circumstances:
 - In children, adolescents and pregnant women who are allergic to or noncompliant with antithyroid drugs
 - In patients with large goiters or severe ophthalmopathy
 - In patients who prefer destructive therapy
 - Many surgeons recommend total or near total thyroidectomy rather than subtotal thyroidectomy because of possibility of recurrent thyrotoxicosis due to thyroid regrowth with subtotal removal.
- Prognosis dependent on cause of the thyrotoxicosis (Box 27-5)
- Thyrotoxic storm or crisis:
 - Relatively rare but represents life-threatening syndrome characterized by exaggerated manifestations of thyrotoxicosis
 - Cardinal manifestations of thyrotoxicosis storm include:
 - Fever: usually $>102^{\circ}\text{F}$ (38.9°C)
 - Tachycardia: out of proportion to fever
 - Gastrointestinal dysfunction: nausea, vomiting, diarrhea, and, in severe cases, jaundice
 - CNS related: marked hyperirritability, anxiety, confusion, apathy, and, in extreme cases, coma
 - Above features in patient with a goiter, Graves disease ophthalmopathy, or a history of partially treated thyrotoxicosis may signal diagnosis of thyrotoxic storm.
 - Causes of thyrotoxicosis storm are:
 - Infection (most common), trauma (including vigorous palpation of the thyroid), surgery, hypoglycemia, stress, cessation of antithyroid drug medication, ^{131}I therapy, diabetic ketoacidosis, cerebrovascular accident, pulmonary ketoacidosis, iodinated contrast dyes
 - Precise mechanism of thyrotoxicosis storm is not fully known and it probably is multifactorial.
 - Laboratory findings:
 - Elevated serum total T_4 and T_3 , T_3 -resin uptake, and 24-hour radioiodine uptake
 - These levels are raised above normal but are not substantially different from those levels in uncomplicated cases of thyrotoxicosis.
 - Owing to potential high mortality, often necessary to initiate treatment without waiting for biochemical confirmation
 - Therapy:
 - Antithyroid drug directed against thyroid gland to decrease thyroidal production and secretion of T_4 and T_3

- Directed against systemic disturbances:
 - Treatment of fever
 - Correction of volume depletion and poor nutrition
 - Supportive therapy
- Amelioration of peripheral actions of thyroid hormone
 - Administration of β -adrenergic antagonist drug
- Treatment of any precipitating or underlying illness

NONAUTOIMMUNE THYROIDITIDES

Acute (Infectious) Thyroiditis (Figs. 27-34 and 27-35)

Definition: Presence of an inflammatory cell infiltrate dominated by polymorphonuclear leukocytes within thyroid gland.

Synonyms: Acute suppurative thyroiditis; infectious thyroiditis; pyogenic thyroiditis

Clinical

- Rare disease
- No gender predilection; may occur in all age groups
- Most often represents an infectious disease but may occur following exposure to radiation
- Tends to develop in immunocompromised and/or malnourished patients, including:
 - Patients with HIV or AIDS
 - Organ transplant patients on pharmacologic immunosuppression

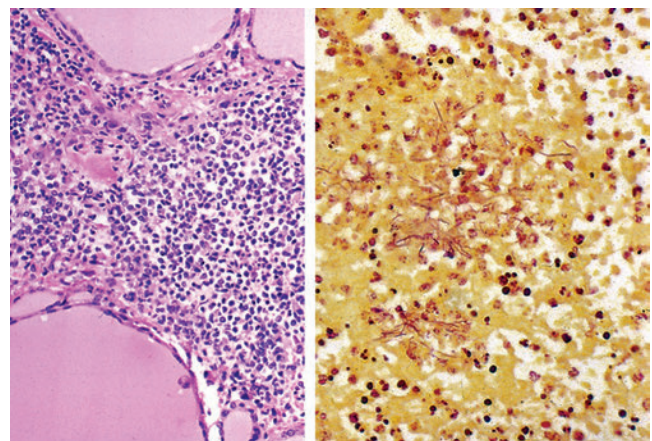


Fig. 27-34. Acute thyroiditis.

Left, Acute thyroiditis characterized by the presence of polymorphonuclear leukocytes in the thyroid. *Right*, Filamentous gram-positive organisms consistent with *Nocardia* species were present.

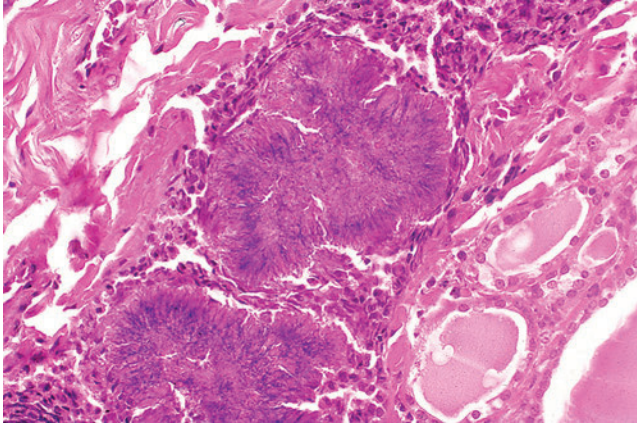


Fig. 27-35. Actinomycotic thyroiditis.

Actinomycotic thyroiditis characterized by the presence of “sulfur” granules typical of *Actinomyces* microorganisms.

- Cancer patients undergoing chemotherapy
- Patients on immunomodulation therapy for other disorders
- Clinical presentation includes:
 - Fever with swelling and pain in neck region that may radiate or be referred to jaw and ear region
 - Additional signs and symptoms may include fatigue, dyspnea, dysphagia, and hoarseness.
 - Not infrequently there is an antecedent or concomitant history of upper aerodigestive tract infection.
 - Not infrequently, associated with concomitant localized infections or as part of a systemic process (i.e., sepsis)
- Thyroid gland is warm to hot on palpation.
- Patients are usually euthyroid, but hyperthyroidism and hypothyroidism may occur.
- Etiologic agents may include:
 - Bacteria, fungi, viruses, and parasites:
 - Causative bacteria include *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pneumococcus*, and less commonly gram-negative bacteria:
 - In adults approximately 80% caused by *Streptococcus haemolyticus*, *Staphylococcus aureus* representing sole pathogen in approximately 70% of cases
 - In pediatric ages approximately 70% caused by alpha and beta-hemolytic *Streptococcus*
 - Causative fungus primarily reported to be *Aspergillus* species:
 - Virtually all affected patients are immunocompromised.
 - Other fungi causing thyroiditis include:
 - *Coccidioides immitis*, *Histoplasma capsulatum*, *Candida albicans*, *Allescheria boydii*, *Nocardia asteroides*

- Causative viruses include cytomegalovirus (in patients with AIDS).
- Other infectious agents may include *Pneumocystis jiroveci* (in patients with AIDS), mycobacteria, and *Actinomyces*.

- Spread of infection to thyroid gland via lymphatics and, less commonly, via hematogenous spread
- Cultures for microorganisms may be of assistance in diagnosis:
 - Microbiologic analysis can be performed on material from fine-needle aspiration.

Pathology

Fine-Needle Aspiration Biopsy

- Polymorphonuclear leukocytes are present.
- Microorganisms can be identified by histochemical analysis.

Gross

- Variable appearance including focal or diffuse enlargement; in some instances, thyroid appears normal
 - Abscess formation as seen by soft purulent areas may be identified.

Histology

- Pathologic process may be suppurative or nonsuppurative.
- Focal to diffuse acute inflammatory cell infiltrate (polymorphonuclear leukocytes) with destruction of follicular epithelial cells
- Areas of abscess formation characterized by dense pool of leukocytes can be seen.
- Areas of necrosis and leukocytic debris can be seen.
- Depending on causative microorganism, offending agent may or may not be identifiable by light microscopy.
- Histochemistry:
 - Histochemical stains (e.g., Gram stain, GMS, PAS, others) may assist in identification of the microorganism.
- Immunohistochemistry or in situ hybridization:
 - May assist, in particular, in viral disease:
 - Cytomegalovirus
 - Herpes simplex virus
- In a severely immunocompromised patient, typical granulomatous inflammatory process may not occur in the face of mycobacterial or fungal infection; instead, changes of acute thyroiditis may be seen.

Treatment and Prognosis

- Treatment predicated on diagnosis and identification of the causative microbe
 - Once identified, appropriate antimicrobial therapy initiated

BOX 27-7 Granulomatous Lesions of the Thyroid Gland

- Infections (mycobacterial and fungal)
 - Sarcoidosis
 - Subacute thyroiditis (including silent thyroiditis)
 - Multifocal granulomatous thyroiditis (palpation thyroiditis)
 - Postoperative necrotizing granulomas
 - Others
-
- Surgical intervention (drainage) may be required in presence of abscess formation.
 - Prognosis especially for bacterial-related acute thyroiditis is excellent with most patients experiencing recovery; rarely, recurrence and even death may occur.
 - Recurrent acute suppurative thyroiditis may occur secondary to a piriform sinus fistula:
 - Usually left-sided
 - Identified by radiographic evaluation
 - Treatment includes fistulectomy

Granulomatous Thyroiditis

Definition: Presence of well-formed granulomas in the thyroid gland.

- More common causes of granulomas in thyroid gland are listed in [Box 27-7](#).

Infectious Granulomatous Thyroiditis (Fig. 27-36)

Definition: Infectious thyroiditis caused by an identifiable microorganism that may (or may not) result in granulomatous inflammation.

Synonym: Acute mycotic thyroiditis

Clinical

- Granulomatous inflammation of thyroid gland caused by a microorganism is extremely uncommon.
- Causative microorganisms include mycobacteriae and fungi.
- Typical clinical setting for this occurrence is an immunosuppressed or immunocompromised patient.
- Rarely reported to be associated with silicone breast implants
- Clinical presentation may be similar to that of acute thyroiditis and may include:
 - Fever with swelling and pain in the neck region radiating or referred to the jaw and ear region
- Thyroid glands are warm to hot on palpation.
- Patients are usually euthyroid but both hyperthyroidism and hypothyroidism may occur.
- Etiologic agents may include various fungi and mycobacteriae.

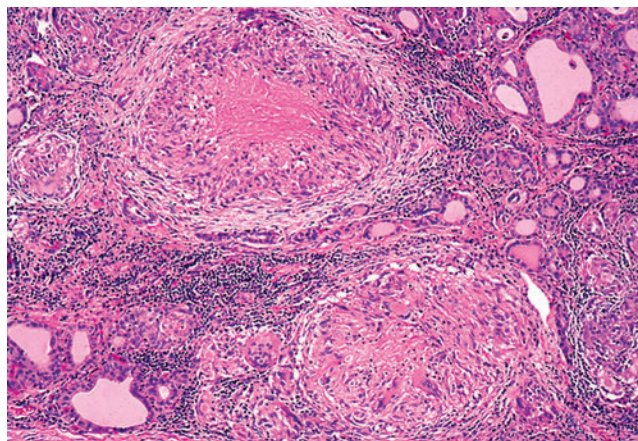


Fig. 27-36. Infectious granulomatous thyroiditis.

Caseating granulomas are seen showing central necrosis surrounded by a histiocytic cell reaction including multinucleated giant cells. Although histochemical staining (AFB, GMS) for microorganisms was negative, the patient proved to have *M. tuberculosis* as determined by molecular testing (i.e., polymerase chain reaction).

- Mycobacterial infection of thyroid is rare even in patients with miliary tuberculosis.
- Cultures for microorganisms may be of assistance in the diagnosis; microbiologic analysis can be performed on material from fine-needle aspiration.

Pathology**Gross**

- Variable but may include soft purulent (caseating) areas, abscess formation, or miliary tubercles

Histology

- Classic caseating granulomas may be present in either mycobacterial or fungal infection and include:
 - Foci of central necrosis surrounded by a histiocytic cell reaction with scattered associated multinucleated giant cells
 - Irrespective of causative organism, histologic picture of mycobacterial infection remains similar
- In immunocompromised patients, typical granulomatous inflammatory process may not occur in the face of mycobacterial or fungal infection; rather, changes of acute thyroiditis are seen:
 - Focal to diffuse acute inflammatory cell infiltrate (polymorphonuclear leukocytes) with destruction of follicular epithelial cell architecture
 - Areas of abscess formation characterized by dense pool of leukocytes can be seen.
 - Areas of necrosis and leukocytic debris may be present.
- Depending on causative microorganism, the offending agent may or may not be identifiable by light microscopy.

- Special stains/testing:
 - Histochemical stains may assist in the identification of the microorganism:
 - Fungal infection:
 - Gomori methenamine silver (GMS), periodic acid-Schiff (PAS), mucin stains
 - Mycobacterial infection:
 - Acid-fast bacilli (AFB) and Ziehl-Neelsen
 - ◻ Special stains based on capability of forming stable mycolate complexes with certain aryl methane dyes referred to as “acid-fastness”; depending on the stain, the organisms when identified appear beaded, showing a red or purple color; organisms are often extremely difficult to identify and may defy detection despite all efforts
 - Immunohistochemistry:
 - Positive immunoreactivity with monoclonal antibody to *Mycobacterium tuberculosis* complex
 - Polymerase chain reaction (PCR)
 - Can be used for identification of *Mycobacterium tuberculosis*

Differential Diagnosis

- Sarcoidosis
- Mycotic infections
- Noninfectious granulomatous processes:
 - de Quervain thyroiditis
 - Palpation thyroiditis
 - Postoperative necrotizing granulomas:
 - Similar in appearance to those occurring in prostate and bladder

Treatment and Prognosis

- Predicated on diagnosis and identification of the causative microbe
 - Once identified, appropriate antimicrobial therapy is initiated.
- Surgical intervention (drainage) may be required in presence of abscess formation.
- Prognosis for fungal infection of the thyroid is poor:
 - Generally is terminal event in immunocompromised patient
- Prognosis of mycobacterial infection of thyroid correlates with that of other organ system involvement.

Sarcoidosis of Thyroid Gland

(Figs. 27-37 and 27-38)

Definition: Multisystem chronic granulomatous disease of unknown cause that may involve the thyroid gland as part of systemic process, or, rarely, localized to thyroid gland.

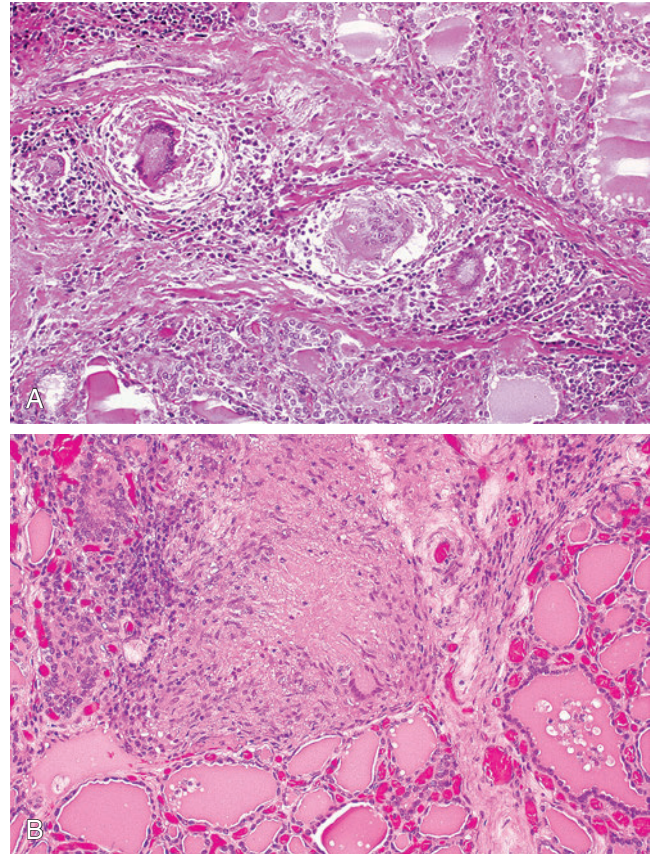


Fig. 27-37. Sarcoidosis of the thyroid gland.

A, Intrathyroidal granulomatous inflammation characterized by the presence of well-formed granulomas with a histiocytic cell infiltrate and multinucleated giant cells without central necrotic material (caseation). **B**, Rarely necrosis may be present in association with sarcoid granulomas.

Clinical (Limited to Thyroid Involvement)

- Uncommon; when it occurs it is more often a part of systemic disease rather than isolated to thyroid gland
 - In this setting, patient generally does not present with symptomatic thyroid disease, but pathologic identification of thyroid involvement is at autopsy.
- Isolated sarcoidosis of thyroid gland is rare.
- No gender predilection; occurs in all age groups but most commonly seen in young adults
- Clinical presentation in symptomatic thyroid disease includes neck or thyroid mass, appearing as a hypo-functioning “cold” nodule on thyroid scanning.
- Clinical presentation as part of systemic disease includes fever, weight loss, and hilar adenopathy.
- No laboratory findings specific for or diagnostic of sarcoidosis:
 - Cutaneous anergy to skin test antigens may be seen (Kveim test).

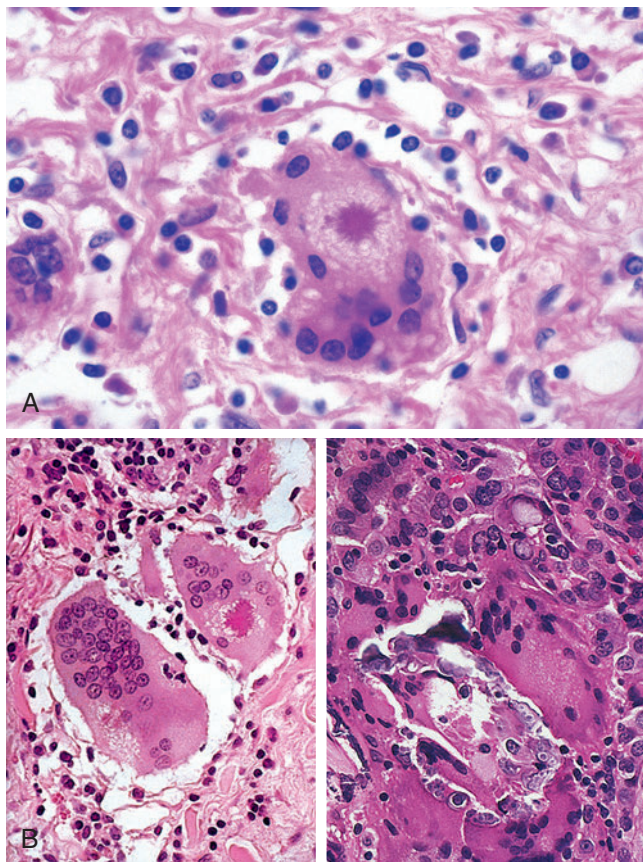


Fig. 27-38. Sarcoidosis of the thyroid gland.

Findings in the cytoplasm of the giant cells in (thyroid) sarcoidosis that may assist in the diagnosis include (**A** and **B, left**): star-shaped structures referred to as asteroid bodies; (**B, right**) calcific laminated bodies called Schaumann bodies.

- Angiotensin-converting enzyme (ACE) levels elevated in association with sarcoidosis:
 - ACE levels directly related to number of organs affected
 - Mature granulomas tend to produce less ACE levels than developing new granulomas.
 - Correlation between disease activity and ACE levels:
 - As disease progresses to fibrosis, ACE levels decline.
 - ACE levels increased in other granulomatous diseases, although not as frequently as in sarcoidosis; frequency of elevation in other granulomatous disorders is 10%.
 - ACE levels increased in other nongranulomatous disorders (e.g., multiple sclerosis, Addison disease, hyperthyroidism, diabetes mellitus, others).
 - Given above, ACE not considered a diagnostic test for sarcoidosis

- Diagnosis generally one of exclusion and made by correlation of clinical, radiologic, and pathologic findings
- May rarely occur in association with papillary thyroid carcinoma and Graves disease

Pathology

Histology

- Noncaseating granulomas consisting of epithelioid histiocytes surrounded by a mixed inflammatory infiltrate and multinucleated (Langhans type) giant cells
- Intracytoplasmic inclusions may be identified, including:
 - Star-shaped referred to as asteroid bodies
 - Calcific laminated bodies referred to as Schaumann bodies
- Intervening thyroid gland essentially unremarkable
- All special stains for microorganisms (Brown and Hopps, Gomori methenamine silver [GMS], acid-fast bacilli, and Ziehl-Neelsen [for acid-fast organisms]) are negative.
- Immunohistochemistry:
 - Absence of thyroglobulin in granulomatous foci

Differential Diagnosis

- Mycobacterial infection
- Fungal infections

NOTE: Pathologic features of sarcoidosis are characteristic but they are not specific; therefore diagnosis of sarcoidosis can be considered only in the absence of identifying an infectious agent.

Treatment and Prognosis

- Those cases presenting with a symptomatic thyroid nodule may have surgical resection of the mass.
- Treatment for systemic sarcoidosis is with corticosteroid therapy.
- Prognosis for systemic disease is generally good, with up to 70% of patients improving or remaining stable following therapy.
- Advanced multisystem disease leading to extensive pulmonary involvement and respiratory failure may occur but is seen in only a small percentage of cases.

Subacute Thyroiditis (de Quervain Thyroiditis) (Fig. 27-39)

Definition: Granulomatous inflammatory condition of thyroid gland with characteristic clinical and pathologic findings.

Synonyms: Pseudogranulomatous or granulomatous thyroiditis; giant cell thyroiditis; acute simple thyroiditis; noninfectious thyroiditis; pseudotuberculous

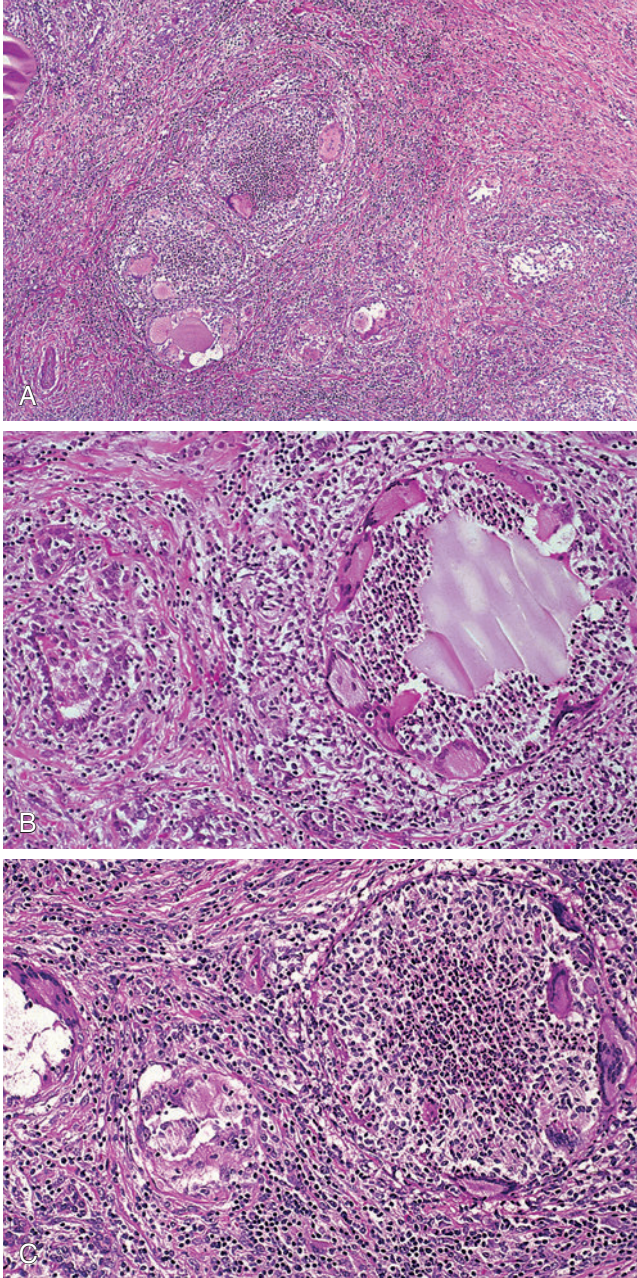


Fig. 27-39. Subacute thyroiditis (de Quervain thyroiditis).

A, There is destruction of the follicular epithelial cells with colonization of the follicles by an inflammatory cell infiltrate that includes multinucleated giant cells. The gland has a lobular appearance with interlobular fibrosis. **B** and **C**, Destruction of the follicular epithelial cells, which are replaced by neutrophils and multinucleated giant cells. In **(B)** colloid is present and appears “floating” within the neutrophilic cell infiltrate; in **(C)** there is loss of colloid.

thyroiditis; migratory “creeping” thyroiditis; struma granulomatosa; thyroiditis acute simplex (as originally described by Mygind)

Clinical

- Less common than Graves disease and chronic lymphocytic (Hashimoto) thyroiditis representing <3% of all thyroid abnormalities
- Affects women more than men (3 to 6:1); most common in second to fifth decades of life:
 - Uncommon in children and in elderly patients
- Clinical presentation includes:
 - Neck pain that may be localized to the thyroid (one lobe or the entire gland) or may radiate to the jaw, ears, face, and chest
 - General (systemic) manifestations may include malaise, fatigue, fever, chills, weight loss, anorexia, and myalgia.
- On palpation, gland is enlarged, exquisitely tender, and firm to hard.
 - Enlargement usually diffuse but may be asymmetric with limited (unilateral) involvement:
 - Postviral painless form of subacute thyroiditis reported referred to as atypical subacute thyroiditis
 - Findings in these patients may include fever of unknown origin.
- Laboratory findings (change with stage of disease):
 - Early or hyperthyroid (thyrotoxic) phase:
 - Due to damage to thyroid follicular cells, hyperthyroid condition resulting from elevated serum levels of T_4 , T_3 , and thyroglobulin
 - Increased serum and urine iodine and decreased serum TSH levels
 - High levels of erythrocyte sedimentation rate and C reactive protein
 - Hypothyroid phase:
 - With progression of disease, hypothyroid state ensues due to destruction of a larger portion of the gland and absence of hormone production and iodine uptake (decreased serum levels of T_4 , T_3 , and thyroglobulin, and increased serum TSH level).
 - Low radioactive iodine uptake:
 - Most often <2% at 24 hours
 - Hypothyroid phase in most patients lasts about 1 to 2 months with an occasional patient remaining permanently hypothyroid.
- Etiology:
 - In all probability associated with infection with strong evidence supporting a viral agent:
 - Clinical presentation may be preceded by an upper respiratory tract infection that may have a prodromal phase characterized by muscle aches and pains, malaise, and fatigue.

- Concomitant elevation of white blood cell count is not present as would be expected in a bacterial-related disease.
- Most often identified in summer months coinciding with summer enterovirus infections
- Antibody studies (acute and convalescent phase serum) have shown circulating antibodies to various viruses, including mumps, measles, influenza, Epstein-Barr virus, coxsackievirus, adenovirus and echovirus.
- Autoimmunity may play a role in development of subacute thyroiditis:
 - Thyroid antibodies found in some patients with subacute thyroiditis
 - These antibodies are transiently present and disappear following resolution of disease.
 - Presence of antithyroid antibodies may represent a reaction to released antigens following follicular epithelial destruction rather than representative of true autoimmune condition
 - Reports link subacute thyroiditis with hepatitis vaccine, influenza vaccine, influenza A virus subtype H1N1 vaccine, during interferon and interleukin-2-therapy and combination interferon and ribavirin therapy
- Genetic association:
 - Association between subacute thyroiditis and HLA-Bw 35 supports a genetic predisposition to the development of this disease:
 - Relative risk of HLA-Bw in subacute thyroiditis ranges from 8.0 to 56.6.
 - Weak association with HLA-DRw8 reported in Japanese patients
 - Familial occurrence has been reported.
- Radiology
 - Radioisotopic scans in early stages of disease show patchy and irregular uptake or no uptake.
 - Ultrasound shows hypoechogenicity in involved areas.

Pathology

Fine-Needle Aspiration Biopsy

- In early stages of disease, acute inflammatory cells with microabscesses can be seen.
- With progression of disease, a mixed inflammatory infiltrate is seen including lymphocytes, histiocytes, plasma cells, multinucleated giant cells, and polymorphonuclear leukocytes.
- Degenerative changes of follicular epithelial cells are present.
- In presence of extensive fibrosis, aspirates may be acellular.

Gross

- On sectioning, thyroid gland is firm to hard, tan-white in appearance with one or more ill-defined

nodules varying in size from a few millimeters to several centimeters.

Histology

Histologic appearance varies with phase of disease:

- Early phase:
 - Destruction of follicular epithelial cells with extravasation and depletion of colloid
 - Colloid may be identifiable “floating” within inflammatory cell infiltrate.
 - Periodic acid-Schiff (PAS) staining is simple and effective stain for identifying colloid.
 - “Colonization” of thyroid follicles by an inflammatory infiltrate consists of polymorphonuclear leukocytes (including microabscesses) in initial stages followed by mature lymphocytes, histiocytes, and multinucleated giant cells.
 - Inflammatory cells may involve adjacent follicles.
- Later phase:
 - Polymorphonuclear leukocytes are replaced by chronic inflammatory infiltrate composed of lymphocytes, histiocytes, giant cells, and plasma cells.
 - Absence of follicular epithelial cells replaced by inflammatory cells
 - Fibrosis seen between follicles and between lobules
- Regenerative phase:
 - Follicular regeneration
 - Minimal residual irregular fibrosis variably present

Differential Diagnosis

- Multifocal granulomatous thyroiditis (palpation thyroiditis)
- Chronic lymphocytic (Hashimoto) thyroiditis
- Mycobacterial infection
- Sarcoidosis
- Neoplastic proliferation (not usually a histologic problem but on the basis of the clinical appearance this may fall within the differential diagnosis)

Treatment and Prognosis

- Self-limited clinical course:
 - Acute phase lasts from 3 to 6 weeks but may last up to 4 months.
- Most effective therapy in more severe cases includes corticosteroids (oral prednisone).
 - Provide dramatic relief of pain and swelling within a few hours of administration:
 - In most cases within 24 to 48 hours
 - Administered for a week followed by tapering over at least 4 to 6 weeks

- Despite clinical response underlying inflammation may persist and symptoms recur if steroids tapered too quickly.
- Symptoms may recur in approximately one third of patients on reduction or cessation of steroid therapy.
 - In these patients readministration of steroids will resolve symptoms and ultimately patients will experience full recovery.
- Salicylates and other nonsteroidal anti-inflammatory medications have been used with good results:
 - Often adequate to decrease pain in mild to moderate cases
- Although surgical intervention is not primary treatment, when resection is performed it can be done safely and with low associated morbidity.
 - Patients with atypical features and patients with euthyroidism are more likely candidates than others for surgical intervention.
- Prognosis is excellent with complete resolution of disease.
 - Permanent hypothyroidism is rare but may occur in 5% to 15% of patients.
- Approximately 50% of hypothyroid patients are symptomatic; however, supplemental T₄ therapy is not required.
- Etiology is uncertain:
 - Viral cause sought but not confirmed
 - Autoimmunity also considered but not confirmed
- Thyroid enlargement occurs in up to 60% of patients:
 - Enlargement may be asymmetric, in which patients have a dominant, firm mass confined to one thyroid lobe.
 - Pain and tenderness is rare and when present is mild.
- Histologic changes:
 - Diffuse or focal lymphocytic thyroiditis
 - Follicular destruction present
 - Oncocytic cytoplasmic change of follicular epithelial cells uncommon but may be focally present
 - Absence of fibrosis
- Differential diagnosis:
 - Postpartum thyroiditis:
 - Similar clinical and histologic feature as painless (silent) subacute thyroiditis
 - Antecedent history of pregnancy
 - Chronic thyroiditis
 - Absence of extensive follicular destruction
- Disease course is similar to that of subacute thyroiditis:
 - Often self-limiting not requiring treatment
 - Adrenergic beta-blockers may be used in hyperthyroid phase
 - Temporary thyroxine replacement in hypothyroid phase
 - 50% of patients return to euthyroid phase
 - Permanent hypothyroidism may develop years later.

Painless (“Silent”) Subacute Thyroiditis

Definition: Form of hyperthyroidism characterized by painless nontender thyroid gland, increased levels of T₄ and T₃, low radioactive iodine uptake, and spontaneously resolving hyperthyroidism.

Synonyms: Atypical subacute thyroiditis; transient hyperthyroidism with lymphocytic thyroiditis

Clinical

- Incidence not known but estimated to be as high as 20% to 30% of all cases of subacute thyroiditis
- Affects women more than men; most common in the third to sixth decades of life but may occur in all age ranges
- Onset and severity of disease is variable:
 - Initial phase includes mild to moderate thyrotoxicosis lasting 1 to 2 months (transient thyrotoxicosis) with reduced radioactive iodine uptake followed by euthyroidism of several weeks duration, which in turn, is followed by hypothyroid phase of several months.
- Clinical presentation of thyrotoxicosis phase is usual one but, in addition, may include some of its unusual manifestations such as:
 - Atrial fibrillation, diffuse myalgia, periodic paralysis, and lid lag and lid retraction
 - Exophthalmos, localized myxedema, and thyroid acropathy do not occur.

Multifocal Granulomatous Thyroiditis (Palpation Thyroiditis) (Fig. 27-40)

Synonym: Martial arts thyroiditis

- Iatrogenetically induced lesions caused by vigorous (traumatic) palpation of thyroid gland:
 - Focal lesion or multifocal lesions due to manipulation of thyroid gland during physical examination with rupture of thyroid follicles and extrusion of colloid in affected area
- No specific demographics or clinical parameters associated with palpation thyroiditis
- Does not cause abnormalities in thyroid function (hypothyroidism or hyperthyroidism)
- Incidental microscopic finding in thyroid glands resected for other reasons

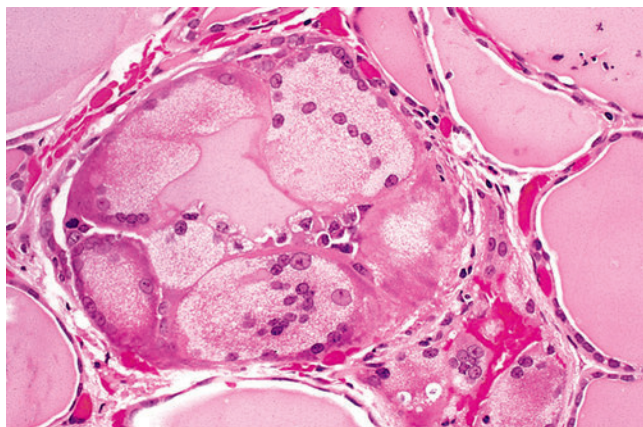


Fig. 27-40. Palpatation thyroiditis.

Palpatation thyroiditis may be a focal or multifocal process in which the thyroid follicular epithelial cells are replaced by histiocytes and multinucleated giant cells.

- Histology:
 - Isolated follicle or groups of follicles show loss of follicular epithelial cells and replacement by a mixed chronic inflammatory cell infiltrate predominantly comprised of histiocytes, as well as lymphocytes and plasma cells; multinucleated (foreign body giant reaction) may be present.
 - Additional histologic changes may include hemorrhage, hemosiderin deposition, and hemosiderin-laden macrophages.
 - Presence of colloid varies:
 - In some cases residual colloid is present and in others it is absent.
 - PAS stain may be of assistance in identifying residual colloid.
 - Necrosis is generally not found but occasionally may be present.
- Differential diagnosis
 - C-cell hyperplasia: differentiation assisted by immunohistochemistry:
 - Palpatation thyroiditis: CD68 (KP1) and lysozyme positive, calcitonin, synaptophysin and chromogranin negative
 - C-cell hyperplasia: calcitonin, synaptophysin, and chromogranin positive, thyroglobulin negative
 - Subacute (de Quervain) thyroiditis:
 - Focality of palpatation thyroiditis with involvement of one to several follicles and associated histologic findings including absence of acute inflammatory cells allow distinguishing palpatation thyroiditis from subacute thyroiditis.
 - Sarcoidosis or infectious granulomatous thyroiditis:
 - In sarcoidosis, granulomas are interstitially located.

– In infectious granulomatous there is usually necrosis, which is not present in palpatation thyroiditis.

- No specific treatment required:
 - Self-limiting; in all probability, there is spontaneous regression of histologic changes
- Not associated with any untoward sequelae

Invasive Fibrous Thyroiditis (Riedel Disease) (Figs. 27-41 through 27-45)

Definition: Fibrosclerosing process of thyroid gland and adjacent soft tissues of neck felt to belong to spectrum of IgG4-related diseases.

Synonyms: Riedel struma; ligneous thyroiditis

Clinical

- Rare disease with reported prevalence of 0.06 to 0.3%
- Affects women more than men; primarily occurs in adults
- Clinical presentation includes:
 - Painless neck mass and/or goiter
 - Pressure in the anterior neck often associated with dysphagia, dyspnea, stridor, tracheal narrowing
 - Rarely, vocal cord paralysis may occur.
- Thyroid enlargement described as woody or stony hard on palpation and adherent or fixed to surrounding structures in the neck:
 - Involvement of thyroid gland may be limited in extent so that one side is predominantly involved but bilateral and complete involvement of thyroid can also occur.
 - Presence of a hard and fixed thyroid mass clinically simulates a neoplastic lesion (i.e., carcinoma).
 - Impression of neoplasm further suspected in cases associated with cervical lymph node involvement
- Laboratory findings:
 - Hypothyroidism occurs in 30% to 40% of patients and is permanent.
 - Hypoparathyroidism may also occur.
 - Serum levels of IgG4 may or may not be elevated.
 - Circulating antithyroid antibodies are usually absent but may be present in small amounts:
 - Presence of antithyroid antibodies may represent a reaction to released antigens following follicular epithelial destruction (similar to subacute thyroiditis) rather than representative of an autoimmune condition.
- Disease process may be localized to thyroid gland and perithyroidal tissues or may be part of a systemic fibrosing disease.

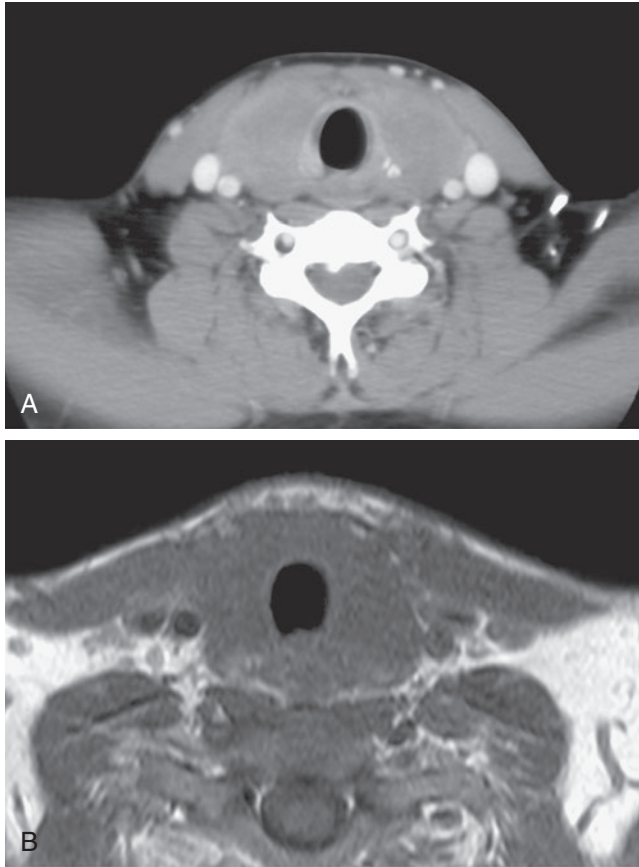


Fig. 27-41. Invasive fibrous thyroiditis (Riedel disease).

A, Axial, contrast-enhanced CT scan shows an enlarged, very-low-attenuation nonenhancing thyroid gland. The fat plane in the upper tracheoesophageal groove is obliterated bilaterally. This patient had Riedel struma (thyroiditis).

B, Axial T1-weighted MR image on a different patient than in part A shows similar findings of a diffusely enlarged gland and infiltration of the tracheoesophageal fat plane bilaterally. This patient had Riedel thyroiditis. This is virtually the only benign thyroid disease that can cause a recurrent laryngeal nerve paralysis. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figs. 41-38 and 41-39, page 2632.)

- Extracervical fibrosclerosis may include:
 - Retroperitoneum, mediastinum, orbital, pancreas, hepatobiliary, lung, sinonasal tract, salivary glands (parotid, submandibular)
- Thyroid involvement may coexist with one of above sites of involvement.
- Evidence supports Riedel thyroiditis being a part of spectrum of IgG4-related diseases:
 - Based on association with extracervical fibrosclerosing lesions, histologic features, immunohistochemical findings, and response to treatment (see below)



Fig. 27-42. Invasive fibrous thyroiditis (Riedel disease) resection specimen.

There is complete replacement of any identifiable tan-brown thyroid tissue by dense, firm to hard tan-white fibrous tissue.

Pathology

Fine-Needle Aspiration Biopsy

- Typically, aspiration generates a scanty amount of cellular material referred to as dry tap.

Gross

- Replacement of thyroid by dense tan-white, firm to hard tissue

Histology

- Destruction and replacement of thyroid parenchyma by dense collagen (keloid-like bands of fibrosis):
 - Fibrosing process not confined to thyroid but also involves extrathyroidal connective tissue structures such as skeletal muscle, adipose tissue, nerves, and vascular spaces
 - Parathyroid glands can also be involved.
- In addition to fibrosis, there is chronic inflammatory cell infiltrate that is:
 - Predominantly composed of mature plasma cells and lymphocytes
 - Eosinophils may be present.
 - Giant cells are not present.
- Vasculitis primarily involving veins (phlebitis) characterized by adventitial inflammation that may “invade” through the full thickness of vessel wall with thrombotic effect:
 - May be readily apparent or may be difficult to identify
 - May not be present in all cases
- Remnant of thyroid follicles may be present (but may be difficult to identify), situated within the dense collagen, showing limited to atrophic changes.

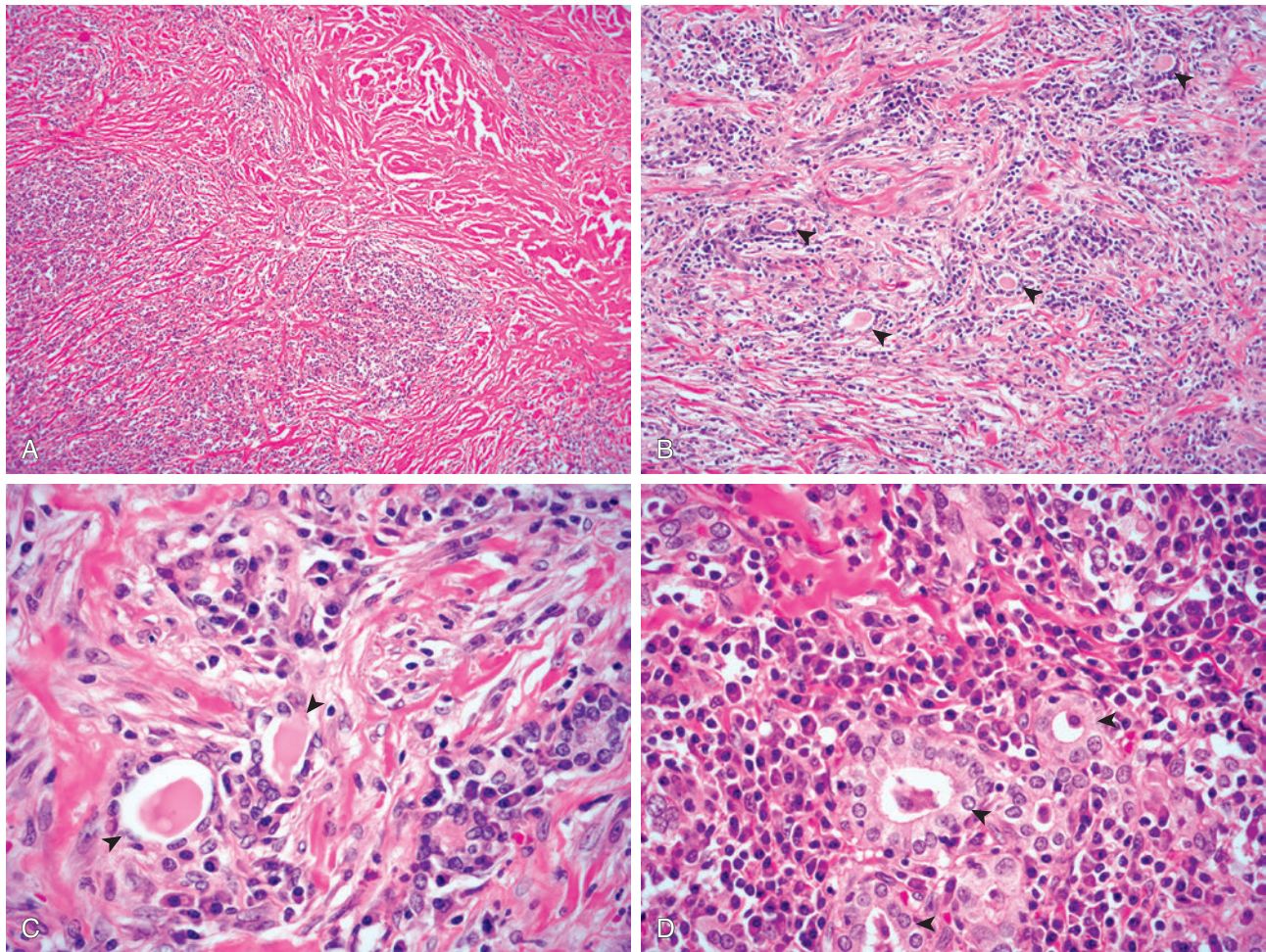


Fig. 27-43. Invasive fibrous thyroiditis (Riedel disease).

A, The thyroid gland parenchyma is completely effaced and replaced by dense keloid-like bands of fibrous tissue with an associated chronic inflammatory cell infiltrate. **B**, Residual colloid-filled thyroid follicles (*arrowheads*) can be seen but most of the thyroid has been replaced by keloid-like fibrosis and chronic inflammatory cells. **C** and **D**, Residual thyroid follicles (*arrowheads*) with and without associated colloid are identified in association with a variable degree of fibrosis and density of mature plasma cell infiltrate. Immunostaining (not shown) included the presence of abundant IgG4+ plasma cells with an increase in the IgG4/IgG ratio.

- Overall histopathologic findings not associated with:
 - Oncocytic metaplasia of follicular epithelial cells as seen in advanced lymphocytic thyroiditis
 - Granulomatous inflammation
- In some cases, preexisting or coexisting lesions may be present such as adenomatoid nodule(s), follicular adenoma, follicular carcinoma, and papillary thyroid carcinoma.
- Histochemistry:
 - Elastic stains may assist in identifying presence of vasculitis.
 - PAS stain may assist in identifying colloid in thyroid follicles.
- Immunohistochemistry:
 - Immunostaining for IgG4 and IgG show:
 - Presence of abundant IgG4+ plasma cells
 - Increase IgG4/IgG ratio
 - Plasma cells:
 - CD138, CD79a positive
 - Kappa and lambda light chain staining:
 - Predominance of expression of lambda chains and IgA reported
 - Thyroid follicular epithelium:
 - Thyroglobulin and TTF1 reactive:
 - Can be used to assist in identification of thyroid follicular epithelium
 - D2-40 staining reported to show increased number of lymphatic vessels:
 - Suggest participation of lymphatic vessels in pathogenesis

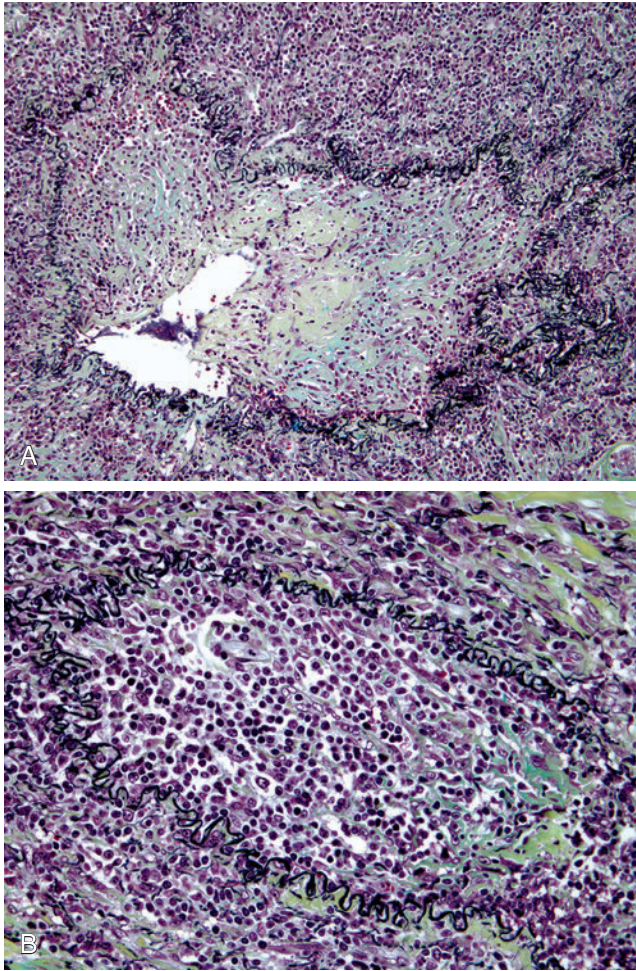


Fig. 27-44. Invasive fibrous thyroiditis (Riedel disease).

Vasculitis in invasive fibrous thyroiditis (Riedel disease) primarily involving veins (phlebitis) characterized by (A) adventitial inflammation that may (B) “invade” through the full thickness of vessel wall with thrombotic effect. The inflammatory cells are composed of mature plasma cells and lymphocytes. In both images elastic stain shows disruption with focal discontinuation of the black staining elastic membranes by the inflammatory cell infiltrate that is present throughout the wall of the vascular spaces.

Differential Diagnosis

- Chronic lymphocytic (Hashimoto) thyroiditis, fibrosing variant:
 - See later in this chapter.
 - Suggestion that fibrosing variant of chronic lymphocytic (Hashimoto) thyroiditis also part of spectrum of IgG4-related diseases but not unequivocally confirmed
 - Rare reported instances of combined Riedel disease and chronic lymphocytic (Hashimoto) thyroiditis:

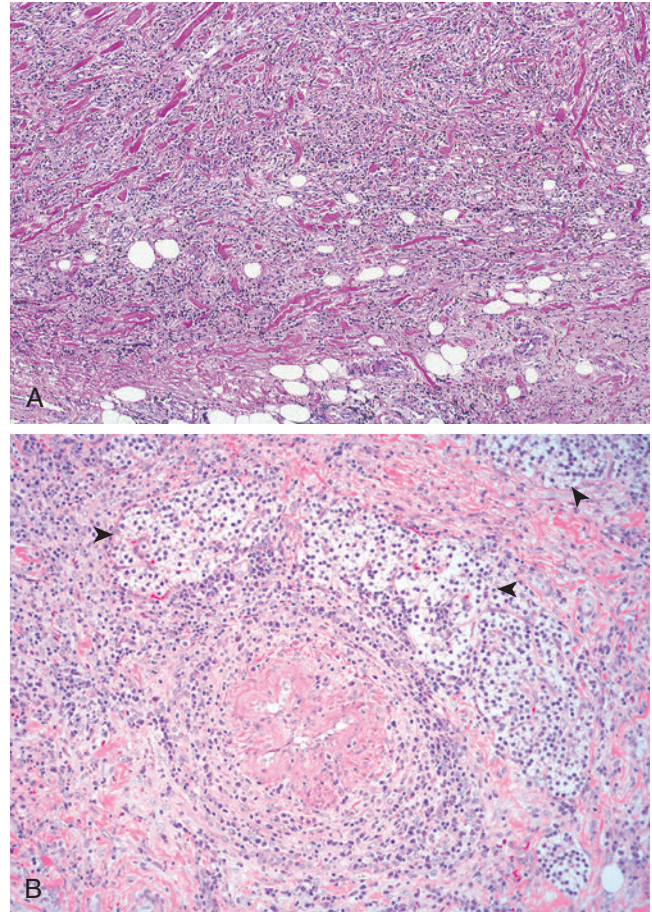


Fig. 27-45. Invasive fibrous thyroiditis (Riedel disease).

The fibrous and mixed chronic inflammatory infiltrate may involve extrathyroidal structures such as the soft tissue of the neck, including (A) mature adipose tissue, (B) parathyroid glands (arrowheads) with angiocentric inflammation (center).

- Characterized by clinical and laboratory findings of Hashimoto disease and pathologic findings of Riedel disease
- Likely a coincidental occurrence
- Findings in Riedel disease that allow for separation from fibrous variant of Hashimoto thyroiditis include:
 - Extension of pathologic (fibroinflammatory) process outside the thyroid gland:
 - Occurs in Riedel disease
 - Does not occur in (fibrous variant of) Hashimoto thyroiditis
 - Cytoplasmic oncocytic cell changes in follicular epithelial cells:
 - Absent in Riedel disease
 - Present in (fibrous variant of) Hashimoto thyroiditis

- Vasculitis/phlebitis:
 - Present in Riedel disease
 - Absent in (fibrous variant of) Hashimoto thyroiditis
- Plasma cells:
 - In Riedel disease express lambda chains and IgA
 - In fibrous variant of Hashimoto thyroiditis predominantly express kappa chains and IgG
- Subacute thyroiditis
- Carcinomas with extensive fibrosis
- Sclerosing lymphomas

Treatment and Prognosis

- Wide surgical resection has been traditional suggested treatment:
 - Uninvolved thyroid need not be resected
- Corticosteroid or rituximab appear to be efficacious treatment (supplanting surgical therapy) associated with:
 - Clinical and radiologic improvement:
 - Reduction in lesion size

- Serologic improvement:
 - Progressive decline in serum IgG4 concentrations
- Serum IgG4 concentrations may remain low and clinical disease activity may remain quiescent in a significant proportion of patients.

Radiation Thyroiditis

Definition: Morphologic alterations of thyroid gland due to external radiotherapy or radioiodine therapy resulting in functional thyroid abnormality (hypothyroidism).

Clinical

External Radiotherapy-Associated Thyroiditis (Fig. 27-46)

- External irradiation to neck used to treat patients with mucosal tumors (typically, squamous cell carcinomas) of the upper aerodigestive tract, metastatic tumors to neck (primarily those originating from

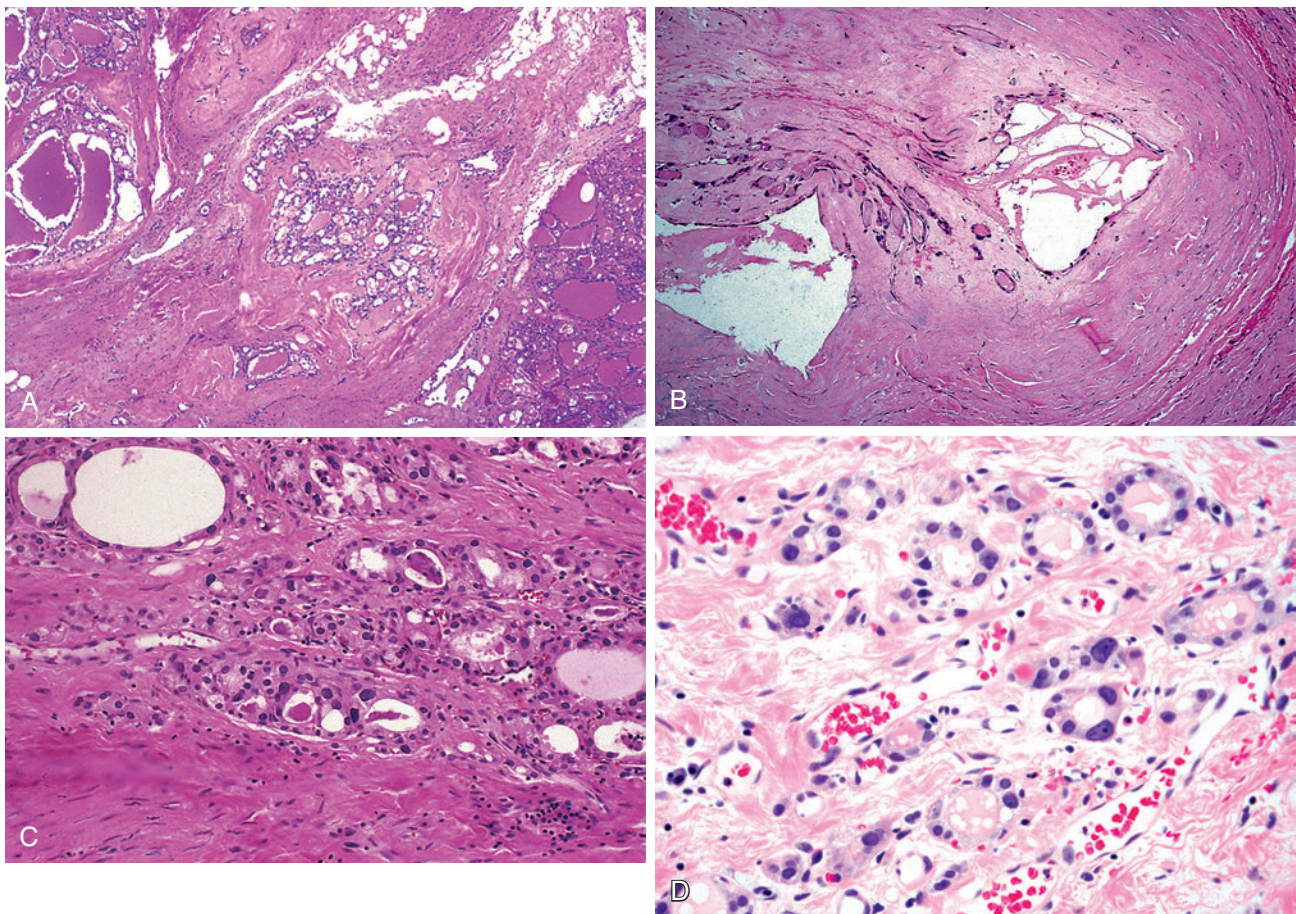


Fig. 27-46. Radiation associated histologic changes in the thyroid gland.

Histologic changes associated with radiation thyroiditis may include **(A)** nodular hyperplasia with irregular fibrosis; **(B)** parenchymal atrophy and sclerosis; **(C and D)** nuclear (endocrine) atypia, including nucleomegaly and hyperchromasia.

the upper aerodigestive tract) and malignant lymphomas:

- In past, external radiotherapy used in treatment of acne, enlarged tonsils and adenoids, thymic enlargement, benign cervical lymphadenopathy, pertussis, epilation, and benign tumors (hemangiomas)
- External radiotherapy-induced hypothyroidism may occur in 25% to 50% of patients so treated.
- Time interval from radiation treatment to development of hypothyroidism usually ranges from 2 to 7 years; however, hypothyroidism may develop within 1 year from time of radiation treatment.
- Effects (hypothyroidism) of external irradiation on thyroid gland is dose related:
 - Higher doses, higher frequencies of hypothyroidism
 - Significant linear radiation dose response for thyroid nodules, including benign nodules and malignant tumors, exists in atomic bomb survivors
 - No significant dose response for autoimmune thyroid diseases
- In most patients, hypothyroidism is subclinical but may be overt.
 - Patients with subclinical hypothyroidism may develop overt hypothyroidism later.
 - In other patients (subclinical) hypothyroidism is transient.
- Acute (weeks to months) effects of external irradiation (i.e., hypothyroidism) result in functional abnormalities (as determined by thyroid function testing) rather than causing any significant morphologic changes.
- Major effect of ionizing irradiation on thyroid tissue is impairment of the reproductive capacity of the follicular cells.

Radioiodine (Iodine-131 [¹³¹I])-Associated Thyroiditis

- ¹³¹I therapy is used in treatment of hyperthyroidism, especially for patients with Graves disease.
- Effects (hypothyroidism) of ¹³¹I on thyroid gland is less a function of dose and more correlated with time:
 - In fact, virtually all patients eventually become hypothyroid following ¹³¹I therapy even 10 years or more after therapy.
 - In patients who received ¹³¹I, overt hypothyroidism is usually preceded by subclinical hypothyroidism.

Pathology in Radiation Thyroiditis

Gross

- Externally irradiated thyroid glands are small and fibrotic.

Histology

- Most common abnormality is nodular hyperplasia.
- Morphologic changes that can be seen include:
 - Increased cellularity with severe cytologic atypia characterized by:
 - Markedly enlarged and bizarre-shaped nuclei (nucleomegaly) with hyperchromasia, prominent nucleoli, and nuclear crowding
 - Cytologic atypia is randomly found.
 - May be limited to one area
 - May be haphazardly found in several foci
 - Atypical nuclear features not specific and can be seen in nonirradiated thyroid glands
 - Papillary growth pattern
 - Follicular atrophy
 - Oxyphilic and/or squamous metaplasia
 - Decreased or absent colloid
- Additional changes may include:
 - Parenchymal fibrosis
 - Chronic (lymphocytic cell) inflammation
 - Vascular sclerosis and intimal thickening (endarteritis obliterans):
 - Vascular changes are fairly specific for irradiated tissues in general, including irradiated thyroid glands.
 - Inflammatory cell infiltrate cuffing vessels can be seen.
- Benign and malignant tumors may develop secondary to external irradiation, including:
 - Adenomatoid nodules and follicular adenomas:
 - May show atypical cytologic features including hypercellularity and markedly enlarged, hyperchromatic bizarre-appearing nuclei
 - Papillary thyroid carcinoma most common malignant neoplasm to develop
 - Follicular thyroid carcinoma may develop.
 - Rarely, undifferentiated (anaplastic) thyroid carcinoma occurs.

Differential Diagnosis

- Cellular adenomatoid nodules
- Dyshormonogenetic goiter
- Papillary carcinoma
- Follicular carcinoma

Treatment and Prognosis

- Hypothyroidism resulting from irradiation of thyroid gland treated by thyroid hormone therapy
- Prophylactic thyroidectomy in patients developing nodular hyperplasia following external irradiation can be considered.
- Complications of externally irradiated thyroid glands include development nodular hyperplasia and development of benign and malignant neoplasms.

- Papillary thyroid carcinoma is most common malignant tumor to occur following external irradiation:
 - May develop many years (decades) following the radiotherapy
 - Risk of developing postirradiation (papillary) carcinoma is small
 - All population ages are at risk of developing postirradiation thyroid cancers.
 - May be single focus or may be multifocal (within one lobe or throughout the entire gland)
 - Histology often that of usual or classic type of papillary thyroid carcinoma
- Papillary carcinomas developing following radiation exposure from nuclear fallout occur over shorter periods of time:
 - Post-Chernobyl radiation-induced papillary thyroid carcinomas
 - Develop over much shorter periods of time as compared with same tumor developing following external beam radiotherapy
 - Solid growth pattern (i.e., solid variant of papillary thyroid carcinoma) may predominate and is most common growth pattern identified, characterized by:
 - Solid nests may be separated by thin fibrovascular stroma, creating an “insular” growth.
 - Characteristic nuclear features
 - Typically lack marked pleomorphism, increased mitotic figures, and necrosis
 - Frequent *BRAF* mutation, *RET/PTC1* rearrangement, and low proliferation indices
 - Associated with higher frequency of lymph node metastases, higher frequency of angioinvasion, and higher frequency of extrathyroidal invasion
 - Other growth patterns may be seen, including follicular, papillary (classic), multiple patterns of growth, and diffuse sclerosing.
- Significance of radiation exposure to genesis of medullary thyroid carcinoma is not known, although a small number of individual cases of medullary carcinoma have occurred in patients with a history of radiation exposure to the neck.
- No evidence that ^{131}I therapy causes thyroid neoplasms.

Drug-Induced Thyroiditis

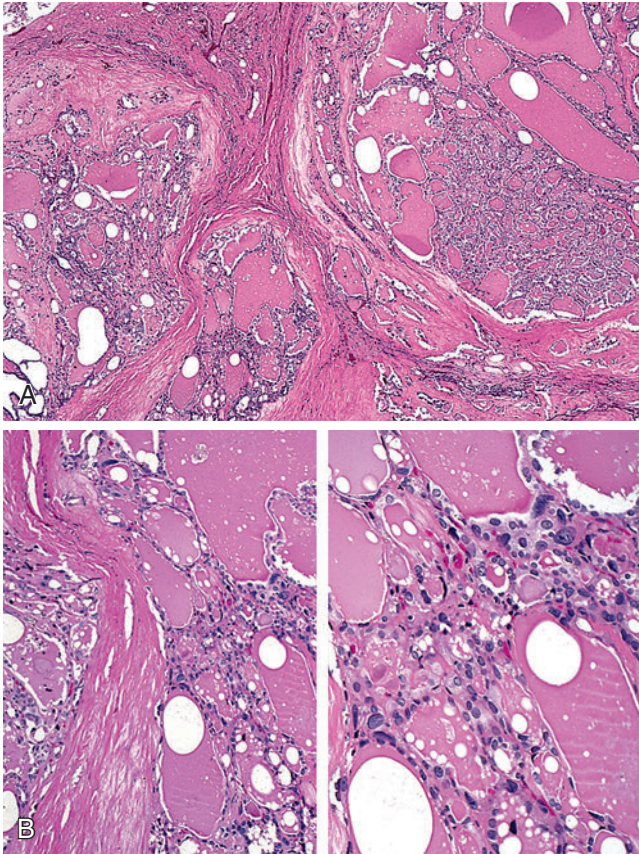
- Ingestion of certain medicines may be associated with the development of thyroiditis; however, prior to indicting any drug as causing thyroiditis, a detailed history and physical exam to include other possible causes of thyroiditis must be excluded.
- Medicinal agents implicated in the development of thyroiditis include iodides, lithium salts, phenytoin, amiodarone, and bromide.

Iodide

- Iodide is used in preparation of patients for surgery, in management of thyrotoxic storm, and as an adjunct after radioiodine therapy.
- Action of iodide includes:
 - Decrease iodide transport
 - Decrease iodide oxidation and organification
 - Rapidly blocks the release of T_4 and T_3 from thyroid
- In patients with preexisting thyroid disease such as toxic nodular goiter, iodide may worsen the hyperthyroidism (Jod-Basedow phenomenon or iodine-induced hyperthyroidism).
- Patients with hyperthyroidism due to Graves disease may have exacerbation of their hyperthyroid condition with iodide therapy.
- In patients with a goiter (endemic or sporadic), iodide added to diet may induce hyperthyroidism.
- Iodine-induced goiter and hypothyroidism occur most often in individuals with pre-existing thyroid disease (patients with chronic lymphocytic [Hashimoto] thyroiditis or treated Graves disease) or thyroid ablative therapy (thyroidectomy or radioiodine):
 - In these patients, hypothyroidism occurs with prolonged use of iodide or even following small doses of iodide, but hypothyroidism is transient and thyroid function returns to normal following cessation of iodide use.
 - Iodine-induced goiter and hypothyroidism may occasionally occur in fetus or neonate secondary to transplacental passage of iodide that was administered to the mother.
- Chronic iodide ingestion may lead to diffuse hyperplasia with papillary growth and lymphocytic cell infiltrate.

Lithium Salts (Fig. 27-47)

- Lithium is used in treatment of manic-depressive disorders.
- Effects of lithium on thyroid are similar to those of iodide and include:
 - Inhibition of thyroid hormone release
 - Inhibition of organification of iodine; the exact mechanisms of lithium's inhibitory action remain uncertain
- In a small percentage of patients (from 5% to 15%), chronic lithium (5 years or more) use may be associated with:
 - Development of a goiter
 - Development of hypothyroidism
 - Both
- Although incidence of lithium-induced hypothyroidism is considered low, it is sufficiently high enough

**Fig. 27-47.**

Lithium-associated changes of the thyroid gland show similar changes to those seen in radiation-treated glands.

A, Nodular hyperplasia with associated fibrosis. **B**, *Left panel*, nodules characterized by increased cellularity and associated dense fibrosis; *right panel*, bizarre-appearing nuclei characterized by nucleomegaly, pleomorphism, and hyperchromasia.

to warrant monitoring of patients who are receiving long-term lithium therapy.

- Histologic changes of lithium include:
 - Diffuse hyperplasia with associated nuclear pleomorphism
 - Similar to chronic lymphocytic (Hashimoto) thyroiditis and include:
 - Lymphocytic cell infiltrates with or without germinal centers, follicular epithelial cell atrophy with or without oncocyctic metaplasia, and fibrosis.
- Presence of antithyroid antibodies appears to be higher in patients with lithium-associated hypothyroidism (subclinical or overt) than those without hypothyroidism.

Anticonvulsant Drugs

- Phenytoin and carbamazepine are used in treatment of epilepsy.

- Mode of action is to reduce serum total and free T_4 , and less so T_3 , levels
 - Serum TSH concentrations are not elevated, but adding lithium to therapy will raise serum TSH levels.
- Clinically significant hypothyroidism associated with these anticonvulsants is uncommon.
- Phenytoin is associated with systemic immune reactions, and an organ-specific reaction (i.e., thyroiditis) may represent a component of the phenytoin-associated autoimmunity.

Amiodarone

- Amiodarone is used in treatment of cardiac arrhythmias and angina.
- Amiodarone tablets contain a large percentage of iodine and there is excess iodine release during the metabolism of this drug.
- Effects of amiodarone on thyroid include:
 - Iodide-related inhibition of thyroid hormone synthesis and secretion
 - Impaired cellular uptake of thyroid hormones
- Amiodarone-induced thyrotoxicosis (AIT) may occur either:
 - In presence of underlying thyroid disease referred to as Type I AIT:
 - Caused by an exacerbation by iodine load of thyroid autonomous function
 - In apparently normal thyroid glands referred to as Type II AIT
 - Probably consequent to drug-induced destructive thyroiditis
 - Mixed or indeterminate forms of AIT encompassing several features of AIT I and AIT II may also be observed.
- Abnormal thyroid function occurs in nearly all patients receiving amiodarone.
- Amiodarone may cause hypothyroidism or hyperthyroidism.
- Symptomatic hypothyroidism:
 - Usually occurs within first year of treatment but may occur later
 - Amiodarone-related (fatal) myxedema coma can occur.
 - Is associated with elevated circulating antithyroid antibodies, and this form of hypothyroidism may be related to an underlying autoimmune thyroiditis
- Amiodarone-induced hyperthyroidism may be a result of follicular cell damage with subsequent thyroid antibody production (antithyroglobulin or antimicrosomal) and/or may induce a thyroid-specific autoimmunity.
- Histologic changes may include follicular epithelial cell degenerative changes with vacuolization and a lymphohistiocytic cell response.

- Discontinuing use of drug often reverses adverse effects.
- Treatment:
 - AIT I usually responds to combined thionamide and potassium perchlorate (KClO₄) therapy.
 - AIT II generally responds to glucocorticoids.
 - Indeterminate forms may require both therapeutic approaches.
 - In patients with AIT I definitive treatment of hyperthyroidism by administration of ¹³¹I advised after normalization of iodine overload
 - To control severe AIT additional treatment with lithium carbonate, use of a short course of iopanoic acid and plasmapheresis has also been proposed.
 - In cases resistant to medical treatment and/or in patients with severe cardiac diseases, total thyroidectomy may be proposed after rapid correction of thyrotoxicosis with combination of thionamides, KClO₄, corticosteroids, and a short course of iopanoic acid.

Autoimmune Thyroid Disease (AITD)

Definition: Broad spectrum of non-neoplastic thyroid diseases with immunologic cause that usually occurs when there is failure of T-cell tolerance as a result of a combination of genetic and nongenetic factors.

- AITD includes two major forms:
 - Graves disease
 - Autoimmune thyroiditis or chronic lymphocytic (Hashimoto) thyroiditis
- AITD (Graves disease and chronic lymphocytic [Hashimoto] thyroiditis) represents:
 - Complex diseases caused by interaction between susceptibility genes and environmental triggers:
 - Genetic susceptibility in combination with external factors (e.g., dietary iodine) believed to initiate autoimmune response to thyroid antigens
 - Epidemiologic data, including family and twin studies, point to a strong genetic influence on the development of AITD.
 - Clinically distinct syndromes share common immunopathogenic mechanisms.
 - Hallmarks include thyrotoxicosis and hypothyroidism.
 - Both characterized by lymphocytic infiltration of thyroid and production of thyroid autoantibodies
 - AITDs are prototypical organ specific autoimmune diseases, but mechanisms that trigger autoimmune response to thyroid are still unclear.
- Although these diseases contrast clinically, their pathogenesis involves shared immunogenetic mechanisms.
 - Genetic data point to involvement of shared and unique genes.
 - Among shared susceptibility genes, *HLA-DRβ1-Arg74* (human leukocyte antigen DR containing an arginine at position β74) confers strongest risk.
 - Recent genome-wide analyses revealed new putative candidate genes.
 - Epigenetic modulation is emerging as a major mechanism by which environmental factors interact with AITD susceptibility genes.
- Of known environmental factors, infection, diet, iodine, and smoking appear most important.
- Considerable progress made in unraveling genetic risk factors for AITD:
 - Originally, only major histocompatibility complex (MHC) class II genes were shown to predispose to AITD.
 - However, several non-MHC susceptibility genes now confirmed to contribute to cause of AITD
 - Some genes are unique for Graves disease:
 - Thyroid-stimulating hormone receptor gene (*TSHR*), *CD40*, *CD25*
 - Some genes unique for chronic lymphocytic (Hashimoto) thyroiditis:
 - 12q (*BTG1*)
 - Some common to both diseases
 - *HLA-DRβ1-Arg7*, *CTLA-4*, *PTPN22*, thyroglobulin gene (*Tg*), *ARID5B*
- Certain genes are common to AITD and other autoimmune diseases.
- Epigenetic influences also identified in cause of AITD, including:
 - DNA methylation
 - Histone modifications
 - RNA interference by microRNA
- In support of including Graves disease and chronic lymphocytic (Hashimoto) thyroiditis as AITD include:
 - Existence of cases sharing features of both diseases, suggesting one may evolve into other:
 - In this scenario immune mediated insult leads diffuse or nodular hyperactivity (i.e., Graves disease), eventually leading to atrophy with oncocyctic cytoplasmic changes of follicular epithelium (i.e., chronic lymphocytic [Hashimoto] thyroiditis).
 - Rare occurrence in which Graves disease occurs following chronic lymphocytic (Hashimoto) thyroiditis with hypothyroidism
- Any lymphocytic infiltrate in thyroid gland is abnormal but is not necessarily an indication of AITD:

- Lymphocytic infiltrate in thyroid glands may be nonspecific (absence of clinical or laboratory findings indicating thyroid disease) and found in glands removed for other reasons representing chronic (focal) lymphocytic thyroiditis.

Chronic (Focal) Lymphocytic Thyroiditis (Fig. 27-48)

Definition: Focal (dense) collections of lymphocytes in thyroid gland incidentally identified in thyroid glands excised for other reasons in absence of clinical or laboratory findings indicating thyroid disease.

Synonym: Nonspecific lymphocytic thyroiditis

Clinical

- Rather common
- More common in women than men; most common in older-age patients
- No specific clinical findings (symptoms)
 - Clinical features correlate to the dominant pathologic process (e.g., nodules, tumor, other) in which the lymphocytic thyroiditis is a secondary finding.
- Thyroid function as determined by laboratory testing is usually within normal limits (euthyroid), although some patients may be hypothyroid but without clinical manifestations of hypothyroidism.
- Laboratory evidence of autoimmune thyroiditis (presence of antithyroid antibodies) usually absent or low levels detected

Pathology

Gross

- No specific findings:
 - Represents incidental finding that does not produce any mass lesion(s)

Histology

- Focal or multifocal aggregates of mature lymphocytes:
 - Typically germinal center formation not present but may present
- No quantitative (total number of lymphocytes) parameters required to diagnose lymphocytic thyroiditis:
 - Any lymphocytic cell infiltrate in thyroid considered abnormal, usually nonspecific, representing chronic (focal) lymphocytic thyroiditis
- Associated fibrosis, oncocyctic cytoplasmic change of follicular epithelial cells, and follicular cell atrophy typically not present but may be seen to a limited extent in any given case

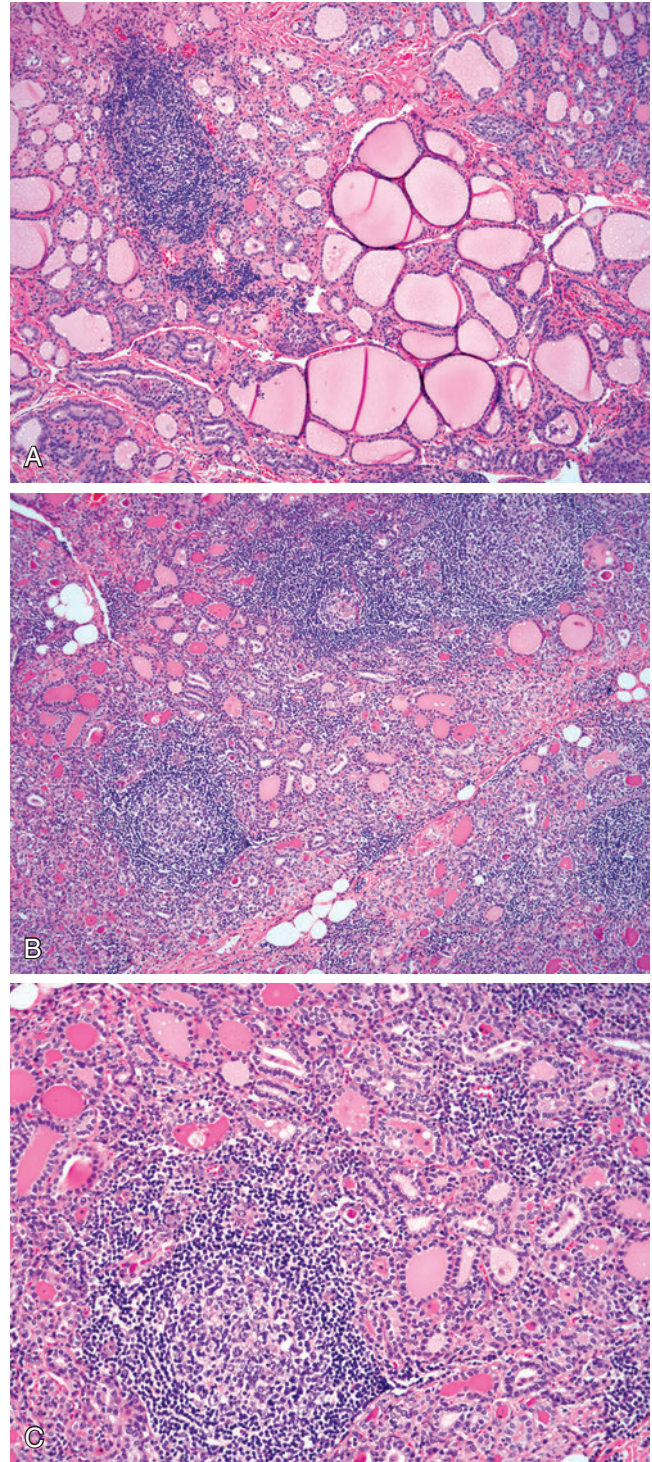


Fig. 27-48. Chronic (focal) lymphocytic thyroiditis.

Incidentally identified lymphocytic infiltrate in the thyroid gland that may include **(A)** focal aggregate of mature lymphocytes without germinal center formation or **(B)** multifocal aggregates of mature lymphocytes with germinal center formation. **C**, Lymphoid aggregate in association with histologically normal appearing thyroid follicular epithelial cells.

Differential Diagnosis

- Generally not a diagnostic dilemma
- Chronic lymphocytic (Hashimoto) thyroiditis
- Malignant lymphoma

Treatment and Prognosis

- No specific treatment required
 - Treatment directed at main pathologic process to which focal lymphocytic thyroiditis secondarily found
- Excellent prognosis with no specific prognostic parameters

Autoimmune Thyroiditis or Chronic Lymphocytic (Hashimoto) Thyroiditis (Figs. 27-49 through 27-53)

Definition: Autoimmune thyroid disease characterized by goiter and elevated circulating thyroid antibodies often associated with hypothyroidism due to thyroid destruction by autoimmune process and/or presence of thyroid-stimulating hormone-blocking antibodies.

Synonyms: Goitrous thyroiditis; struma lymphomatosa; classic form of autoimmune thyroiditis; lymphadenoid goiter; “classic” Hashimoto thyroiditis

- Considered most common autoimmune disease
- Autoimmune thyroiditis includes several different clinical entities (Box 27-8); most important include:
 - Chronic lymphocytic (Hashimoto), goitrous thyroiditis or “classic” Hashimoto thyroiditis
 - Chronic atrophic thyroiditis
 - In addition several other clinicopathologic entities recognized, including:
 - Fibrous variant
 - IgG4-related thyroiditis (distinct from fibrous variant; see Fibrous Variant below)
 - Juvenile form
 - Painless thyroiditis (sporadic or postpartum)
 - Hashitoxicosis
- All forms characterized pathologically by infiltration of thyroid gland by lymphocytic and plasma cell infiltrate in interstitium among thyroid follicles,

although specific features can be recognized in each variant.

- Diagnosis relies on demonstration of circulating antibodies to thyroid antigens (mainly thyroperoxidase and thyroglobulin) and reduced echogenicity on thyroid sonogram in a patient with proper clinical features.

Clinical

- Much more common in women than in men (10:1); frequency increases with age but may occur over wide age range:
 - Rare in children but represents most common cause of sporadic goiter in children
- Wide variation in clinical features:
 - Many patients present with no signs or symptoms and diagnosis made on basis of laboratory tests of thyroid function, screening done for thyroid antibodies or incidentally found in thyroid glands surgically excised for other reasons
 - Presentation may include presence of mass lesion (goiter):
 - Typically, there is bilateral diffuse symmetric enlargement of the thyroid.
 - Infrequently, dominant mass lesion confined to one lobe may be seen, simulating neoplastic proliferation.
 - In some patients, an enlarged thyroid is the only clinical manifestation.
 - Signs of tracheal, esophageal, or recurrent laryngeal nerve compression uncommonly occur.
 - Feeling of tightness in neck is common but tenderness and pain are uncommon.
- In many patients, clinical evidence of hypothyroidism is present (see previous discussion under Hypothyroidism):
 - May occur in patients who are euthyroid
 - Rarely occurs in patients with hyperthyroidism
 - In patients who are not hypothyroid at presentation, evidence of hypothyroidism may develop with time.
- Laboratory evidence of hypothyroidism includes:
 - Overt hypothyroidism:
 - High serum TSH levels
 - Low serum free thyroxine (T_4) levels
 - Possibly decreased free triiodothyronine (T_3), although the latter may be normal
 - Subclinical hypothyroidism:
 - High serum TSH levels
 - Normal serum free T_4 levels
- Laboratory evidence of autoimmune thyroiditis includes presence of two principal autoantibodies:
 - Anti-thyroglobulin antibodies
 - Anti-thyroid peroxidase (antimicrosomal) antibody

BOX 27-8 Types of Autoimmune Thyroiditides

- Chronic lymphocytic (Hashimoto) thyroiditis (autoimmune thyroiditis)
- Fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis
- IgG4-related thyroiditis
- Fibrous atrophy or atrophic thyroiditis (primary myxedema)
- Juvenile type of lymphocytic thyroiditis
- Silent (“painless”) thyroiditis
- Postpartum thyroiditis
- Chronic nonspecific (focal) lymphocytic thyroiditis

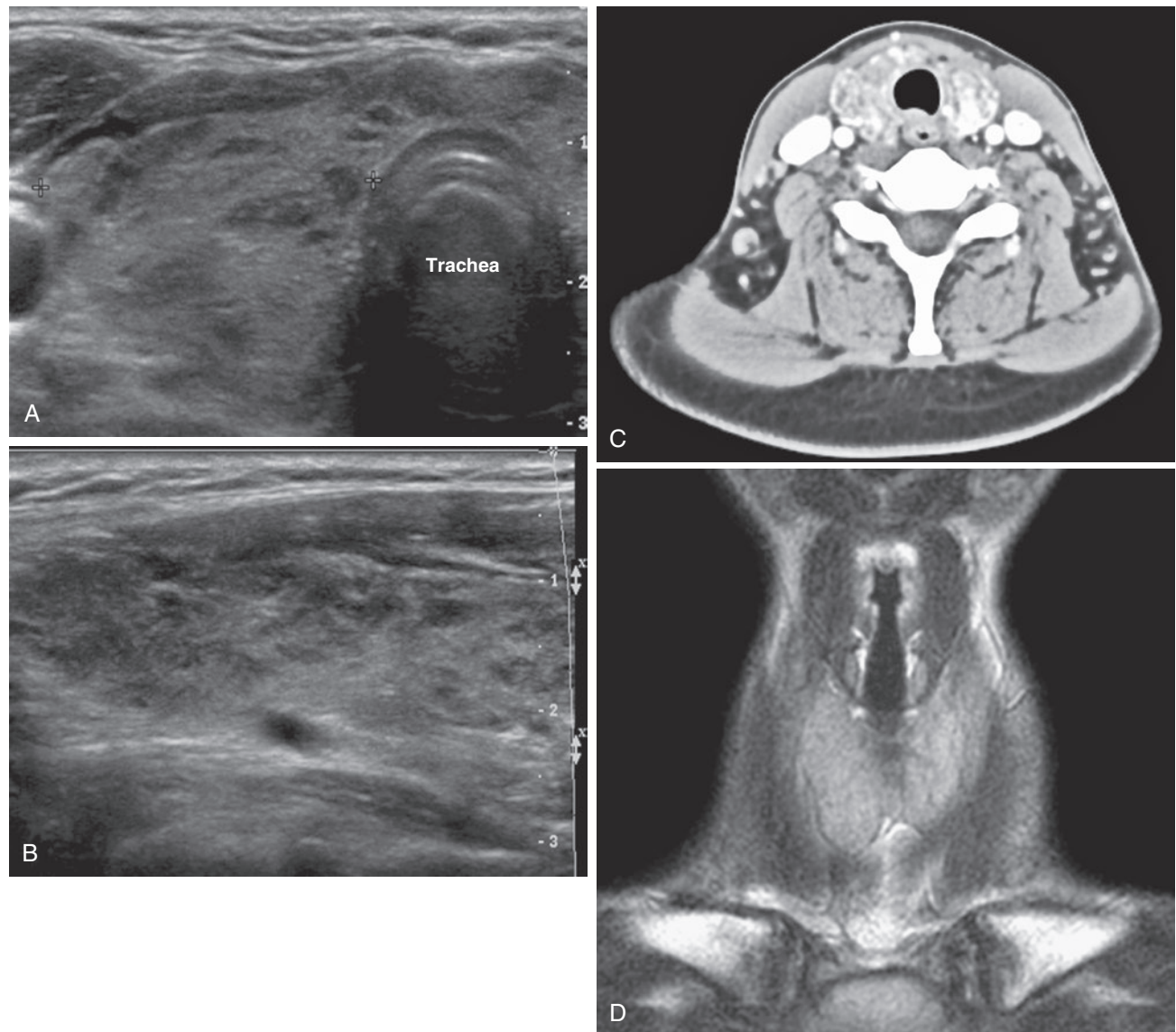


Fig. 27-49. Chronic lymphocytic (Hashimoto) thyroiditis.

Hashimoto thyroiditis (chronic lymphocytic thyroiditis). **A**, Transverse sonographic image shows subcentimeter micronodules ranging from 0.1 to 0.80 cm in size throughout the right lobe of the thyroid gland (calipers). These micronodules characteristic of Hashimoto thyroiditis are hypoechoic and surrounded by mildly echogenic rims. **B**, A different patient with chronic lymphocytic thyroiditis shows findings similar to those of the patient in **A**. **C**, Axial CT scan shows a moderately enlarged thyroid gland with a mottled, slightly nonhomogeneous appearance. This is a typical finding in Hashimoto disease. There is also scattered adenopathy, which is another expected finding in this disease. **D**, Coronal T1-weighted MR image shows a diffusely enlarged thyroid gland. Although this is a nonspecific finding, it is a typical finding in Hashimoto disease. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figs. 41-33, 41-34 and 41-35, pages 2630-2631.)

- Other components of thyroid tissue may serve as autoantigens, including:
 - Thyrotropin (TSH) receptor
 - Less commonly, sodium/iodide cotransporter and pendrin
- Precise antigen(s) that cause autosensitization are unknown but presence of anti-thyroglobulin and anti-thyroid peroxidase antibodies suggest these antigens as being involved:
 - Thyroglobulin and thyroid peroxidase share epitopes; it is possible that initial antigen may result in a sequential response to other antigen(s).
 - Patients with AITD (chronic lymphocytic [Hashimoto] thyroiditis, Graves disease) show a higher prevalence of autoantibody not only against thyroid-specific but also nonthyroid-specific antigens (antibodies to nucleus, smooth muscle and

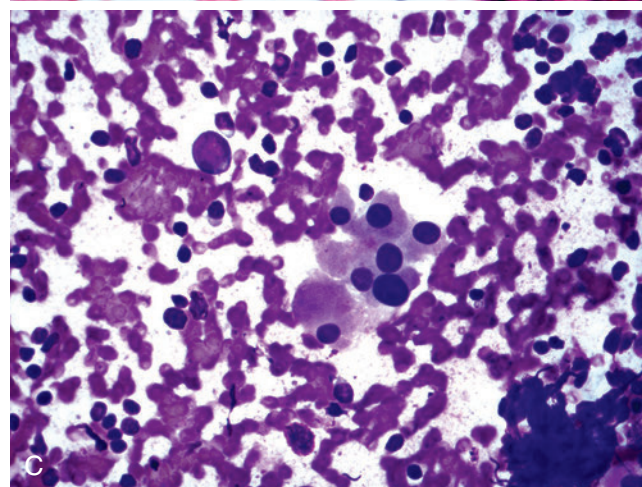
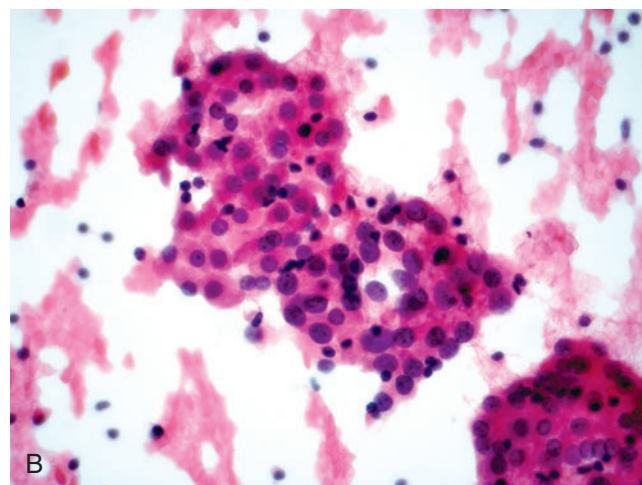
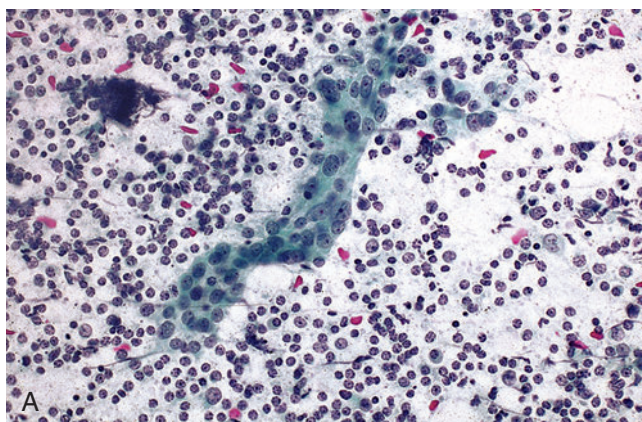


Fig. 27-50. Fine-needle aspiration biopsy in chronic lymphocytic (Hashimoto) thyroiditis.

A, Aspirate is characterized by a prominent mixed lymphoplasmacytic infiltrate. Follicular epithelium is frequently scanty and may exhibit oncocytic cytoplasmic change as well as nuclear enlargement, and variable nuclear pleomorphism. The epithelium is usually arranged in sheetlike fragments. In more florid cases colloid may be difficult to identify (Papanicolaou stain). **B**, Follicular epithelial cells appear in small clusters characterized by abundant eosinophilic granular cytoplasm (oncocytes), large nuclei, and variably sized nucleoli. **C**, Anisonucleosis may be prominent (Diff-Quik).



Fig. 27-51. Chronic lymphocytic thyroiditis (Hashimoto thyroiditis), resection specimen.

Symmetrically enlarged thyroid gland characterized by multilobulated appearance; the lobules are tan-white and replace most of the thyroid parenchyma.

single-stranded DNA) than matched control patients.

- In contrast to Graves disease, in which thyroid-stimulating antibody is almost always present, this antibody is only occasionally present in chronic lymphocytic (Hashimoto) thyroiditis.
- Patients with chronic lymphocytic (Hashimoto) thyroiditis have increased incidence of different HLA-DR haplotypes, including HLA-DR3, DR4, and DR5.
 - Patients with HLA-DR2 and HLA-DQ1 have protective effect against AITD.
- Additional laboratory findings:
 - No elevation of serum IgG and/or IgG4 levels
- Radiology:
 - Ultrasound: variety of patterns may be seen including normal glandular enlargement or diffuse abnormality with heterogeneous echogenicity:
 - In end-stage disease, gland may appear atrophied and fibrotic resulting in heterogeneous echotexture.
 - CT:
 - Inhomogeneous distribution of iodine

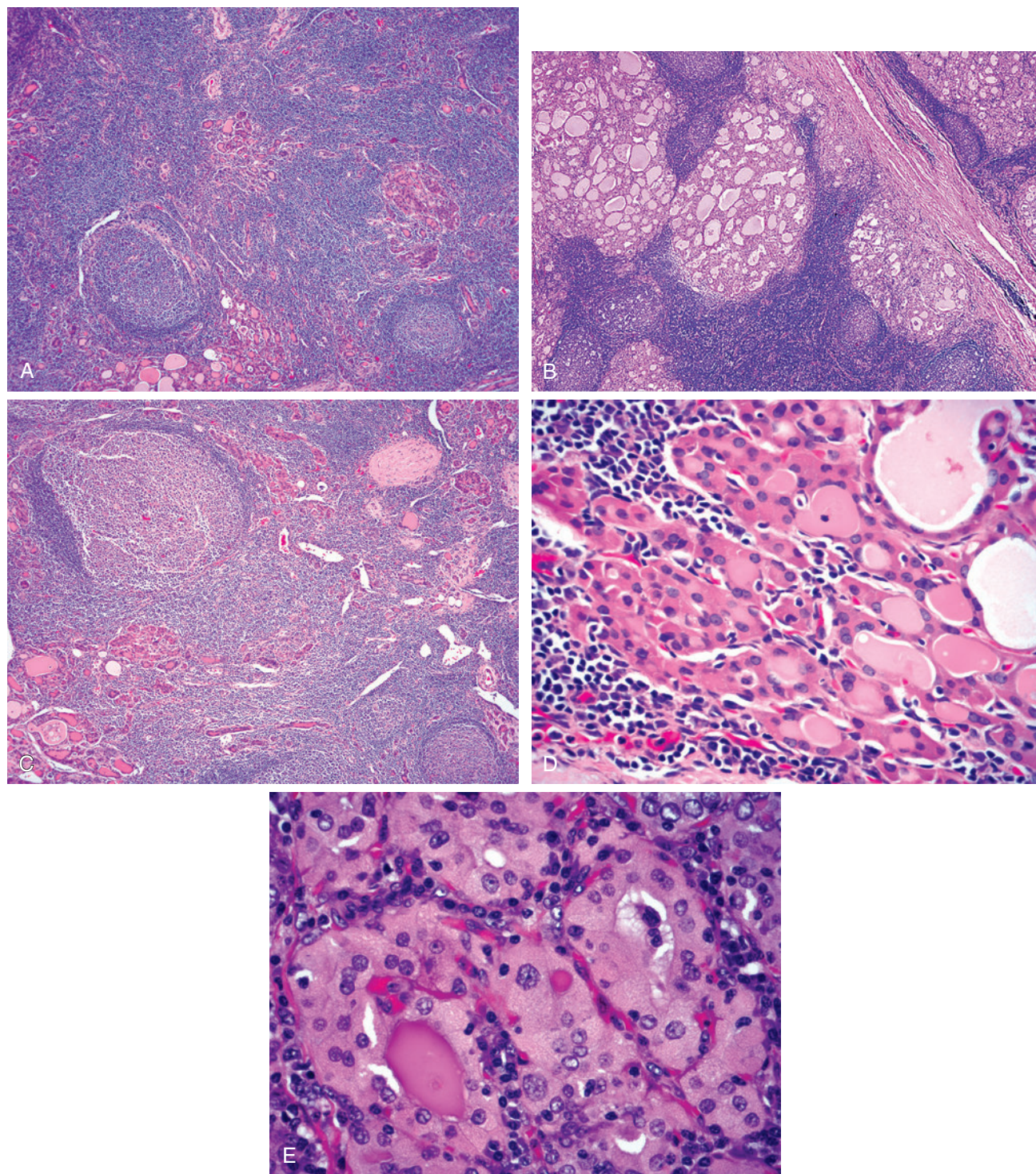


Fig. 27-52. Chronic lymphocytic (Hashimoto) thyroiditis.

A, Histologic features include the presence of diffuse involvement of the thyroid gland by a lymphocytic cell infiltrate with or without germinal centers, and atrophy of thyroid follicles; in this example there is an absence of fibrosis. **B**, Another case showing nodularity and associated fibrosis but the amount of fibrosis is limited with slight to moderate thickening in interlobular septa. **C**, Diffuse lymphocytic cell infiltrate with germinal center formation and associated follicular atrophy. **D**, Follicular epithelial cell showing oncocytic cytoplasmic change. **E**, Oncocytic follicular cells are characterized by the presence of a prominent granular eosinophilic cytoplasm that may be associated with nuclear enlargement, prominent eosinophilic nucleoli, and dispersed to optically clear-appearing nuclear chromatin. These changes may be misinterpreted as those of papillary thyroid carcinoma (PTC), but the distribution pattern of the follicular cells in a background of diffuse lymphocytic cell infiltrate is not the usual feature seen in PTC and, more importantly, the constellation of cytomorphicologic (nuclear) features associated with PTC are absent.

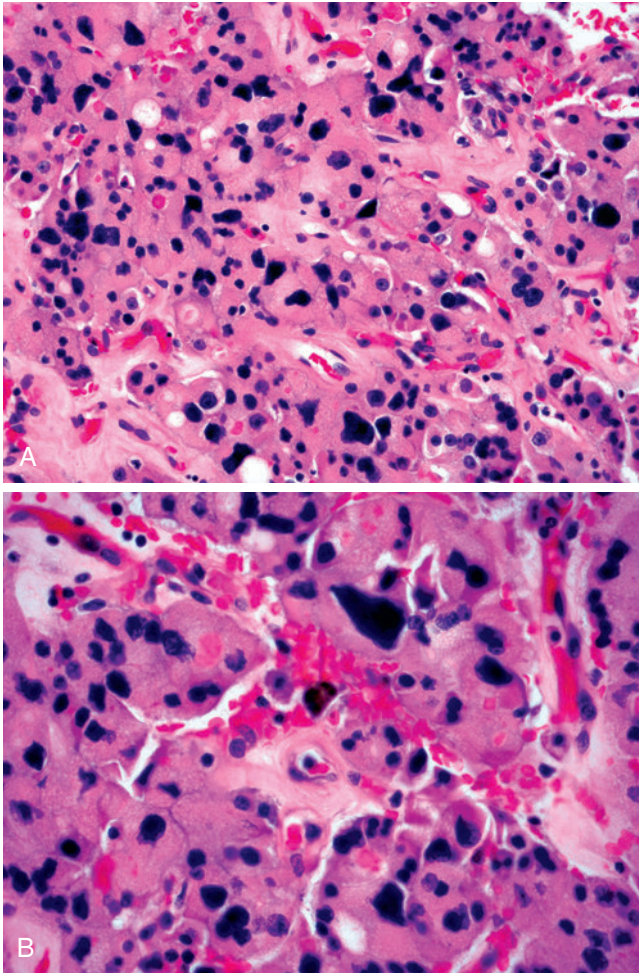


Fig. 27-53. Follicular epithelial dysplasia.

In chronic lymphocytic (Hashimoto) thyroiditis, especially in severe cases, foci with more pronounced cytological atypia may be identified. **A** and **B**, Such changes in these follicular cells with oncocytic cytoplasmic change include nucleomegaly and hyperchromasia.

- MR:
 - T2-weighted images show areas of increased signal intensity.
 - Following contrast administration, regions that enhance more than other regions of the gland may be seen.
- Pathogenesis includes genetic and nongenetic factors:
 - Genetic factors:
 - Major histocompatibility complex (MHC) class II genes:
 - Encode products that delete autoreactive T-cells, select for presentation of autoantigenic peptides, or activate suppressor T-cells
 - Other MHC genes:
 - Potential effects on antigen presentation
 - Cytokine tumor necrosis factor and some complement components also encoded in MHC
 - T-cell response genes:
 - Cytotoxic lymphocyte antigen-4 (CTL4) important in terminating T-cell activation:
 - Polymorphic variants may fail to control autoreactive T-cells fully.
 - *PTPN22* encodes T-cell activation inhibitor.
 - Interleukin-2 receptor alpha chain (*IL2RA*) encodes receptor for T-cell-activating cytokine IL-2.
 - Other immune response genes:
 - *CD40* encodes stimulatory signal for B-cells.
 - Tissue autoantigen genes:
 - Polymorphisms in genes encoding thyrotropin (TSH) receptor and thyroglobulin may predispose to distinct types of AITD.
 - Epidemiologic data, including family and twin studies, point to strong genetic influence in development of AITD.
 - Nongenetic factors:
 - Infectious agents:
 - May release autoantigens, alter expression of surface molecules, directly affect immune system, or contain immunologic sequences (epitopes) that mimic autoantigens
 - Dietary factors:
 - Diverse potential effects:
 - Iodide may enhance immunogenicity of thyroglobulin, alter thyroid-cell function, or form toxic metabolites with oxygen
 - Vitamin D deficiency may predispose to development of autoimmune disease through effects on dendritic cells and T-cells.
 - Toxins, pollutants:
 - Diverse potential effects
 - Hormones:
 - Diverse potential effects:
 - Estrogens enhance most immune responses.
 - Glucocorticoids, androgens suppress immune responses
 - Stress:
 - May alter neuroendocrine interactions with immune system
 - Drugs:
 - Diverse potential effects on immune system:
 - Lithium, interferon- α , interleukin-1 β , and some other cytokines exacerbate or promote progression of autoimmune thyroiditis.

- AITD may appear as part of immune reconstitution syndrome after bone marrow transplantation from affected donor, alemtuzumab (monoclonal antibody against CD52) treatment, or highly active antiretroviral treatment for HIV infection.
 - Familial association:
 - Up to 5% of first-degree relatives with chronic lymphocytic (Hashimoto) thyroiditis have anti-thyroid antibodies.
 - Association with other diseases:
 - High prevalence with Down syndrome, Turner syndrome, and familial Alzheimer disease
 - Patients with chronic lymphocytic (Hashimoto) thyroiditis are at greater risk of having other coexisting autoimmune diseases, including:
 - Endocrine:
 - Insulin-dependent diabetes mellitus, Addison disease (adrenal insufficiency), autoimmune oophoritis, hypoparathyroidism, and hypophysitis
 - Chronic lymphocytic (Hashimoto) thyroiditis is well-recognized component of autoimmune polyglandular syndromes (APS), which are:
 - Heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organ, although nonendocrine organs can be affected; two major types of APS include APS-1 and APS-2; both have Addison disease as a prominent component
 - Major autoimmune polyendocrine syndromes have a strong genetic component with the type 2 syndrome occurring in multiple generations and type 1 syndrome in siblings.
 - Autoimmune polyendocrine syndrome-type 2 (APS-2) also referred to as Schmidt syndrome:
 - Most common form of polyglandular failure syndromes
 - Patients at higher risk when they carry a particular human leukocyte antigen genotype (*DQ2*, *DQ8*, and *DRB1*0404*)
 - Affects women to a greater degree than men (75% occur in women)
 - Major components include (two major components are required to qualify as the syndrome): autoimmune thyroid disease (Graves disease; chronic lymphocytic [Hashimoto] thyroiditis), Addison disease (autoimmune adrenalitis), type 1 diabetes mellitus
 - Other components may include pernicious anemia, primary hypogonadism (less common), vitiligo, celiac disease, myasthenia gravis.
 - Major components of autoimmune polyglandular syndrome type 1 (APS-1) include:
 - Addison disease
 - Hypoparathyroidism
 - Chronic mucocutaneous candidiasis
 - In APS-1, chronic autoimmune thyroiditis occurs in 10% to 15% of patients.
 - Nonendocrine:
 - Sjögren syndrome, myasthenia gravis, pernicious anemia, thrombocytopenic purpura
- Chronic lymphocytic (Hashimoto) thyroiditis and Graves disease share common features, including:
 - Aggregation of both conditions in same families or within the same thyroid gland
 - Cases of identical twins in which one twin has chronic lymphocytic [Hashimoto] thyroiditis and other has Graves disease
 - Lymphocytic infiltration and various immunoglobulins found within thyroid in both disorders
 - Thymic enlargement and thyroid autoantibodies are found in both diseases.
 - Graves disease may evolve into chronic lymphocytic (Hashimoto) thyroiditis with hypothyroidism, and, rarely, chronic lymphocytic (Hashimoto) thyroiditis (with or without hypothyroidism) may evolve into Graves disease with hyperthyroidism.
 - In spite of these shared features, there are sufficient differences (genetic, clinical, immunologic, and pathologic) to consider these diseases as distinctly different and not the opposite ends of spectrum of a single entity.

Pathology

Fine-Needle Aspiration Biopsy

- Usually cellular consisting of mixed population of follicular cells with oncocytic cytoplasm (so-called Hürthle cells) and lymphocytes with minimal to absent colloid
- Follicular epithelial cells:
 - Usually appear in sheets or small clusters but may appear as single cells
 - Oncocytic cells characterized by abundant eosinophilic granular cytoplasm, large nuclei, and prominent nucleoli
 - Anisonucleosis may be prominent.
 - Mild nuclear atypia, nuclear clearing, and grooves may be present.
- Mixed inflammatory cell infiltrate, including mature lymphocytes, larger reactive lymphoid cells, and plasma cells:
 - Macrophages and multinucleated giant cells may be present.

- Presence of germinal centers may be reflected by a variety of lymphocytes and tingible body macrophages.

Gross

- Diffusely enlarged gland with firm consistency, pale, and irregular or bosselated surface:
 - Enlargement usually symmetric
 - Pyramidal lobe may be prominent.
 - Usually weighs 2 to 3 times more (e.g., 40 g) than normal weight
- Cut surface, gland appears tan-yellow characterized by prominent multilobulated appearance:
 - Lobules tend to bulge from cut surface and are separated by fibrous tissue.
- Bilateral diffuse thyroid enlargement, as compared to a single dominant mass, assists in decreasing clinical suspicion for neoplastic proliferation.
- Thyroid is not adherent to surrounding structures.

Histology

- At low magnification, lobules or nodules are seen separated by fibrous tissue.
- Histologic hallmarks associated with chronic lymphocytic (Hashimoto) thyroiditis include:
 - Diffuse involvement of thyroid gland
 - Mature lymphocytic cell infiltrate with or without germinal centers
 - Atrophy of thyroid follicles
 - Oncocytic metaplasia of follicular epithelial cells

NOTE: Diagnosis of chronic lymphocytic (Hashimoto) thyroiditis is one made on a combination of clinical, laboratory, and morphologic findings and should not be a diagnosis purely made on morphologic grounds.

- Inflammatory cell infiltrate:
 - Composed primarily of mature lymphocytes with admixed mature plasma cells:
 - Distributed within and around lobules
 - Often prominent germinal centers are present.
 - T-cells predominate over B-cells.
 - In addition, macrophages and giant cells may be present:
 - Giant cells are seen within the follicles but are limited in extent and number unlike those present in subacute thyroiditis and a neutrophilic infiltrate is not seen.
- Thyroid atrophy includes presence of small follicles with limited to absent colloid formation.
- Fibrosis within and around follicles:
 - Interlobular fibrosis gives gland a nodular appearance.
 - Amount of fibrosis usually scanty with slight to moderate thickening in interlobular septa
 - Fibrosis not usually extensive as seen in fibrous variant (see later in chapter) or as identified in Riedel thyroiditis

- Does not extend outside the thyroid gland
- Rare examples of coexisting chronic lymphocytic (Hashimoto) thyroiditis and Riedel thyroiditis
- Oncocytic cytoplasmic change:
 - Characterized by cells with prominent granular eosinophilic cytoplasm (so-called Hürthle cells)
 - Often associated with nuclear enlargement, prominent eosinophilic nucleoli, and dispersed to optically clear-appearing nuclear chromatin
 - These changes may be confused with those of papillary thyroid carcinoma but additional architectural and/or cytomorphologic are absent, including but not limited to variation in nuclear size and shape.
 - Foci with more pronounced cytological atypia may be identified that some authors have variably termed atypical follicular epithelium, atypical cell clusters, or follicular epithelial dysplasia (FED):
 - Particularly prominent in cases of severe chronic lymphocytic (Hashimoto) thyroiditis but lack invasive growth, papillary architecture, or intranuclear pseudoinclusions
- Additional changes that can be seen include:
 - Squamous metaplasia of follicular epithelial cells (more common in the fibrous variant; see below)
 - Intrathyroidal cysts:
 - Squamous epithelial cell-lined
 - Ciliated respiratory epithelial-lined:
 - May attain fairly large sizes and bordered by lymphocytic infiltrate, suggesting branchial cleft cysts
 - Similar cysts can be seen in absence of thyroiditis.
- Immunohistochemistry:
 - Lymphoid infiltrate includes:
 - Reactivity for B-cell (CD20) and T-cell (CD3) markers
 - B-cells and plasma cells exhibit kappa and lambda staining (i.e., lack light chain restriction) and exhibit IgG, IgM, and IgA heavy chains.
 - B-cells are most often of the IgG kappa type.
 - Follicular epithelial cells:
 - Focal expression of HBME1, galectin3 (GAL3), cytokeratin 19 (CK19):
 - Similar expression profile may be seen in papillary thyroid carcinoma.
 - In contrast to papillary thyroid carcinoma, diffuse expression of HBME1, GAL3, CK19 not present in chronic lymphocytic (Hashimoto) thyroiditis
 - Further, immunoreactivity for HBME1, GAL3, and CK19 not specific or sensitive for papillary thyroid carcinoma

- So-called follicular epithelial dysplasia (FED) reported to be immunoreactive for:
 - Thyroglobulin and TTF-1
 - p63 (26 %)
 - Strong diffuse staining for HBME-1 (86 %), CK19 (96 %), galectin-3 (40%)
 - Immunohistochemical profile similar to papillary thyroid carcinoma (PTC) supporting concept of premalignant lesion preceding PTC arising in context of severe chronic inflammation
 - However, absence of *BRAF* mutation in HBME1 and CK19 positive atypical cell clusters or FEDs in chronic lymphocytic (Hashimoto) thyroiditis support that they may not be preneoplastic.
- Cytogenetics and molecular genetics:
 - Presence of RET/PTC rearrangements reported even in absence of morphologic findings diagnostic for papillary thyroid carcinoma:
 - This finding coupled with reports showing immunohistochemical comparable features to those of papillary thyroid carcinoma (see above) suggest possibility of early, focal premalignant transformation in some cases of chronic lymphocytic (Hashimoto) thyroiditis.
 - Despite above findings reported in literature, from a practical perspective, absence cytomorphic (i.e., nuclear features) reaching level diagnostic for papillary thyroid carcinoma preclude such a diagnosis, and the concept of early, focal premalignant transformation remains to be proven.
 - Absence of *BRAF* mutation in areas with atypical cell clusters or FEDs suggest:
 - *BRAF* is less frequent mechanism of tumorigenesis in background of chronic lymphocytic (Hashimoto) thyroiditis
 - *BRAF* mutation not present in the atypical cell clusters or FEDs

Differential Diagnosis

- Non-Hodgkin malignant lymphoma
 - In contrast to neoplastic lymphoid population of thyroid gland malignant lymphoma, lymphocytic cell infiltrate of chronic lymphocytic (Hashimoto) thyroiditis:
 - Is confined to thyroid gland and does not extend beyond the thyroid capsule into perithyroidal soft tissue
 - Presence of “colonization” of thyroid follicles (as appears in malignant lymphoma) may occur but usually is absent.
- Papillary thyroid carcinoma:
 - See above.

Treatment and Prognosis

- Thyroxine (T_4) therapy is preferred treatment for all patients with hypothyroidism (overt or subclinical) as a result of autoimmune thyroiditis:
 - Treatment generally is lifelong as hypothyroidism will recur with cessation of thyroxine.
 - Proper response to T_4 therapy will include a decrease in levels of thyroid antibodies.
- Immunosuppressive (corticosteroid) therapy may result in regression of thyroid enlargement and decrease in thyroid antibody levels; however, due to serious side effects of steroids and the efficacy of thyroxine therapy, immunosuppressive therapy is not indicated.
- Appropriate therapy for patients who are euthyroid but have enlarged glands (goiter) remains uncertain.
 - T_4 administration may result in a decrease in the size of the gland, whereas in others there will be no diminution in size but rather progressive enlargement of the thyroid.
 - Further, up to 10% to 15% of patients may become hypothyroid.
- Surgery can be used in those patients who do not respond to thyroxine therapy and have continued enlargement (with or without local symptoms) of their thyroid glands.
- Graves disease may follow (or precede) chronic lymphocytic (Hashimoto) thyroiditis.
- Patients with coexisting thyrotoxicosis should be treated accordingly.
- Complications include potential development of:
 - Hematolymphoid malignancy (lymphoma or leukemia)
 - Strong association with primary B-cell lymphoma of thyroid gland
 - Presumably due to prolonged stimulation of intrathyroidal B-cells resulting in malignant clone
 - Follicular epithelial-derived tumors, including:
 - Papillary thyroid carcinoma
 - Follicular carcinoma
 - Patients with autoimmune thyroiditis are at no increased risk of developing a thyroid neuroendocrine neoplasm (i.e., medullary thyroid carcinoma), although coincidental medullary thyroid carcinomas may occur in setting of chronic lymphocytic (Hashimoto) thyroiditis.

Fibrous Variant of Chronic Lymphocytic (Hashimoto) Thyroiditis (Figs. 27-54 through 27-56)

Synonym: Advanced lymphocytic thyroiditis

- Makes up approximately 10% to 12% of all cases
- As compared to the “classic type,” fibrous variant is:



Fig. 27-54. Fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis.

Resection specimen showing a diffusely enlarged thyroid that was firm to hard with grossly identifiable (white) fibrotic areas creating a prominent nodular/lobulated appearance.

- More common in men than in women
- Occurs in older-age patients
- Patients present with symptoms of large goiter that may produce dysphagia and dyspnea.
- Laboratory findings:
 - High titers of antithyroglobulin antibodies
 - Severe hypothyroidism
 - Elevated serum TSH levels
- Relationship to IgG4-related diseases:
 - Suggestion that fibrosing variant of chronic lymphocytic (Hashimoto) thyroiditis also part of spectrum of IgG4-related diseases (IgG-RD) but not unequivocally confirmed:
 - Evidence accumulating that supports including fibrosing variant of chronic lymphocytic (Hashimoto) thyroiditis but relationship to IgG4-RD remains unproven
 - Support for inclusion within spectrum of IgG4-related diseases includes:
 - Reported instances, albeit rare, of combined Riedel disease and chronic lymphocytic (Hashimoto) thyroiditis:
 - Characterized by clinical and laboratory findings of chronic lymphocytic (Hashimoto) thyroiditis and pathologic findings of Riedel disease
 - Likely a coincidental occurrence
 - 21% (5/24) patients in one study had >135 mg/dL of IgG4 representing serum criterion of IgG4-related disease.
 - Levels of IgG and IgG4 positively correlated with titers of anti-thyroglobulin antibody or anti-thyroid peroxidase antibody

- Increased numbers of IgG4-positive plasma cells and increase IgG4:IgG ratio in chronic lymphocytic (Hashimoto) thyroiditis
- Although a proportion of cases show elevated numbers of IgG4 positive plasma cells, there is an absence of histologic features typically associated with IgG4-RD (see under differential diagnosis below for histologic findings seen in IgG4-related Riedel disease but absent in chronic lymphocytic [Hashimoto] thyroiditis)
- Despite above findings, designation IgG4-related thyroiditis being suggested as distinct from fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis characterized by:
 - Younger age population
 - Lower female-to-male ratio
 - Subclinical hypothyroidism
 - Diffuse sonographic echogenicity
 - Rapid progression requiring surgical treatment
 - Higher levels of thyroid autoantibodies
 - High IgG4 level in serum
 - Increased IgG4-positive plasma cells in thyroid
 - Serum IgG4 concentrations decreased significantly after thyroidectomy
 - Histopathologically, show higher grade of stromal fibrosis, lymphoplasmacytic infiltration, and follicular cell degeneration than non-IgG4 thyroiditis
 - For those cases that do not qualify as being an IgG4-related thyroiditis, terminology of non-IgG4-related thyroiditis has also been used.

Pathology

Fine-Needle Aspiration Biopsy

- Due to marked fibrosis, aspiration generally yields little material.

Gross

- Diffusely enlarged thyroid gland that is firm to hard, pale tan, and characterized by presence of fibrosis and a prominent lobular appearance
- Thyroid glands may weigh as much as 200 g or more.
- Thyroid not adherent to surrounding structures

Histology

- Characteristic features at low power include:
 - Presence of obvious nodular or lobular pattern of growth with associated dense fibrosis and a chronic inflammatory cell infiltrate
- Fibrosis:
 - Keloid-like with irregular broad bands of acellular fibrous tissue coursing in and around remnant of thyroid parenchymal tissue

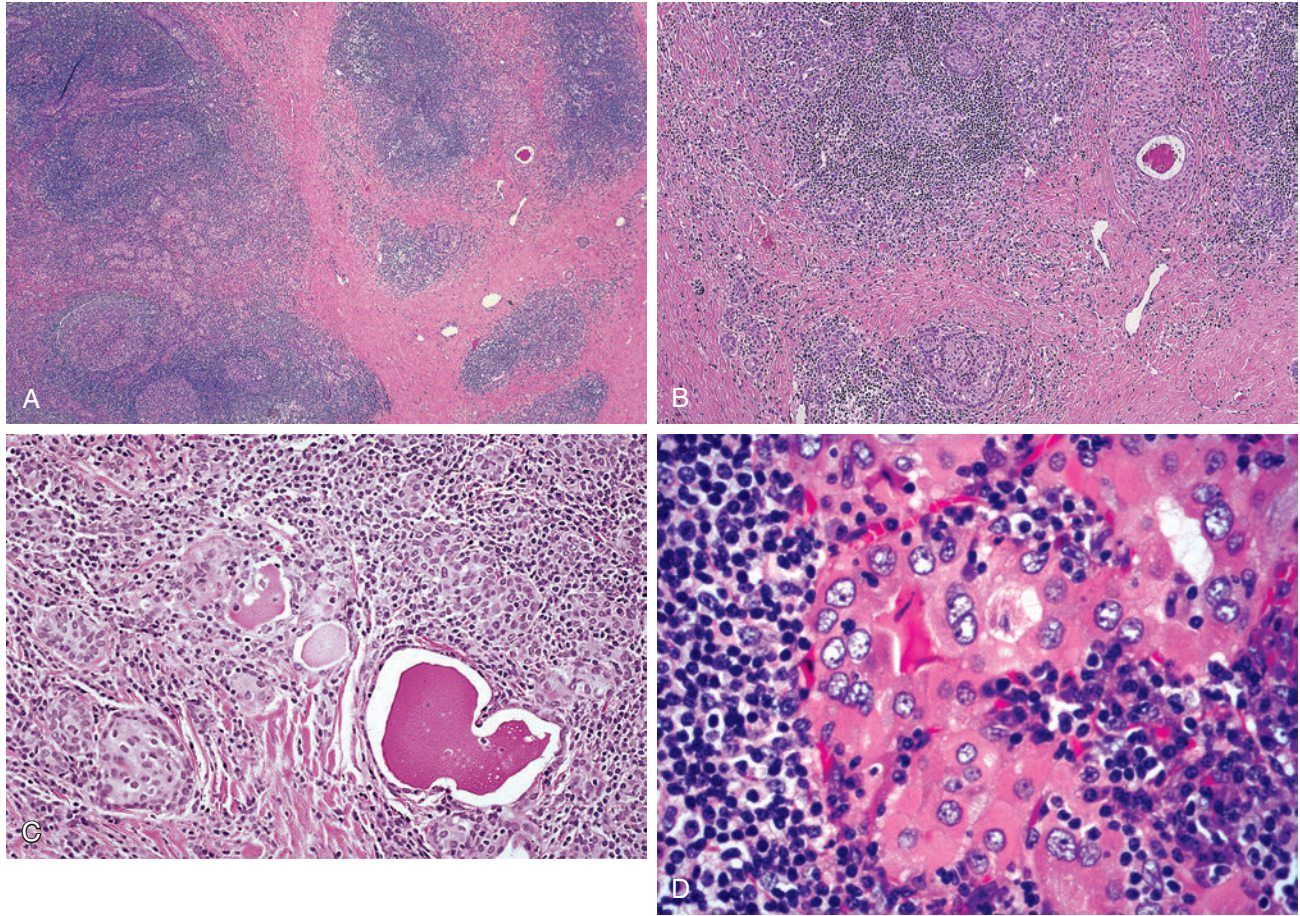


Fig. 27-55. Fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis.

A and **B**, The low magnification features include the presence of a nodularity, keloid-like fibrosis with irregular broad bands of acellular fibrous tissue coursing in and around remnant of thyroid parenchymal tissue, chronic inflammatory cell infiltrate (with or without germinal centers), and atrophy of the follicular epithelial cells. **C**, Keloid-like fibrosis, mixed lymphoplasmacytic cell infiltrate and atrophic thyroid follicles. **D**, Follicular epithelial cells showing oncocytic cytoplasmic change characterized by the prominent granular eosinophilic cytoplasm, nuclear enlargement, variably sized nucleoli, and dispersed to clear-appearing nuclear chromatin; associated lymphoplasmacytic cell infiltrate is present.

- Inflammatory infiltrate:
 - Includes mature lymphocytes and plasma cells (lymphoplasmacytic cell infiltrate)
 - Seen within fibrotic tissue
- Remnant of thyroid tissue shows the changes of chronic lymphocytic thyroiditis, including:
 - Mature lymphocytic cell infiltrate with or without germinal centers
 - Severe follicular atrophy
 - Oncocytic metaplasia of follicular epithelial cells
- Squamous metaplasia may be prominently seen:
 - May include keratinization and intercellular bridges and/or squamous eddies or whorls
- Mucous cell metaplasia rarely may be present.
- Immunohistochemistry:
 - Staining for IgG and IgG4 may allow for determination whether any given case might be

classified as IgG4-related thyroiditis or non-IgG4-related thyroiditis

- See discussion in Section 6, Salivary Gland, for diagnostic criteria related to IgG and IgG4 immunoreactivity.

Differential Diagnosis

- Riedel disease
 - Findings in Riedel disease that allow for separation from fibrous variant of Hashimoto thyroiditis include:
 - Extension of pathologic (fibroinflammatory) process outside the thyroid gland:
 - Occurs in Riedel disease
 - Does not occur in (fibrous variant of) Hashimoto thyroiditis

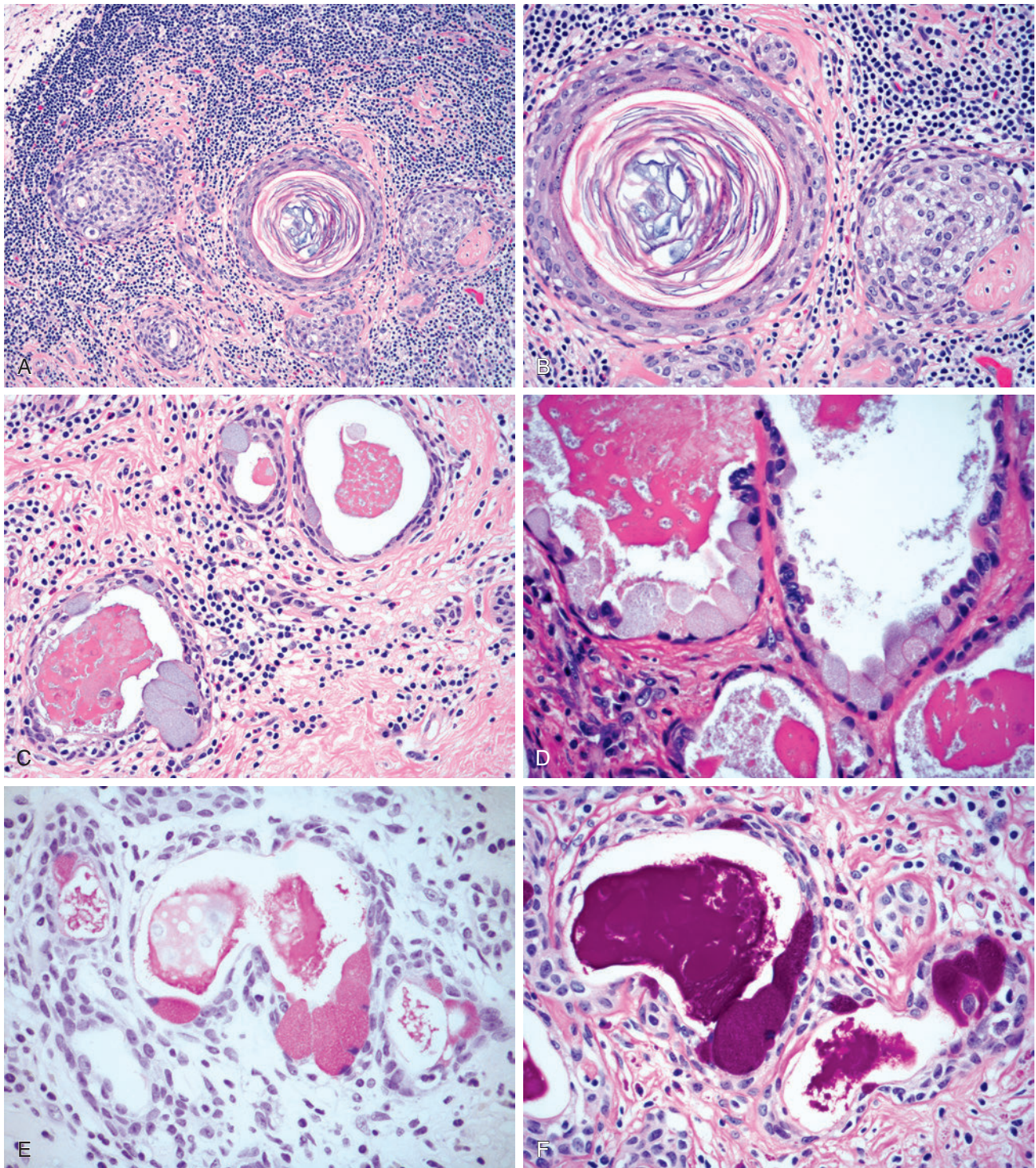


Fig. 27-56. Fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis.

Metaplastic changes that may be seen in the fibrous variant of chronic lymphocytic (Hashimoto) thyroiditis include **(A and B)** squamous metaplasia including keratinization with keratohyaline granules and squamous morule and **(C and D)** mucous cell metaplasia including intracytoplasmic **(E)** mucicarmine and **(F)** diastase-resistant, periodic acid-Schiff positive material.

- Cytoplasmic oncocyctic cell changes in follicular epithelial cells:
 - Absent in Riedel disease
 - Present in (fibrous variant of) Hashimoto thyroiditis
- Vasculitis/phlebitis:
 - Present in Riedel disease
 - Absent in (fibrous variant of) Hashimoto thyroiditis
- Plasma cells:
 - In Riedel disease express lambda chains and IgA
 - In fibrous variant of Hashimoto thyroiditis predominantly express kappa chains and IgG
- Carcinoma:
 - Presence of fibrosis and associated epithelial islands showing squamous metaplasia may raise concern for possible diagnosis of thyroid squamous cell carcinoma:
 - Absence of cytomorphic features indicative of squamous cell carcinoma
 - In presence of squamous and mucous cell metaplasia consideration may be given for a diagnosis of primary thyroid mucoepidermoid carcinoma:
 - Diffuse rather than focal changes weigh against a diagnosis of mucoepidermoid carcinoma
 - Absence of significant cytologic atypia and absence of invasive growth weigh against a diagnosis of mucoepidermoid carcinoma.

Treatment and Prognosis

- Surgical removal of the thyroid (total thyroidectomy) is indicated.
- Prognosis is considered good following removal of the gland with relief of symptoms.

Fibrous Atrophy of Thyroid Gland (Atrophic Thyroiditis, Idiopathic Myxedema, Primary Myxedema)

- More common in women than in men; occurs in older-age patients
- Aside from the enlarged goitrous thyroid, clinical presentation and laboratory findings are similar to the fibrous variant of lymphocytic thyroiditis, including:
 - Severe hypothyroidism
 - High titers of antithyroglobulin antibodies
- Thyroid gland is small, often weighing from 1 to 6 g.
- Histologically:
 - Similar changes to those of fibrous variant of lymphocytic thyroiditis (but gland is much smaller), including:
 - Prominent keloid-like fibrosis
 - Chronic inflammatory cell infiltrate

- Marked follicular atrophy with oncocyctic and squamous metaplasia
- Thyroid parenchyma may not be recognizable replaced by dense tan-white fibrous tissue.

- Given the similarities in their clinical findings and histopathologic appearance, fibrous atrophy of the thyroid and fibrous variant of lymphocytic thyroiditis may be related, with former representing end stage in clinical and morphologic continuum from latter.

Juvenile Form of Chronic Lymphocytic Thyroiditis (Juvenile Autoimmune Thyroiditis; Juvenile Lymphocytic [Hashimoto] Thyroiditis)

- Much more common in females than in males; most common in adolescents and young adults
- Clinically may present with or without goiter (goitrous versus atrophic form) with or without (mild) hypothyroidism:
 - Goitrous form more common
- Some patients may present with signs and symptoms of thyrotoxicosis (tachycardia, nervousness, increased pulse pressure) rather than hypothyroidism.
- Mild to marked elevated antithyroglobulin antibodies may be present:
 - Prevalence of thyroid autoantibodies of 20% to 30% in children with type I diabetes mellitus
 - Prevalence of elevated serum TSH levels of around 10% found
 - Recommended that all children with diabetes mellitus be screened for autoimmune thyroid disease
- May be strong family history of thyroid disease (e.g., asymptomatic goiter, hypothyroidism, and Graves hyperthyroidism)
- Most commonly occurs in absence of abnormalities in another endocrine organ
 - Most common clinical entity is autoimmune polyglandular syndrome type 2 (APS-2) or Schmidt syndrome, characterized by a combination of Hashimoto thyroiditis and lymphocytic adrenalitis resulting in adrenal insufficiency (Addison disease).
- Histologically characterized by:
 - Lymphoplasmacytic infiltrate
 - Oncocyctic cytoplasmic changes of follicular epithelial cells
 - Focal or absent follicular atrophy
 - Squamous metaplasia may be present.
- Follicular epithelial hyperplasia may be present, correlating with a hyperthyroid state.

- Variable biology including spontaneous remission, progressive atrophy of thyroid with progression to (severe) hypothyroidism or recurrent hyperthyroidism

Painless (“Silent”) Thyroiditis with Hyperthyroidism

- Primarily affects women in younger age groups at puerperium or postpartum
 - May occur in men
- Patients present with:
 - Painless, nontender thyroid gland
 - Elevated levels of free T_4 and T_3
 - Elevated antithyroglobulin antibodies
 - Episodic hyperthyroidism
 - Low radioactive iodine uptake
 - Spontaneous resolving hyperthyroidism
- Similar histomorphologic changes to juvenile form of lymphocytic thyroiditis, including:
 - Variable lymphocytic infiltration with preservation of lobular architecture:
 - Inflammatory infiltrate may be focal or diffuse.
 - Oncocytic cytoplasmic changes of follicular epithelial cells is uncommon; when present often focal
 - Fibrosis usually absent; when present is focal
 - Follicular destruction present in all cases
- Variable biology including complete resolution, recurrent hyperthyroidism or, rarely, progression to hypothyroidism
- Although initially considered a form of subacute thyroiditis, this entity differs from so-called painless “silent” subacute thyroiditis in that it:
 - Is an autoimmune disease (and belongs to the spectrum of autoimmune thyroiditides)
 - Is associated with elevated antithyroglobulin antibodies
 - Lacks histomorphologic features of subacute granulomatous thyroiditis; specifically, there is no granulomatous inflammation and/or multinucleated giant cells
 - Is associated with a greater risk of permanent hypothyroidism and a higher recurrence rate
- Associated with:
 - Antithyroid antibodies:
 - Usually antiperoxidase antibodies
 - Low serum TSH together with elevated free T_4 and T_3
 - Low radioactive iodine uptake:
 - Due to destructive nature of disease
 - Late hypothyroid phase, which may last for years:
 - Serum TSH level >3.6 mU/L with free T_4 <0.6 ng/dl
- Immunologically related disease:
 - Association with haplotypes consistent with AITD:
 - HLA-A1, -B8, HLA-A26, -BW46, -BW67
 - Lower frequency of HLA-BW62 and -CW7
 - HLA class II also present
 - Significant elevation of circulating antibodies
- Histopathology:
 - Lymphocytic infiltration
 - Slight follicular hyperplasia
 - Variable disruption of follicular cells
- Self-limiting disease:
 - Transient hypothyroid state related to depletion of thyroglobulin owing to destruction of follicular epithelial cells
- Prognosis:
 - Thyrotoxicosis always resolves.
 - Recurrence relatively common
 - Permanent hypothyroidism may develop in 20% to 30% of patients.

Hashitoxicosis (Hyperthyroiditis)

- Includes some of categories listed above, including:
 - Juvenile form of chronic lymphocytic thyroiditis
 - Painless thyroiditis with hyperthyroidism
- Patients present with clinical evidence of Graves disease (with or without laboratory confirmation) and histologically demonstrate features of chronic lymphocytic (Hashimoto) thyroiditis, including:
 - Lymphoplasmacytic infiltration with germinal centers
 - Oncocytic cytoplasmic changes of follicular epithelial cells
 - Follicular atrophy and metaplasia
- In some cases, follicular hyperplasia is present with minimal or absent follicular atrophy and oxyphilic metaplasia.

Postpartum Thyroiditis

- Affects women in first year after delivery
- Patients present with:
 - Painless, nontender thyroid gland
 - Transient thyrotoxicosis about 14 weeks postpartum followed by transient hypothyroidism
 - Occasionally hypothyroid state may develop first
 - Not all patients develop both thyroid states:
 - Thyrotoxic episode may escape detection owing to its short duration.

Graves Disease (Diffuse Toxic Goiter; Autoimmune Hyperthyroidism Disease) (Fig. 27-57 through 27-66)

Definition: Organ specific autoimmune disorder caused by production of autoantibodies characterized by

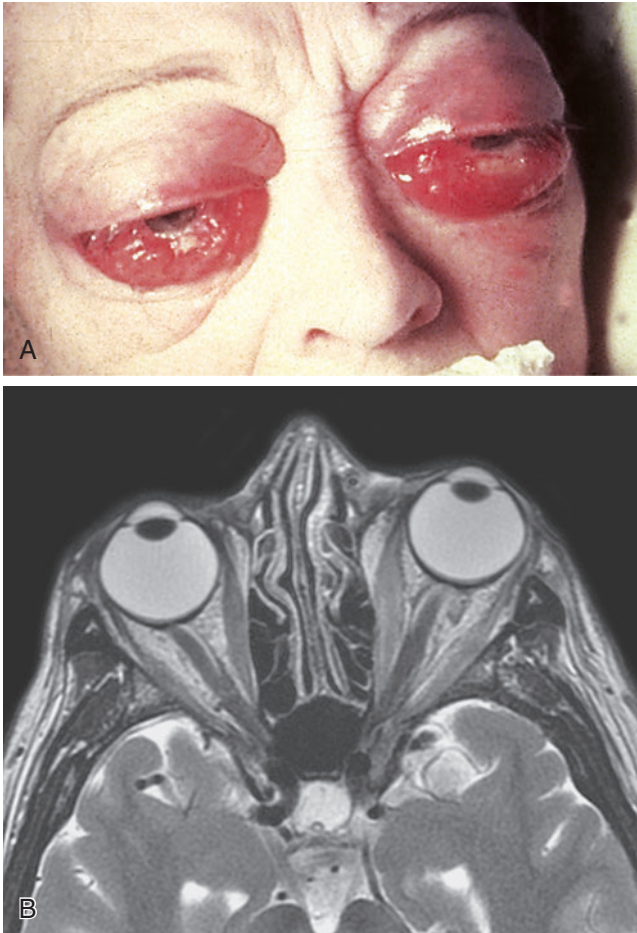


Fig. 27-57. Graves ophthalmopathy.

Diffuse hyperplasia (Graves disease). **A**, Among the more obvious clinical manifestations associated with Graves' disease patients is the presence of ophthalmopathy. **B**, Axial T2-weighted MR image of the orbits shows thickening of the muscle bellies of the extraocular muscles bilaterally. There is tapering down to normal size at the anterior tendon insertions to the globe. In addition, the muscle signal intensity is higher than normal indicating the presence of some inflammation. There is also proptosis. Thyroid ophthalmopathy. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-19, page 2621.)

variable combination of hyperthyroidism, ophthalmopathy, and dermatopathy.

Synonym: Basedow disease

- Pathogenesis:
 - Graves disease is a unique human autoimmune disease with stimulating autoantibodies to thyrotropin (TSH) receptor as major pathogenic feature:
 - These antibodies represent markers of disease but are also responsible for hyperthyroidism that occurs in these patients.

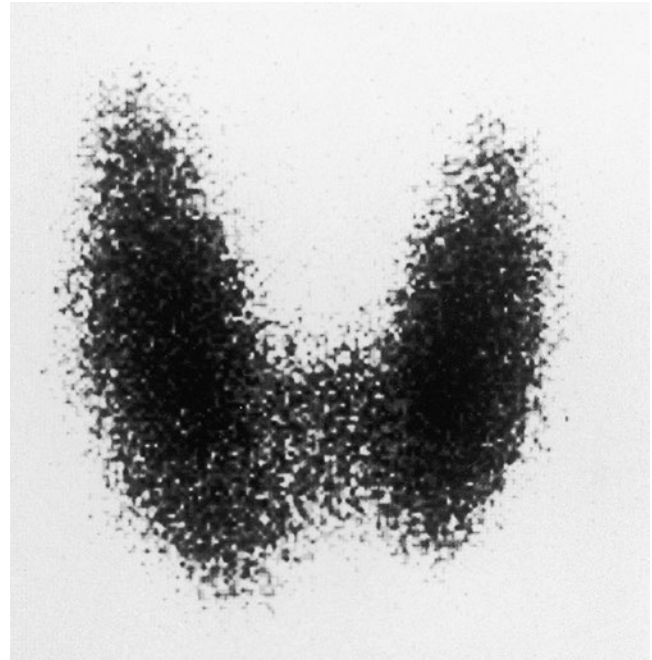


Fig. 27-58. Graves disease.

Frontal ^{131}I scintigraph of a patient with Graves disease shows diffuse increased uptake of the radiotracer throughout the gland. The 2-hour uptake was 25% and the 24-hour uptake was 57%, with the upper limits of normal being 10% and 30%, respectively. (Case is courtesy of Dr. Joseph Sam.) (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-31, page 2629.)

- B- and T-lymphocytes known to be directed at three well-recognized thyroid autoantigens:
 - Thyroglobulin (Tg)
 - Thyroid peroxidase (TPO)
 - Thyroid-stimulating hormone receptor (TSHR):
 - ◻ Most evidence suggests only TSHR is primary autoantigen of Graves disease.
 - ◻ Immune responses to other thyroid antigens only reflective of concomitant thyroiditis
- Antibodies bind to thyroid-stimulating hormone receptors (TSHR) on thyroid follicular epithelial cells leading to overstimulation and enlargement of the thyroid gland with overproduction of thyroid hormones, suppression of TSH production from pituitary gland, and clinical manifestations of hyperthyroidism.
- TSHR antibody that stimulates thyroid gland was originally called long-acting thyroid stimulator (LATS).
- In patients with Graves disease, thyroid gland no longer under control of pituitary TSH but is continuously stimulated by circulating antibodies with TSH-like activity:

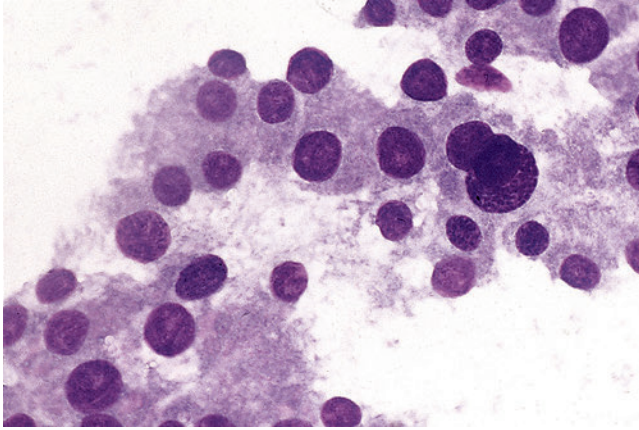


Fig. 27-59. Fine-needle aspiration biopsy in Graves disease.

The aspirate included high cellularity and lack of colloid in which there were flat sheets of follicular epithelial cells with abundant oncocytic appearing cytoplasm. These features may suggest a follicular neoplasm with oxyphilia. The clinical history is most helpful in arriving at a correct interpretation. Note the prominent granularity of the cytoplasm, a common feature in Graves disease (Diff-Quik stain).

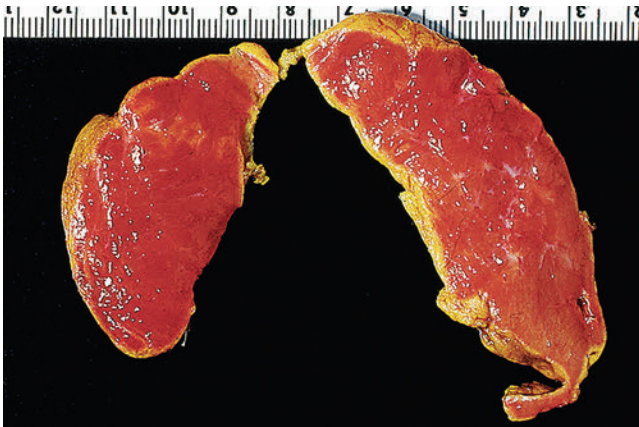


Fig. 27-60. Graves disease.

Total thyroidectomy specimen in Graves disease showing diffuse symmetric enlargement of the gland, which has a beefy red appearance.

- Not possible to suppress thyroid gland using exogenous TSH because thyroid-stimulating antibodies are unaffected

Clinical

- Reported incidence in the United States from 0.02% to 0.4% of population
- Represents most common cause of hyperthyroidism, accounting for approximately 70% to 80% of all cases

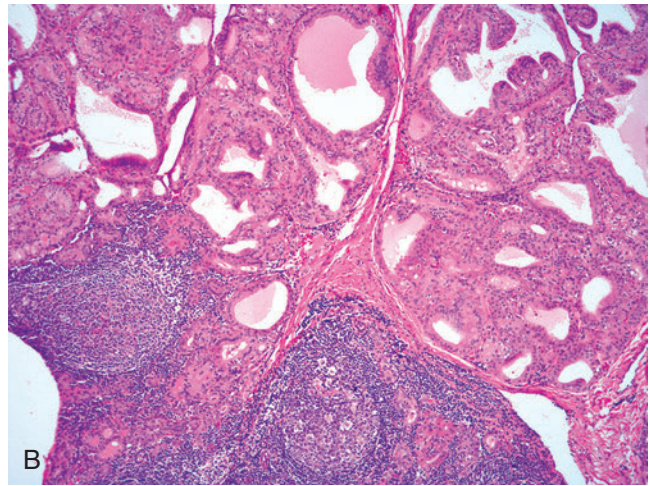
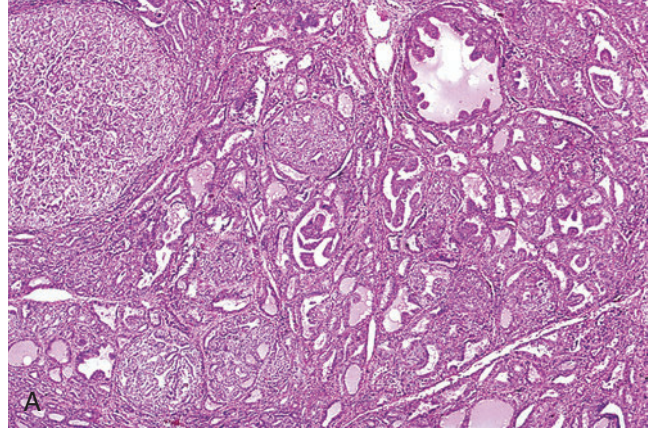


Fig. 27-61. Graves disease, untreated.

- A,** At low magnification there is diffuse hyperplasia with prominent papillary architecture, solid foci with increased cellularity and relative absence of colloid with no identifiable histologically normal thyroid parenchyma.
- B,** In addition, a lymphocytic cell infiltrate including germinal centers is present.

- Much more common in women than in men; may occur at any age but is most commonly seen in the third to sixth decades of life:
 - May occur in children; in this age group Graves disease represents most common cause of hyperthyroidism
- Most patients with Graves disease have hyperthyroidism and goiter.
- Graves disease causes most florid signs and symptoms of thyrotoxicosis, including:
 - Nervousness, fatigue, muscle weakness, tremor, increased perspiration, warm and moist skin, nonpitting edematous changes of the skin, heat intolerance, palpitation, tachycardia, cardiac arrhythmia, systolic hypertension, hyperactivity, hyperreflexia, increase in appetite, loss of weight,

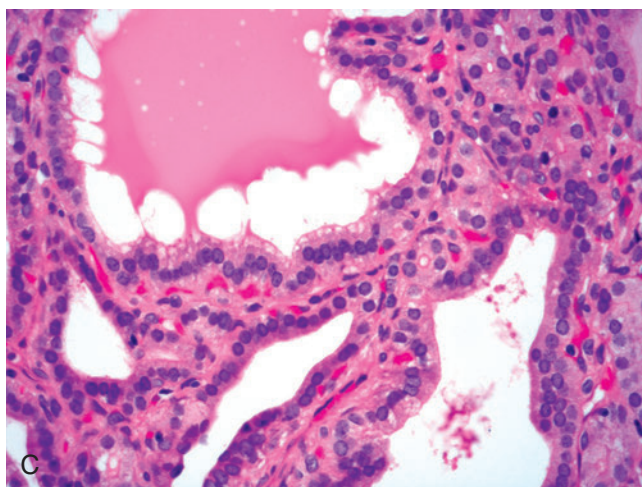
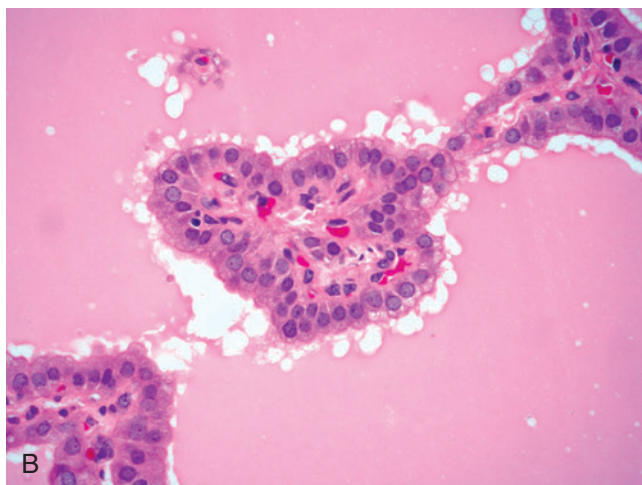
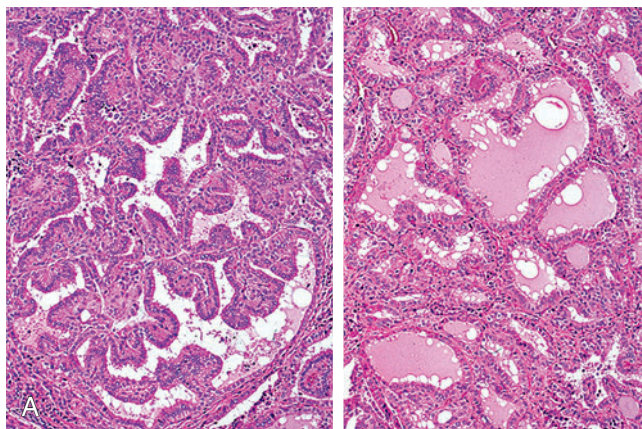


Fig. 27-62. Graves disease, untreated.

A, Left panel, Papillary hyperplasia may simulate the features seen in papillary thyroid carcinoma; **right,** colloid is distorted due to fixation and has a “scallop” appearance. The nuclear features in Graves disease whether **(B)** associated with papillae or **(C)** lining follicles with or without (scallop appearing) colloid are small, round to oval with smooth nuclear contours lacking the nuclear findings seen in papillary thyroid carcinoma.

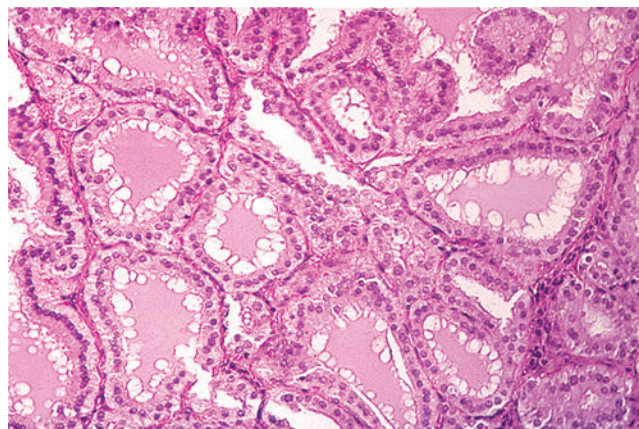


Fig. 27-63. Treated Graves disease.

The involutional changes associated with radioiodine therapy include reversion of the follicular epithelial cells to their usual appearance (cuboidal to flat) with greater degree of restoration of colloid.

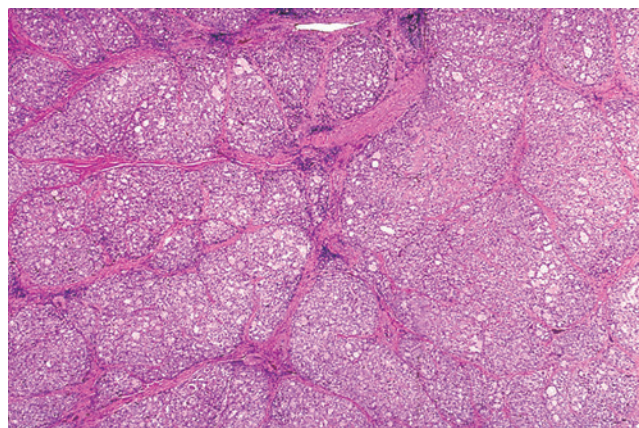


Fig. 27-64. Treated Graves disease.

Prolonged treatment with radioiodine therapy in Graves disease may be associated with fibrosis creating a nodular-appearing thyroid gland.

- menstrual disturbances, stare, and eyelid retraction
- Enlargement of thyroid gland:
 - Characteristically, diffuse, symmetric bilateral enlargement, but asymmetric enlargement is not uncommon
 - Lobulations or (multi)nodules can occur.
 - Glands generally not tender or painful, but these symptoms may present.
- Continuous or systolic (palpable) thrills or (audible) bruits over one or both thyroid lobes are present in a minority of patients.
- Extrathyroidal manifestations of Graves disease include:

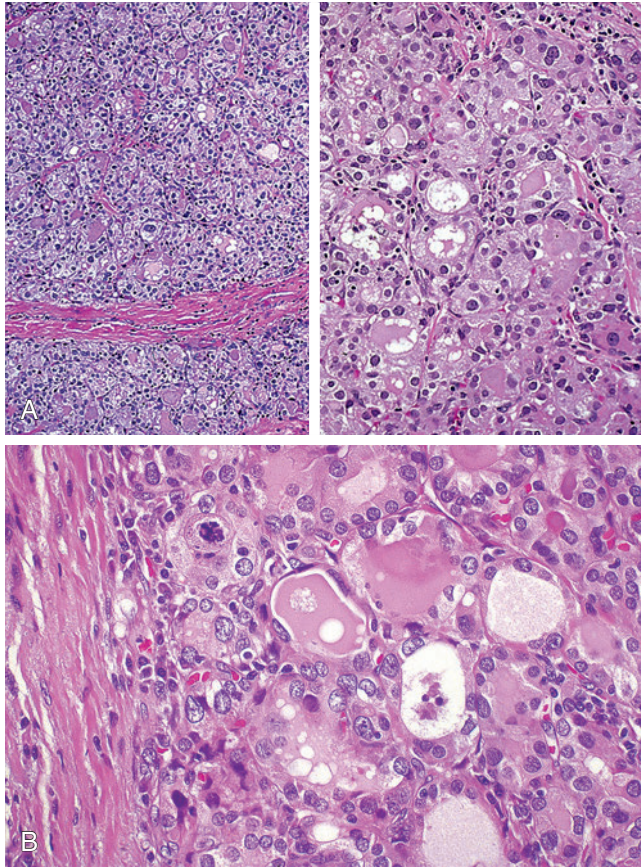


Fig. 27-65. Treated Graves disease.

In addition to the fibrosis and nodularity, prolonged radioactive iodine therapy may result in (**A**, left and right) atypical-appearing nodules with increased cellularity and markedly bizarre-appearing nuclei (nucleomegaly, pleomorphism, and hyperchromasia); (**B**) scattered mitotic figures may be seen but generally are low in numbers and there is an absence of necrosis.

- Ophthalmopathy:
 - Proptosis or staring appearance (most common), blurred vision, diplopia, photophobia, lacrimation, retroocular pressure; histologically, there is edema, lymphocytic cell infiltration, glycosaminoglycan deposition, and fibrosis of the extraocular muscles
- Dermopathy:
 - Localized myxedema (nonpitting) resulting from circumscribed accumulations of glycosaminoglycans
 - Most frequently seen on skin of anterior lower legs (pretibial myxedema)
 - Additional forms of Graves dermatopathies include:
 - Sharply circumscribed, tuberos, or nodular lesions

- An elephantiasis form, also known as thyroid acropachy, which includes edematous and nodular thickening of the extremities; thyroid acropachy is least common Graves dermatopathy and most patients with this dermatopathy have clinically significant ophthalmopathy and localized myxedema
- Pathogenesis for Graves-associated ophthalmopathy and localized myxedema remains unclear; however, recent evidence has shown that cytokines implicated in pathogenesis:
 - In patients with autoimmune thyroid disease cytokines can be found in the thyroid gland and extrathyroidal sites.
 - Cytokines affect autoimmune process through a number of mechanisms, including recruitment of inflammatory cells and upregulation of molecules essential for perpetuation of the inflammatory response in the affected site.
 - Cytokines interfere with thyroid hormone synthesis, implicating them directly in thyroid dysfunction.
 - Cytokines can modulate function of cells in orbital tissue, which results in localized edema, indicating a central role for cytokines in development of proptosis.
- Laboratory findings:
 - Thyroid function testing:
 - Hyperthyroidism with high serum total and free thyroxine (T_4) and T_3 concentrations with increased radioactive iodine uptake in association with low serum TSH concentrations
 - T_3 predominant Graves disease is variant of Graves disease in which there is increased serum T_3 levels in presence of therapy-induced low T_4 levels.
 - In a patient with ophthalmopathy and diffuse goiter, presence hyperthyroidism is diagnostic of Graves disease, and measurements of thyroid-stimulating antibody are not needed for diagnostic purposes.
 - Pituitary-hypothalamic testing:
 - Decreased to negligible levels of thyroid-stimulating hormone and TRH (tripeptide hypothalamic hormone)
 - Autoimmune basis:
 - Presence of elevated circulating TSH receptor antibodies
 - Higher incidence of genetic predisposition to this and other autoimmune diseases
 - Presence of HLA-DR type II antigen on follicular epithelial cell surfaces
- Patients with autoimmune thyroid disease show a higher prevalence of autoantibody not only against thyroid-specific but also nonthyroid-specific antigens

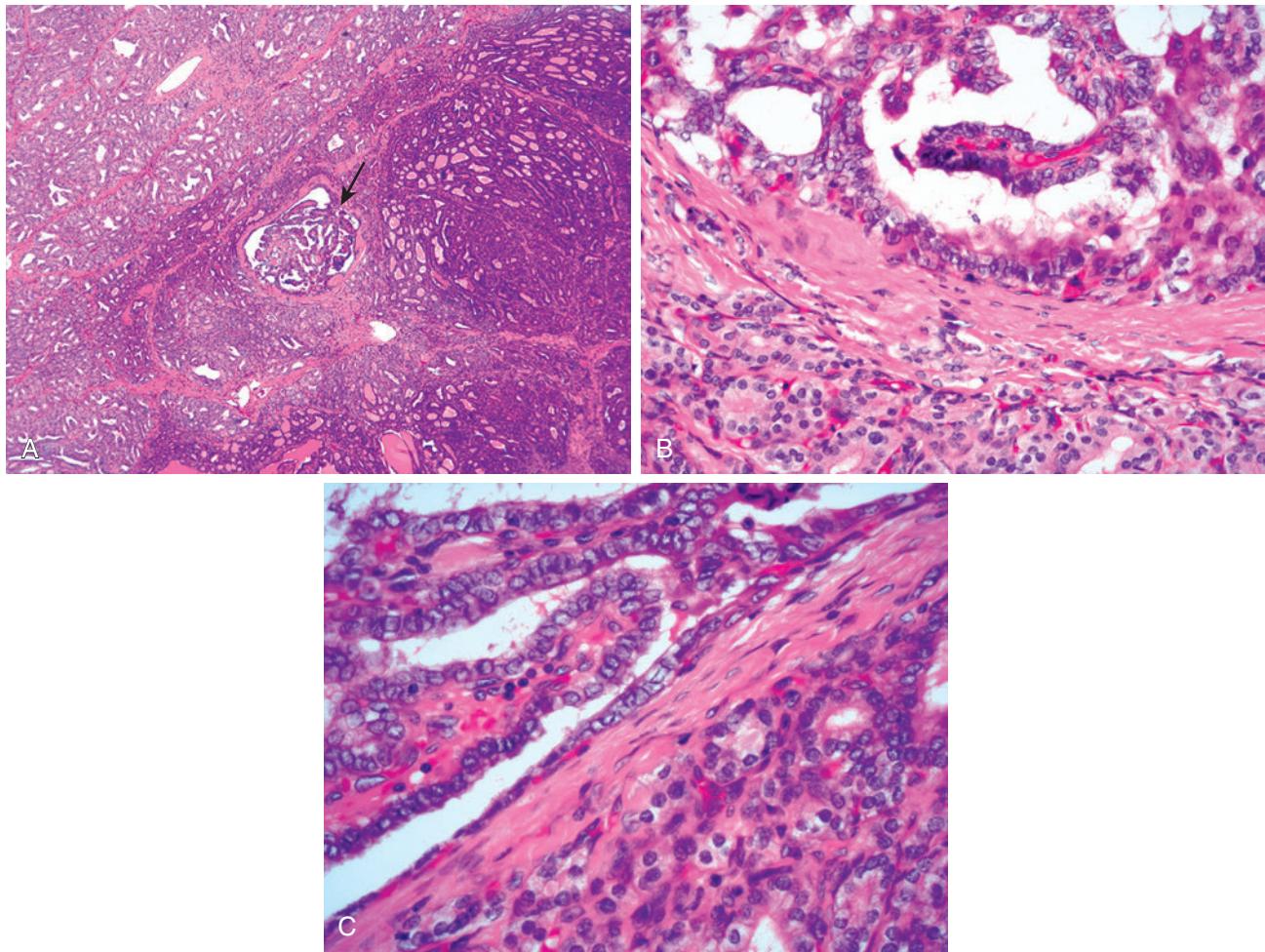


Fig. 27-66. Graves disease with papillary thyroid carcinoma.

Papillary thyroid carcinoma is perhaps the most common malignant thyroid tumor that may arise in association with Graves disease. **A**, Incidentally identified microscopic focus of papillary carcinoma appearing as a small discrete nodule (*arrow*) from the surrounding diffusely hyperplastic thyroid parenchyma. **B** and **C**, At higher magnification, the nuclei of papillary carcinoma (*top*) are enlarged with irregularities in size and shape, have clear to dispersed-appearing chromatin, and show crowding and overlapping. In comparison, the nuclei in association with Graves disease (*bottom*) are small, rather uniform in shape with smooth nuclear contours, and have more hyperchromatic-appearing nuclear chromatin.

- (antibodies to nucleus, smooth muscle, and single-stranded DNA) than matched control patients.
- Radiology:
 - Most hyperthyroid patients have increased (high) radioiodine uptake.
 - In some hyperthyroid patients, there is decreased (low) radioiodine uptake, including those hyperthyroid patients with subacute thyroiditis, painless thyroiditis, exogenous hyperthyroidism, and patients receiving iodide-containing drugs.
- Risk factors:
 - Susceptibility genes:
 - Complex diseases with large number of gene loci involved
 - Susceptibility genes fall into two distinct groups:
 - Immune response genes including *HLA*, *CTLA-4*, *PTPN22*, *FCRL3*, and *CD40*
 - ◻ Associated polymorphisms in these genes are common to many autoimmune diseases.
 - Thyroid-specific genes including *TSHR* and *Tg*
 - Caused by interaction between susceptibility genes and environmental triggers
 - External factors:
 - Infection: long-standing theory suggests variety of viral infections may lead to virus becoming persistent endogenous thyroid antigen or by epigenetic influences may lead to overexpression of thyroid antigens
 - Sparse evidence related to AITD

- Nutrition
- Trauma
- Stress
- Iodine intake
- Irradiation
- Internal factors:
 - Thyroid autoantibodies:
 - Presence of anti-TPO and anti-Tg doubles risk of autoimmune thyroiditis
 - Sex steroids:
 - More women than men have Graves disease, and evidence suggests sex steroids (estrogen and progesterone) may contribute to difference in susceptibility.
 - Further, evidence in favor of sex steroid influence includes fact that Graves disease uncommon before puberty
- Pregnancy
- Genetic susceptibility

Pathology

Fine-Needle Aspiration Biopsy

- Cellular aspirate
- Orderly sheets of follicular epithelial cells with a “honeycomb” pattern
 - Nuclei enlarged but are round with regular contours, coarse nuclear chromatin, and may show prominent nucleoli
 - Cytoplasmic oncocyctic (oxyphilic) change with prominent cytoplasmic granularity:
- “Flame cells” represented by marginal cytoplasmic vacuoles with red to pink frayed edges may

be seen but are not specific for Graves disease and may be seen in other non-neoplastic thyroid lesions as well as in neoplasms (e.g., follicular adenoma and carcinoma, papillary carcinoma).

- Absent to minimal colloid
- In presence of supporting clinical history, more specific diagnoses may be used, including:
 - Consistent with chronic lymphocytic (Hashimoto) thyroiditis
- In absence of supporting clinical history, descriptive diagnosis may be used, including:
 - Numerous polymorphic lymphoid cells with admixed benign follicular cells with prominent oncocyctic cytoplasmic changes (so-called Hürthle cells) consistent with chronic lymphocytic (Hashimoto) thyroiditis in proper clinical setting

Gross

- Diffuse and symmetric enlargement of thyroid gland is norm
 - Asymmetric enlargement is not uncommon.
 - Lobulations or (multi)nodules can occur.
- Gland appears beefy red, is rubbery to firm, attaining weights of 150 g or more.

Histology (Table 27-1)

Untreated Graves Disease

- Diffuse follicular hyperplasia with prominent papillary architecture
 - Overall lobular architecture of gland is retained but there is no histologically identifiable normal thyroid parenchyma.

TABLE 27-1 Histology of Graves Disease (Untreated and Treated) Versus Papillary Carcinoma

Features	Untreated Graves Disease	Treated Graves Disease	Papillary Carcinoma, Classic Type
Extent of disease	Diffuse; affects the entire thyroid gland with no residual normal (uninvolved) thyroid tissue seen	Diffuse; affects entire thyroid gland with no residual normal (uninvolved) thyroid tissue seen	Limited; residual uninvolved thyroid tissue is present
Architecture	Diffuse hyperplasia	Variegated appearance; hyperplastic foci are haphazardly arrayed with areas in which hyperplastic changes are not present	Not a diffuse process, rather neoplastic features are focally seen; non-neoplastic (normal) thyroid is identifiable
Papillae	Simple without complex branching	Simple without complex branching	Complex branching
Colloid	Minimal to absent; scalloping is present	Restored	Present; often colloid is darker than in non-neoplastic thyroid
Cyto-morphology	Columnar appearing follicular epithelial cells with enlarged nuclei, amphophilic cytoplasm, and indistinct cell borders; nuclei are round and regular with coarse chromatin and are arranged along basal aspect of cell	In nonhyperplastic areas, there are cuboidal to flattened follicular epithelial cells	Enlarged nuclei with irregularities in size and shape; dispersed to optically clear appearing nuclear chromatin with margination of chromatin along nuclear membrane; nuclear grooves; nuclear inclusions; crowding and overlapping nuclei; loss of basal polarity of the nuclei

- Follicular epithelial cells tend to be columnar in appearance with enlarged nuclei, amphophilic cytoplasm, and indistinct cell borders:
 - Nuclear enlargement with clear appearance can be seen, potentially raising some concern relative to a diagnosis of papillary thyroid carcinoma.
 - In contrast to papillary thyroid carcinoma:
 - Nuclei are round and uniform without irregularities in size and shape, have coarse and not optically clear or dispersed nuclear chromatin pattern, retain their orientation along basal aspect of the cell and are not haphazardly arrayed with crowding or overlapping, lack many nuclear grooves, and usually lack intranuclear inclusions.
 - Papillae are simple lacking complexity in growth (branching or arborization) as seen in papillary thyroid carcinoma.
- Minimal to absent colloid production:
 - Colloid that is present may only be focally seen, not appearing in all lumens, and is artifactually distorted due to fixation creating a “scalloped” appearance adjacent to the follicular epithelial cells.
- Mature lymphocytic cell infiltrate, with or without germinal centers, seen within stroma:
 - Range from minimal to extensive
 - Mixed B- and T-cell lymphocytes:
 - T-cells predominate among epithelial cells and in interstitial tissue.
 - B-cells numerous in lymphoid follicles/germinal centers
 - Dendritic cells may be increased in numbers.
- Prominent vascularity seen
- Minimal fibrosis or sclerosis is present.
- Rarely, psammoma bodies can be seen in absence of papillary thyroid carcinoma.
- Additional changes that can be seen in long-standing cases of Graves disease include:
 - Fibrosis, oncocytic cytoplasmic change of follicular epithelial cells, and cytologic atypia including enlarged, bizarre-appearing nuclei (endocrine atypia)
- Immunohistochemistry:
 - Immunostaining for HLA-DR positive in cytoplasm of follicular epithelial cells and lymphoid cells

Differential Diagnosis

- Papillary thyroid carcinoma (see [Table 27-1](#))
- Dyshormonogenetic goiter:
 - Histology of dyshormonogenetic goiter (see later in chapter) also includes diffuse hyperplasia in absence of residual normal appearing thyroid parenchyma, but in contrast to changes in Graves disease, an associated lymphocytic infiltrate (component of Graves disease) is not a feature seen.

Treatment and Prognosis

- Medical therapy is preferred treatment and includes:
 - Antithyroid drugs:
 - Inhibit synthesis of T_4 and T_3 , leading to reduction of their serum concentrations
 - Heterocyclic compounds known as thionamides and include:
 - Methimazole, carbimazole, and propylthiouracil
 - ◻ Intrathyroidal actions: inhibition of oxidation and organification (iodination of tyrosine residues in thyroglobulin), inhibition of iodotyrosine coupling, possible alteration of structure of thyroglobulin, possible inhibition of thyroglobulin biosynthesis
 - ◻ Extrathyroidal actions: inhibition of conversion of T_4 and T_3
 - Iodine therapy (potassium iodide)
 - Major actions include:
 - ◻ Transient decrease of T_4 and T_3 synthesis by inhibiting iodine oxidation and organification
 - ◻ Block release of T_4 and T_3 from thyroid by inhibiting thyroglobulin proteolysis
 - Major uses of iodide include:
 - ◻ Preparation of patients for surgery
 - ◻ Treatment of thyrotoxic storm
 - ◻ After radioiodine therapy
 - Beta-blockers
 - Propranolol (sustained release) or long-acting beta-blockers such as metoprolol or atenolol
 - Control peripheral manifestations of disease
 - Do not result in histopathologic changes in appearance of thyroid gland

Treated Graves Disease

- Iodine treatment results in involutional changes of thyroid as a result of vascular ablation
 - Medical therapy produces no changes in histologic appearance of Graves thyroid.
- Histologic findings include:
 - Follicular epithelial cells revert to cuboidal or flat appearance.
 - Restoration of colloid
 - Papillary hyperplasia reduced but can still be seen
- With continued iodine treatment:
 - Follicular atrophy and fibrosis are seen.
 - Increased fibrosis results in prominent nodular appearance to thyroid gland.
- These changes are variably seen in treated thyroid gland so that remnants of hyperplastic-appearing thyroid can still be present even in a gland that shows treatment effects.

- Radioactive iodine:
 - Widely used in patients with thyrotoxicosis caused by Graves disease
 - Effective, safe, and relatively inexpensive
 - Initially causes cellular necrosis that provokes inflammatory response
 - Over time, chronic inflammation and fibrosis result in substantial decrease in size of thyroid gland, perhaps inevitably resulting in hypothyroidism.
- Surgery (total or near total thyroidectomy) is performed for patients:
 - Who are allergic to or noncompliant with medical therapy
 - Who are pregnant women and allergic to thionamides
 - With large goiters or severe ophthalmopathy
 - Who prefer ablative (surgical) therapy to radioiodine therapy
- Course of hyperthyroidism in Graves disease is variable:
 - Some patients have cyclic course characterized by cycles of remission and relapse of variable duration.
 - Some patients have unremitting disease course.
 - Some patients only have a single episode of disease.
- Patients treated with antithyroid drugs are more apt to achieve remission:
 - In about 10% to 15% of patients who have a remission, spontaneous hypothyroidism due to Hashimoto thyroiditis ultimately occurs (decades later).
- Thyroid cancer may develop in Graves disease:
 - Most are incidental papillary thyroid carcinomas but follicular carcinomas may develop in this setting.
 - Role of thyroid-stimulating antibodies in development of thyroid cancer suggested, but there is no evidence to support this hypothesis.
 - Thyroid cancers that occur in Graves disease may behave more aggressively.

Toxic Nodular or Multinodular Goiter (Fig. 27-67)

Definition: Presence of thyrotoxicosis (hyperthyroidism) in association with a nodular or multinodular thyroid gland.

Synonyms: Toxic adenoma; Plummer disease

- Incidence unknown
- Usually occurs in patients older than 50 years, predominantly women, who have a goiter for many years (decade or more)
 - Can occur in younger-aged individuals without gender predilection

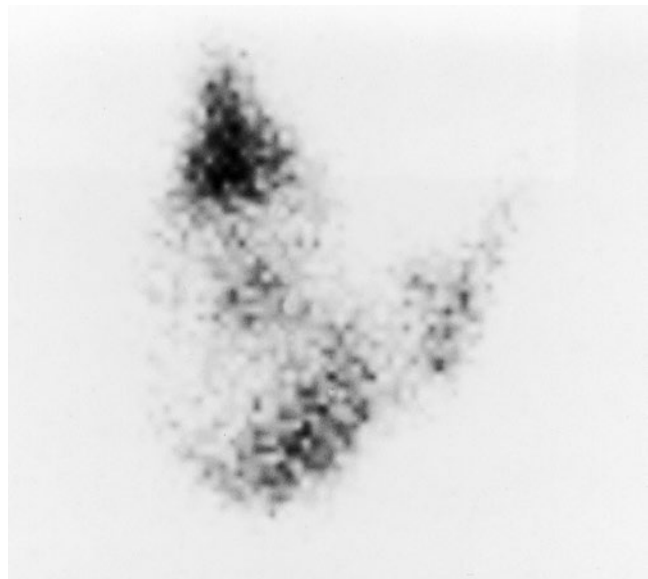


Fig. 27-67. Toxic multinodular goiter.

^{99m}Tc pertechnetate scans show enlargement of the thyroid gland with regions of increased and decreased uptake. (From Som P, Curtin H: *Head and neck imaging*, ed 4, St Louis, 2003, Mosby.)

- Principal clinical manifestations include:
 - Cardiovascular: atrial fibrillation or tachycardia
 - Weakness and muscle wasting are common.
- Radioactive iodine uptake:
 - Show increased and decreased uptake in an enlarged gland:
 - Distinct pattern from homogeneous uptake in Graves disease
 - Overall uptake not as avid as in Graves disease
 - In toxic adenoma uptake is limited to a single nodule.
- Histomorphology:
 - Similar to diffuse toxic goiter (Graves disease), except that changes are limited to nodular foci rather than representing a diffuse process with involvement of the entire thyroid gland
 - Hyperactive nodules are usually well demarcated with discrete fibrous capsule.
 - Papillary hyperplasia consists of follicles with tall columnar cells.
 - Retrogressive changes may be present.
- Nodules are usually benign but there are rare examples of hyperfunctioning follicular carcinomas (primary or metastatic).
- Goal of therapy is to remove autonomous functioning nodule(s)
- Treatment options include:
 - Radioiodine therapy:
 - Preferred treatment

BOX 27-9 Non-Neoplastic Goitrous Lesions

- Endemic goiter
- Dyshormonogenetic goiter or inborn error of thyroid metabolism
- Amyloid goiter
- Diffuse toxic goiter (Graves disease)
- Nodular toxic goiter

- Preferred treatment for older patients who may be poor surgical candidates
- Surgery (partial or subtotal thyroidectomy)
- Antithyroid drugs
 - Induction of euthyroid state by antithyroid medication has been used prior to surgery or radioiodine therapy.
- Recurrence of toxic nodules may occur but is uncommon.

Goiters

Definition: Nonspecific term used for enlargement of thyroid gland.

- Variety of etiologies (Box 27-9)
- Use of the term goiter does not reflect functional activity.
- Presently, use of term goiter is in reference to benign (non-neoplastic) glandular enlargement (i.e., hyperplasia) of thyroid gland.
- In presence of an intact hypothalamic-pituitary axis, any deficiency of circulating thyroid hormone will cause an increase in production of thyroid stimulating hormone (TSH or thyrotropin), which leads to increased activity of thyroid follicular cells, resulting in compensatory glandular enlargement (hyperplasia):
 - Same compensatory hyperplasia will also occur in presence of circulating antibodies to thyroid follicular epithelial cells
- Most common cause of deficiency of circulating thyroid hormone is dietary deficiency of iodine (iodine-deficiency goiter):
 - Endemic goiter used when more than 10% of a given population is affected and is common in regions where nutritional iodine is insufficient or deficient
 - Sporadic (nodular) goiter most common in regions where nutritional iodine is sufficient (e.g., United States)
 - Goitrogenic factors possibly linked to the development of sporadic goiters include dietary goitrogens (cyanoglucosides, cassava [manioc], naturally occurring goitrogens in groundwater, soybeans and in specific plant genus [Brassicaceae]), goitrogenic drugs (lithium salts, iodides,

aminoglutethimide, antithyroid drugs [propylthiouracil, methimazole, perchlorate, thiocyanate]), physical agents (radiation)

- No functional or morphologic features that distinguish sporadic from endemic goiter
 - Difference between these types of goiter is that endemic goiter is most often caused by an extrathyroidal growth-stimulating factor (i.e., iodine deficiency) leading to increased TSH secretion whereas sporadically occurring goiter is not.

Adenomatoid Nodule(s)

(Figs. 27-68 through 27-78)

Definition: Diffuse enlargement(s) of thyroid gland with varying degrees of nodularity not associated with hyperthyroidism or hypothyroidism and not resulting from autoimmune thyroid disease, inflammation, or malignancy.

Synonyms: Nodular goiter; nodular hyperplasia; multinodular goiter; simple nontoxic goiter; colloid goiter

Clinical

- Most common thyroid disease:
 - Clinically detectable nodules found in 3% to 5% of population
 - If thyroid nodules found at autopsy and on histologic examination of thyroid gland are taken into consideration, then incidence increases to 40% to 50% of population.
 - Most common thyroid gland pathologic lesion encountered by surgical pathologist
- Tends to be more common in women than in men; occurs over a wide age range but predominantly seen in adult populace
- Symptoms include:
 - Patients with relatively small goiter and normal thyroid function usually asymptomatic
 - Large lesions may cause:
 - Neck discomfort
 - Dyspnea, respiratory stridor, cough, choking sensation, dysphagia, neck pain, or pressure owing to tracheal and/or esophageal displacement or compression
 - Facial disfigurement
 - Hoarseness, unilateral or bilateral vocal cord paralysis:
 - Owing to pressure on recurrent laryngeal nerve lying in close proximity
 - May be transient or permanent
 - Horner syndrome, including ptosis, miosis, and decreased facial sweating:
 - Owing to cervical sympathetic chain compression

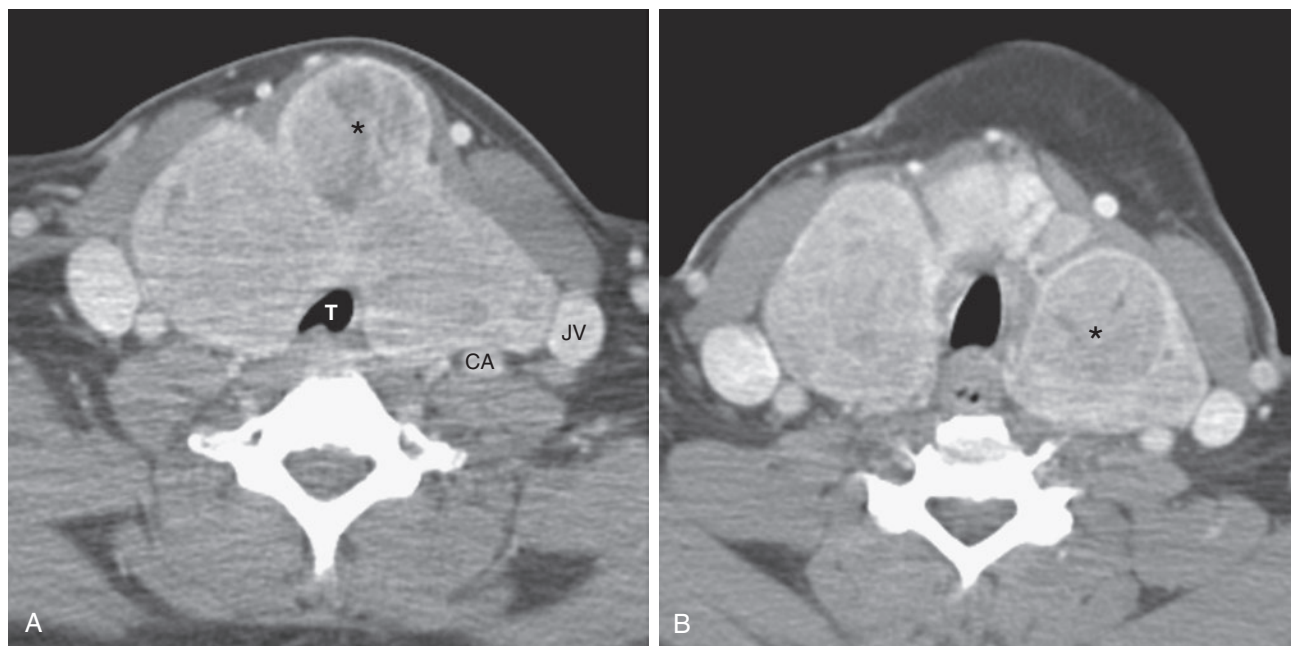


Fig. 27-68. Nodular goiter.

Nodular goiter with dominant nodules. **A**, Axial contrast-enhanced CT scan shows marked, diffuse enlargement of the thyroid gland. There is long-standing mass effect on the trachea (*T*), posterior displacement of the left common carotid artery (*CA*), and posterolateral displacement of the left internal jugular vein (*JV*). A dominant 2.8-cm nodule is present in the isthmus of the gland (*). **B**, Axial contrast-enhanced CT scan shows diffuse enlargement of the gland with little intervening normal tissue. A second dominant nodule (*) is noted in the left lobe of the thyroid gland. Fine-needle aspiration under ultrasound guidance revealed hyperplastic nodules. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-40, page 2633.)

- Pemberton sign (see Substernal Thyroid):
 - Owing to vascular compression
- Hemorrhage in lesion may result in sudden enlargement and pain.
- Thyroid enlargement may be nodular or diffuse:
 - Isolated (single) dominant nodule may create clinical concern for a neoplasm.
 - In multinodular enlargement, there may be one or more dominant nodules.
 - No site predilection
 - Some located substernally (substernal goiter); see previous discussion in this chapter
 - Some located in lateral neck anatomically separated from main gland proper and referred to as parasitic nodule (see previous discussion in this chapter)
- Majority of patients are euthyroid:
 - Most patients have normal levels of TSH.
 - Some patients may have hyperfunctioning nodules (elevated TSH).
 - Serum thyroglobulin often elevated
 - In small percentage of patients, toxic or hyperfunctioning nodules may develop in setting of multinodular goiter:
- Thyrotoxicosis (hyperthyroidism) in multinodular goiters referred to as Plummer disease (see Toxic Nodular Goiter):
 - Tends to affect older people with long-standing goiters
 - Produces a “hot” nodule
- Radiology:
 - High-resolution ultrasound is most sensitive method of detecting thyroid nodules and may reveal small nodules that are not able to be palpated.
 - Multinodular glands appear as enlarged symmetric or asymmetric glands containing nodules of varying density.
 - Following contrast enhancement, nodules may show uniform enhancement or there may be poor enhancement due to secondary degenerative changes such as hemorrhage, cyst formation, or necrosis.
 - Areas of calcification can be seen in a high percentage of cases.
 - Large nodules may extend into mediastinum (anterior > posterior) and/or may compress adjacent structures such as the trachea, esophagus, and large vessels.

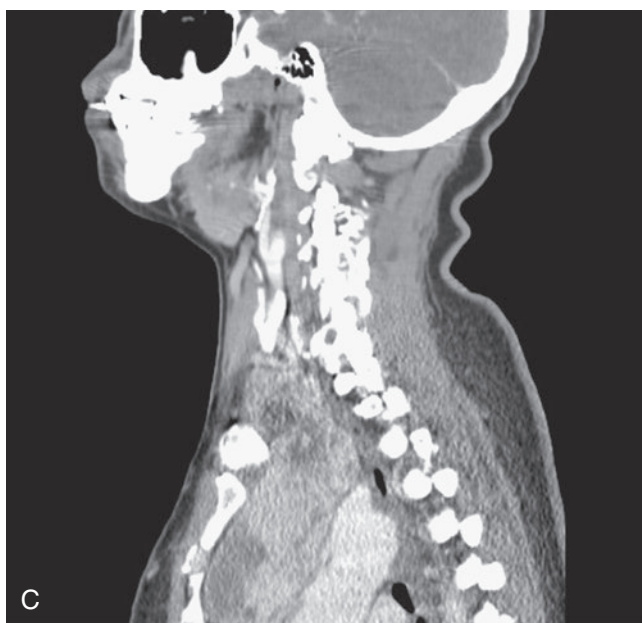
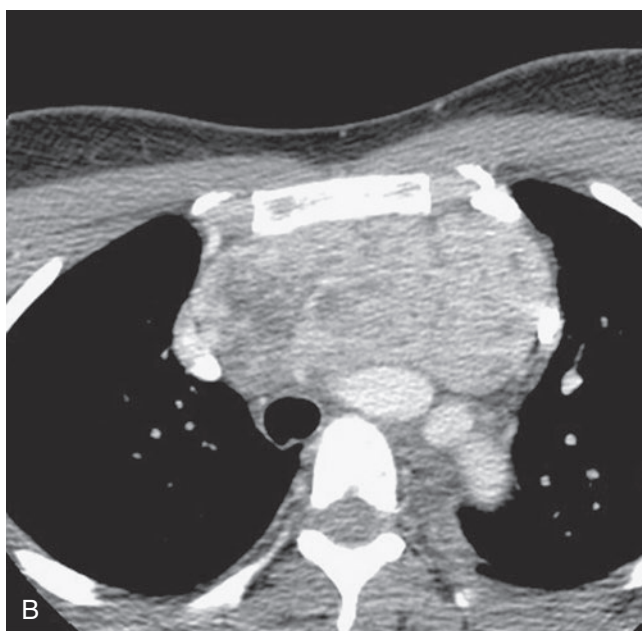


Fig. 27-69. Multinodular goiter.

A, Axial CT scan shows the lower end of a multinodular goiter extending down into the substernal space. The length of extension below the top of the manubrium should be noted in the radiology report. This goiter remained above the innominate vessels. Axial CT scan (**B**) and a sagittal reconstruction (**C**) on another patient show a large goiter extending down into the substernal region and anterior mediastinum. Notice that there is no posterior mediastinal extension or extension up behind the pharynx. (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-48, page 2635.)

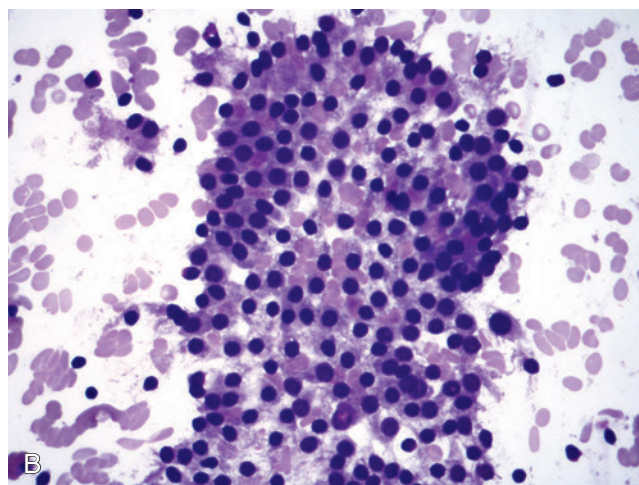
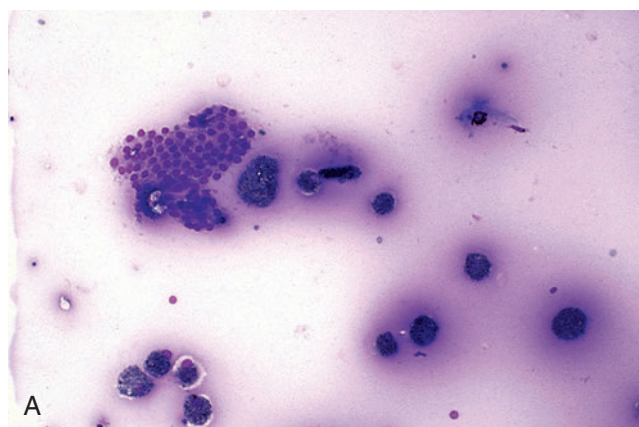


Fig. 27-70. Cytology of adenomatoid nodule.

Adenomatoid nodule, fine-needle aspiration biopsy. **A**, Abundant colloid with scant cluster of follicular epithelium. **B**, Benign follicular cells that are evenly spaced about the size of red blood cells (Diff-Quik stain).

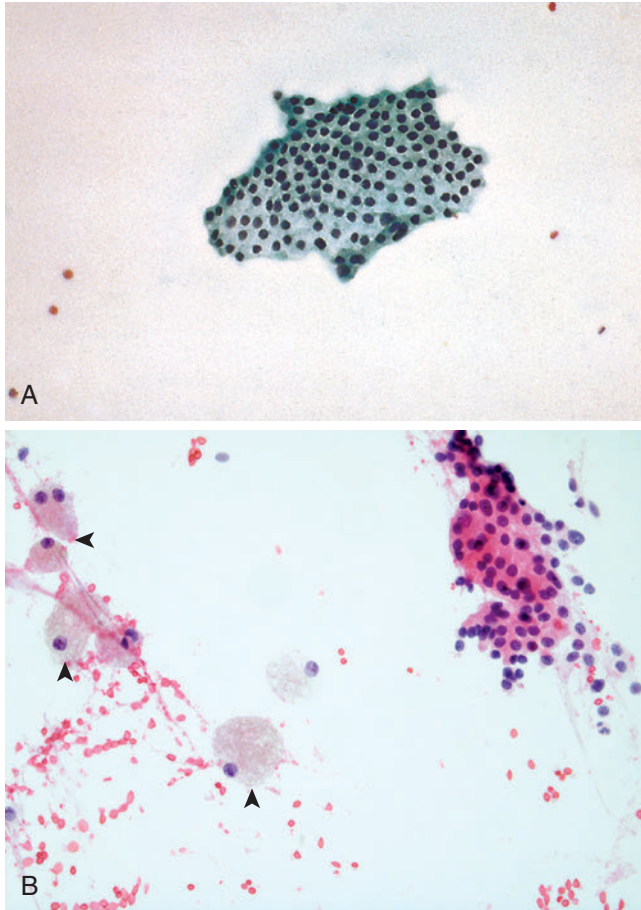


Fig. 27-71. Adenomatoid nodule, fine-needle aspiration biopsy.

A, Flat sheet of follicular epithelium including cells arranged in an orderly honeycomb fashion with distinct cell borders. **B**, Another example showing benign follicular cells with round to oval monomorphic nuclei and finely granular chromatin; hemosiderin-laden macrophages (arrowheads) are present a finding seen in lesions with cystic degeneration (Papanicolaou stain).

- Radioactive iodine uptake usually normal but may be increased
- Etiology:
 - Worldwide, iron deficiency is most important factor increasing risk for development of endemic sporadic goiter
 - Prevalence inversely proportional to iodine intake
 - Direct correlation between degree of iodine deficiency and size of goiter representing physiologic adaptation to lack of iodine:
 - Decrease in blood iodine levels leads to decrease in thyroxine (T_4) levels, which in turn stimulates secretion of TSH (in effort to

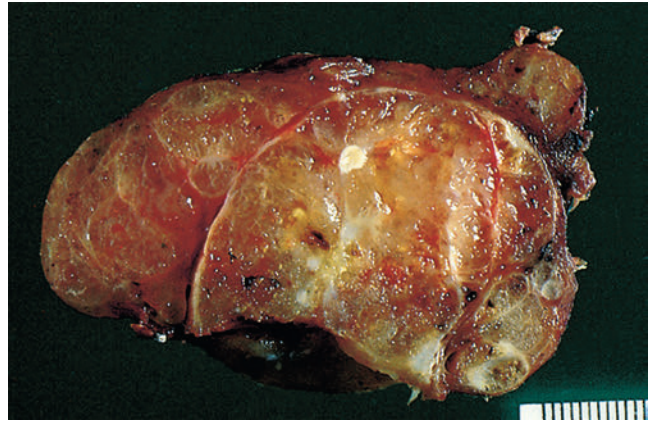


Fig. 27-72. Adenomatoid nodules.

Resection specimen showing separate delineated colloid nodules with reddish to brownish, glistening appearance. Intranodular and internodular fibrosis can be seen and foci of calcifications are present.

enhance iodine uptake and restore T_4 blood levels); in turn TSH stimulates follicular cell hyperplasia and hypertrophy

- Subsequently, nodules become autonomous and secrete thyroid hormone independently of TSH due to activating mutations of thyrotropin receptor.
- Iodine excess has goitrogenic effect due to its action in decreasing synthesis and secretion of thyroid hormones.

Pathology

Fine-Needle Aspiration Biopsy

- Designation “benign follicular nodule” applies to samples adequate for evaluation consisting of:
 - Predominantly colloid
 - Benign-appearing follicular cell in varying proportions
- In presence of supporting clinical history, more specific diagnoses may be used, including:
 - Colloid nodule
 - Adenomatoid nodule
 - Hyperplastic nodule
- Secondary degenerative (retrogressive) changes may be present, including:
 - Reactive epithelial changes may include:
 - Oncocytic cytoplasm, prominent nucleoli, cytoplasmic hemosiderin
 - Hemorrhage:
 - Recent (fresh hemorrhage)
 - Remote in form of hemosiderin-laden macrophages
 - Mixed inflammatory cells:
 - Lymphocytes

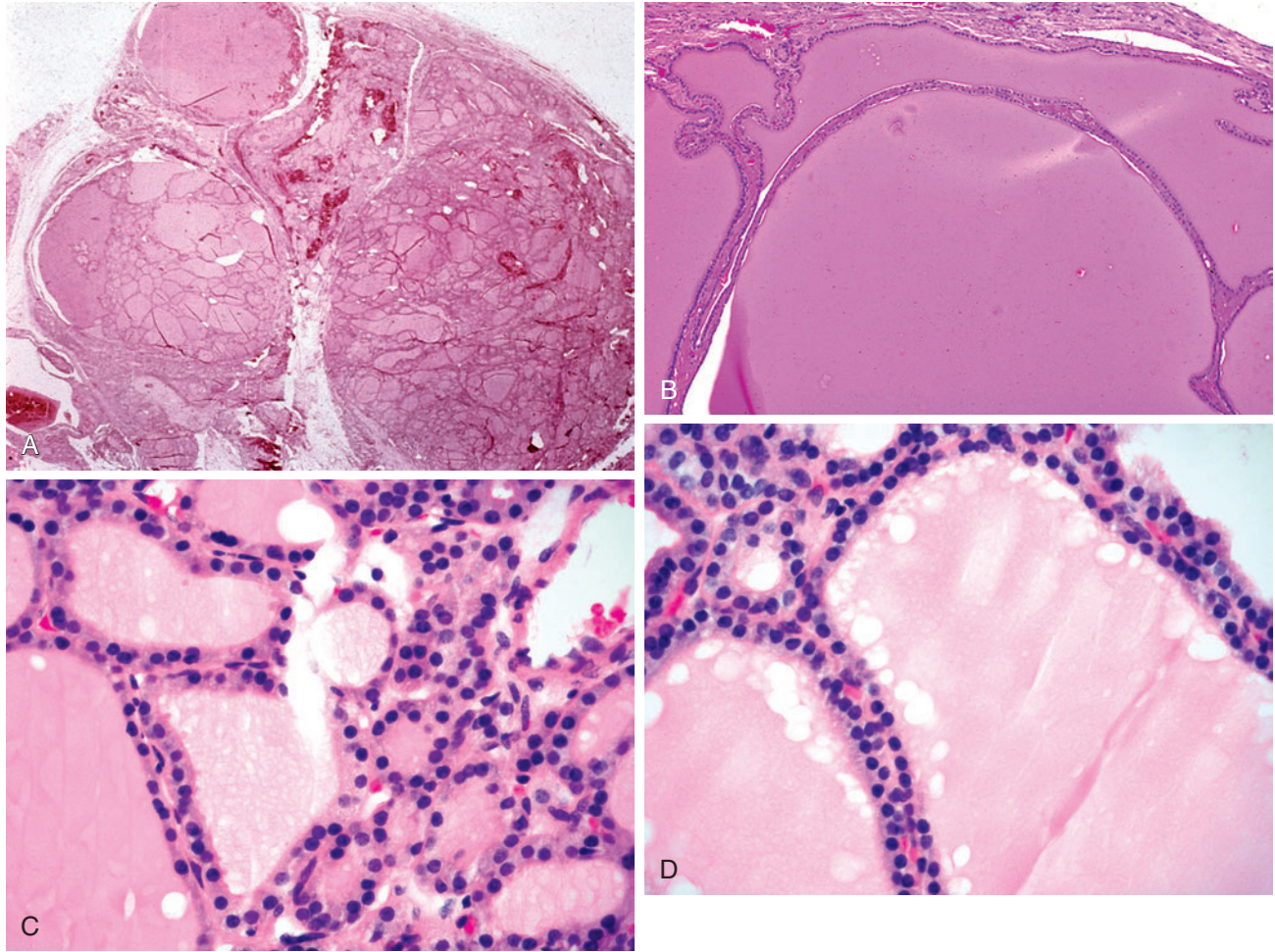


Fig. 27-73. Adenomatoid nodules.

A, Three separate circumscribed but unencapsulated histologically similar-appearing nodules. **B**, Nodule with markedly dilated colloid-filled follicles. **C** and **D**, Higher magnification shows bland cytomorphic features including round to oval monomorphic nuclei with finely granular (coarse-appearing) chromatin.

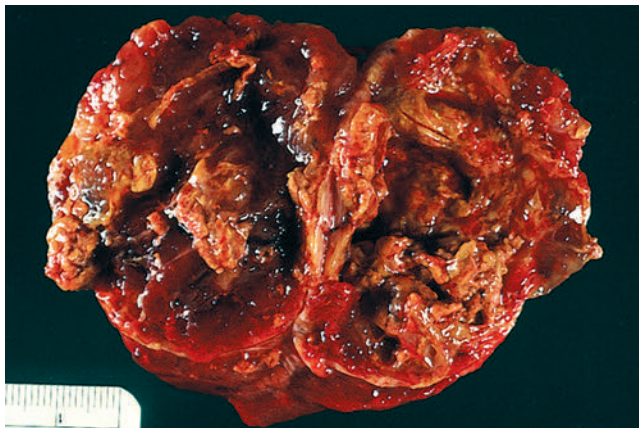


Fig. 27-74. Adenomatoid nodule.

Adenomatoid nodule with retrogressive changes including cyst formation and hemorrhage.

- Foamy histiocytes, macrophages, multinucleated giant cells
- Calcific debris
- In hyperplastic lesions, follicles predominate and there is increased cellularity with scant colloid.
 - Despite increased cellularity, epithelial cells are bland, relatively uniform in appearance without significant variation in size and shape of nuclei, irregularities in size and shape, or inclusions. Nuclear grooves can be identified.
- In involuted lesions, minimal cellularity and abundant colloid may be seen.
- Features that favor an adenomatoid nodule over follicular neoplasm include presence of:
 - Abundant colloid, few follicles, and low cellularity:
 - Amount of thyroid follicles, follicular epithelial cells, and colloid are variable.

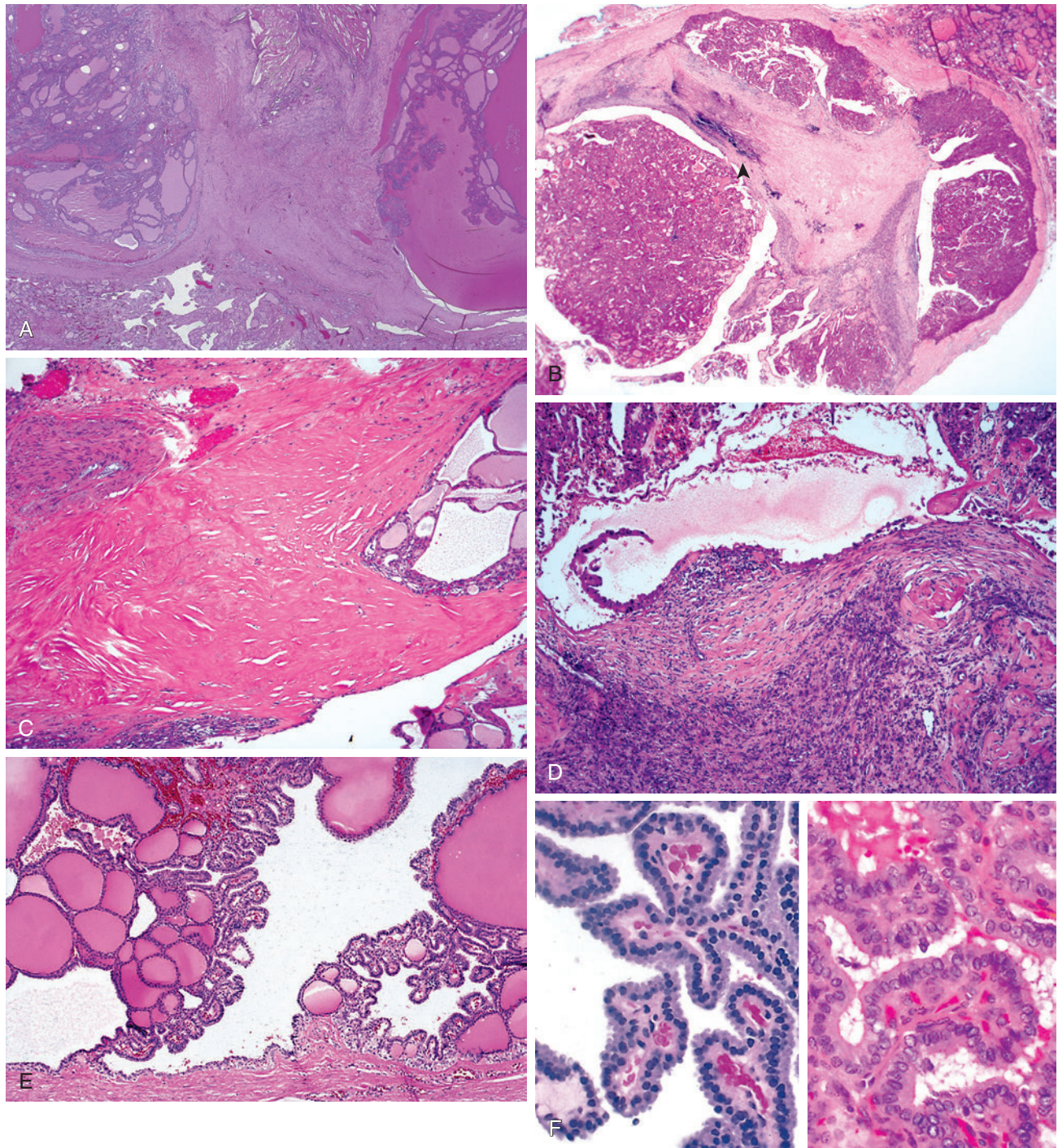


Fig. 27-75. Retrogressive changes in adenomatoid nodules.

Adenomatoid nodules with retrogressive changes may include **(A)** cyst formation and irregular fibrosis, the latter within the lesion but also enveloping the nodule(s) suggesting encapsulation; **(B)** nodule with greater cellularity but also with retrogressive changes including irregular fibrosis and foci of calcifications (*arrowhead*). The fibrosis is within the nodule as well as surrounding (enveloping) the nodule suggesting encapsulation. **(C)**, In contrast to relative uniformity in thickness and linear/parallel arrangement of fibers in a true capsule, fibrous tissue as part of retrogressive changes is irregular with thicker and thinner areas and with disorganization in arrangement of its fibers; **(D)** cyst formation and granulation tissue; **(E)** papillary architecture; **(F)** *left*, papillae in adenomatoid nodules are lined by cells with orderly arrayed small round to oval monomorphic and hyperchromatic nuclei; *right*, in contrast the nuclei in papillary carcinoma are haphazardly arrayed with crowding and overlapping nuclei that are enlarged with clear-appearing nuclear chromatin.



Fig. 27-76. Dominant adenomatoid nodule.

Adenomatoid nodules may present as a single dominant lesion (corresponding histologically to increased cellularity, see next image). This nodule appears encapsulated suggesting the gross appearance of a true neoplastic growth (adenoma or carcinoma). In this case, the patient was irradiated in childhood and this nodule was cellular with associated fibrosis.

- Follicular cells isolated or in sheets with a honeycomb pattern
- Follicular epithelial cell nuclei are round and relatively uniform in appearance with rare nucleoli and opaque to coarsely granular cytoplasm:
 - Nuclear grooves can be identified.
 - Absence of constellation of nuclear features diagnostic for papillary thyroid carcinoma
- Colloid appears as amorphous blue to orange material.

Gross

- Vary in appearance depending on number and size of nodules:
 - Generally, thyroid glands in setting of adenomatoid nodules are enlarged (slight enlargement to massive enlargement) and may achieve weights of several hundred grams to a kilogram or more.
- Cut section:
 - May reveal one or multiple delineated nodules separated by normal-appearing parenchyma
 - Nodules are reddish to brownish and have a glistening appearance.
- Secondary degenerative changes are common and may include:
 - Cyst formation, fibrosis, calcification, hemorrhage, and necrosis

Histology

- One or more nodules may be seen.
- Nodules may be:

- Circumscribed to appearing encapsulated
- Unencapsulated or partly encapsulated
- Follicles are dilated and filled with abundant colloid:
 - Some dilated follicles have a cluster of small follicles along one aspect (pole) of a follicle protruding into a dilated follicle, a finding referred to as Sanderson polster.
- Cellularity varies:
 - In some nodules cellularity is not increased and follicular epithelial cells have a flattened (attenuated) appearance.
 - Other nodules may have increased cellularity (cellular nodules) with variable appearing cells including cells with:
 - Oncocytic and/or clear cytoplasmic changes
 - Signet ring appearance
 - Spindle cell metaplasia
- Nuclei
 - Round to oval without irregularities in size and shape
 - Coarse nuclear chromatin pattern (hyperchromatic)
 - Inconspicuous to small, centrally located nucleoli
 - More or less retain linear basal orientation in cell
- In any given nodule there may be nuclear alterations raising concern for a diagnosis of papillary thyroid carcinoma including presence of:
 - Nuclear grooves
 - Dispersed or vesicular appearing chromatin
 - Crowding and overlapping
 - Intranuclear inclusions not typically identified but may be present:
 - Presence of nuclear inclusions alone not definitively diagnostic for papillary thyroid carcinoma in absence of additional diagnostic nuclear features:
 - Nuclear inclusions seen in papillary thyroid carcinoma that may be seen in other lesions appear eosinophilic with distinct margination.
 - Presence of so-called “bubble artifact,” which is a function of poor fixation, may be mistaken for intranuclear inclusions associated with papillary thyroid carcinoma.
 - “Bubble” artifact often are seen in more central and less fixed portions of lesion.
 - In contrast to intranuclear inclusions of papillary thyroid carcinoma, which have distinct margination and appear eosinophilic, bubble artifact “inclusions” show indistinct margination with clear appearance.
 - “Bubble” artifact can be present in a wide variety of thyroid lesions.

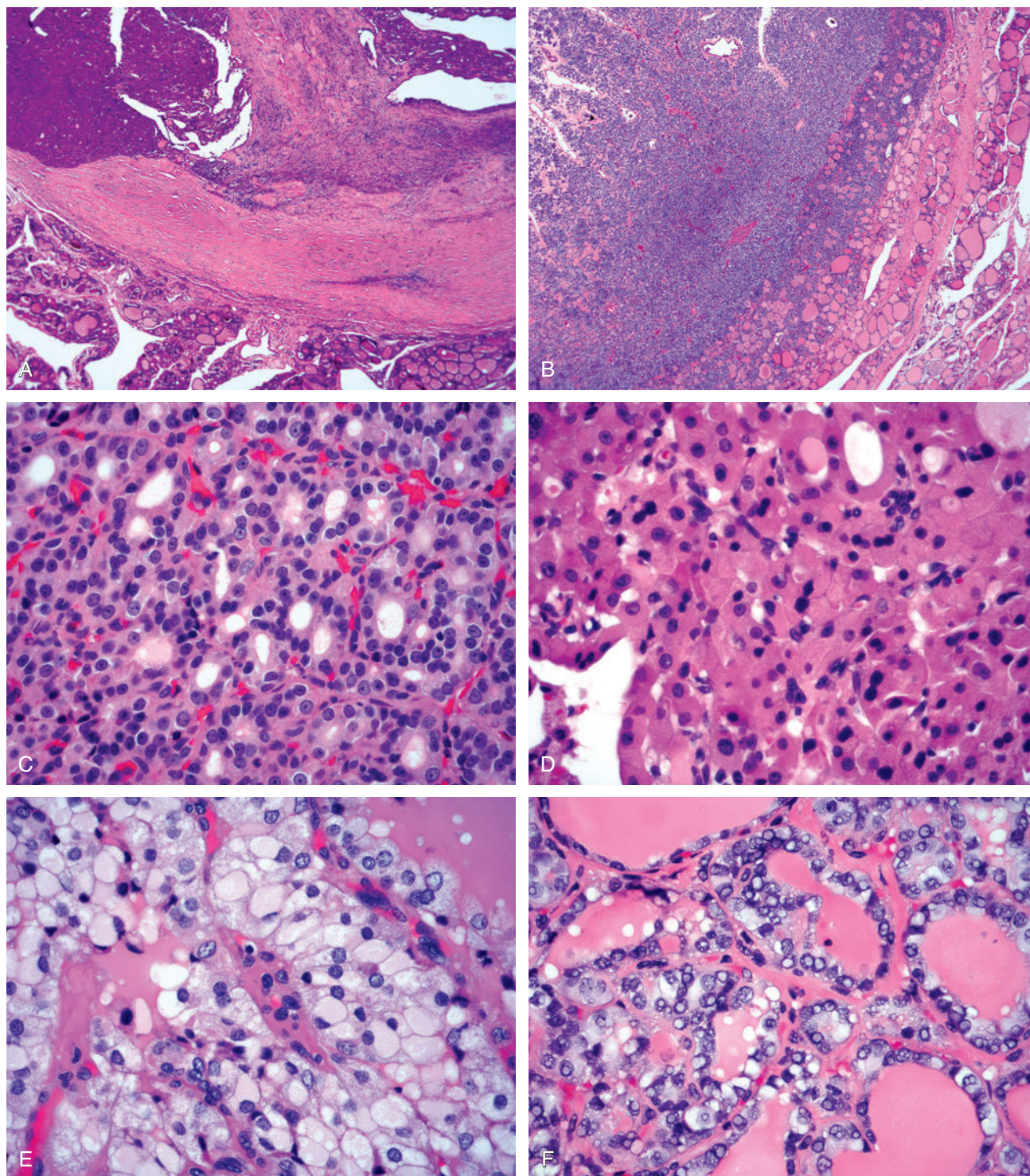


Fig. 27-77. Cellular adenomatoid nodule.

A, Irregular fibrosis that in areas envelopes the cellular lesion but also is present within the lesion as are other retrogressive changes. **B**, In this example, there is an unencapsulated cellular follicular epithelial proliferation. **C**, Microfollicular growth composed of cells with small round to oval monomorphic nuclei with coarse nuclear chromatin. **D**, Oncocytic cells may be present in adenomatoid nodules whether a component of a histologically "usual" nodule or one with increased cellularity. **E**, Signet ring cells may be present focally or representing a more significant component of the nodule. **F**, Intranuclear holes or so-called "bubble" artifact may be present and may be mistaken for intranuclear inclusions associated with papillary thyroid carcinoma; in contrast to intranuclear inclusions of papillary thyroid carcinoma, which have distinct margination and appear eosinophilic, artifactual "inclusions" have indistinct margination with clear appearance.

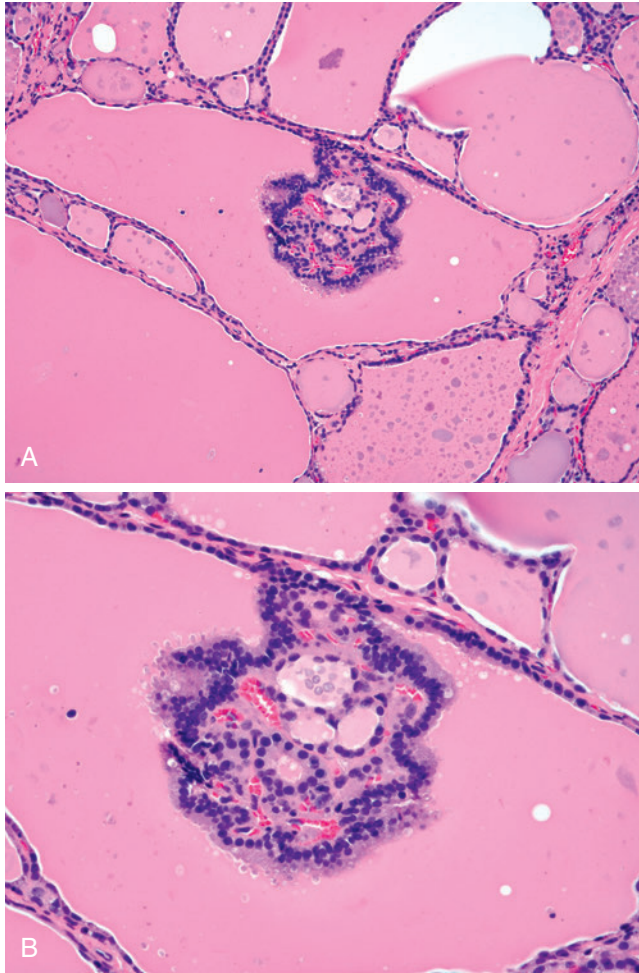


Fig. 27-78. Sanderson polster.

A, B, Sanderson polsters represent dilated follicle with cluster of small follicles along one aspect (pole) of follicle protruding into dilated follicle.

- Non-nodular thyroid essentially normal without hyperplastic changes:
 - Thyroid parenchyma adjacent to nodules not compressed and shows comparable growth pattern and cell type(s) as seen within nodule
- Mixed chronic inflammatory cell infiltrate including lymphocytic and plasma cell may be seen in nodule or in adjacent normal thyroid parenchyma.
- Reactive and degenerative (retrogressive) changes can be seen occurring spontaneously or secondary to a traumatic event such as prior fine-needle aspiration biopsy and may include:
 - Cyst formation
 - Papillary architecture
 - Irregular fibrosis
 - Hemorrhage (recent and remote in form of hemosiderin-laden macrophages)
 - Cholesterol granuloma formation
- Cells with oncocytic cytoplasmic changes
- Squamous metaplasia
- Calcifications:
 - Tend to be coarse and variably distributed
 - Lack concentric laminations of psammoma bodies
- Osseous and cartilaginous metaplasia may be present.
 - Thickened vascular spaces with associated calcifications (within media) can be seen at periphery.
- Reactive fibrosis versus encapsulation:
 - In any given case, there may be a dominant nodule or even multiple nodules that appear enveloped by fibrous tissue, suggesting complete encapsulation and a diagnosis of a true follicular neoplasm.
 - In contrast to relative uniformity in thickness and linear/parallel arrangement of fibers in a true capsule, fibrous tissue surrounding one or more adenomatoid nodules is:
 - Irregular with thicker and thinner areas and shows disorganization in arrangement of fibers
 - Present within as well as around lesion
 - Such findings support presence of reactive fibrosis and should allow for differentiating from a follicular adenoma.
 - Often such irregular fibrosis is accompanied by other retrogressive findings (see above), allowing for consideration and diagnosis of adenomatoid nodule.
 - In presence of irregular fibrosis coupled to tangential sectioning lesional tissue may appear separate from main lesion identified in fibrous tissue within as well as around lesion raising concern for presence of capsular invasion and a possible diagnosis of follicular carcinoma:
 - In such settings, quality of fibrosis (irregular and disorganized), location of fibrosis (within and around lesion), presence of additional retrogressive changes, as well as overall histology of lesion including cellularity and similar cytomorphology to cells in surrounding parenchyma should allow for diagnosis of adenomatoid nodule and discrimination from follicular carcinoma.
- Endocrine atypia:
 - Endocrine atypia includes cells with nuclear hyperchromasia and marked nuclear pleomorphism.
 - Usually focal but may be multifocal or more widespread
 - Absence of associated mitotic activity or necrosis
 - Felt to represent benign reactive process (e.g., post-fine-needle aspiration biopsy)

- Not an indicator of malignancy
- Can be seen in non-neoplastic proliferations (e.g., dyshormonogenetic goiter, others) and in follicular adenoma
- Atypical nuclear features in adenomatoid nodules:
 - Occasionally, an otherwise nondescript nodule may show isolated focus or separate small foci without evidence of invasive growth in which nuclear characteristics are those of papillary thyroid carcinoma, follicular variant.
 - In such examples, diagnostic possibilities may include:
 - Entire nodular lesion represents papillary thyroid carcinoma:
 - This is an example in which lesion appears to be an adenomatoid nodule, but in fact entire lesion represents papillary thyroid carcinoma, follicular variant.
 - Focus or foci of papillary thyroid carcinoma represent(s) cancer developing in setting of adenomatoid nodule(s).
 - Focus or foci of papillary thyroid carcinoma represent(s) intrathyroidal/intranodular spread from separate focus of papillary thyroid carcinoma located elsewhere in gland.
 - Of note is wide discrepancy and lack of consensus among pathologists in evaluation/determination of diagnostic nuclear features for papillary thyroid carcinoma and diagnostic “handling” of such cases remains problematic and to a large extent subjective
 - To date, no consensus how to diagnostically handle such cases as described above:
 - Some authorities use varying terms, including:
 - Adenomatoid nodule with atypical features
 - Atypical follicular lesion neoplasm of uncertain malignant potential
 - Some authorities render a diagnosis of microscopic focus/foci of papillary thyroid carcinoma arising in adenomatoid nodule(s).
 - No established quantitative measurement (e.g., percentage of given lesion) in trying to decide when lesion does or does not represent papillary thyroid carcinoma:
 - If significant percentage (too many areas in single or multiple slides) of lesion shows nuclear features diagnostic for papillary thyroid carcinoma, then designation of entire lesion as papillary thyroid carcinoma, follicular variant would appear justified.
 - If there are insufficient findings to render a diagnosis of papillary thyroid carcinoma, a conservative diagnostic approach (i.e., benign lesion) appears justified, given indolent biology associated with such lesions lacking invasive growth:
 - Many such lesions may fall within potential histologic spectrum of so-called follicular variant of papillary thyroid carcinoma that:
 - In absence of invasion essentially behaves as a benign neoplasm (i.e., follicular adenoma) with minimal to no risk of metastatic disease and/or death from tumor
 - Have molecular biologic findings identical to those of follicular adenoma (and follicular carcinoma) including presence of *RAS* mutation and absence of *RET/PTC* and *BRAF*
 - For more details see Follicular Variant of Papillary Thyroid Carcinoma, including the recent recommendation to replace this diagnostic designation with noninvasive follicular tumor [NIFT] with papillary-like features.
 - A view that entire nodule represents papillary thyroid carcinoma does not alter prognosis as the lesion is noninvasive, amenable to surgical resection, and associated with an excellent prognosis; however, therapeutic implications include fact that any such lesion measuring more than 1 cm and diagnosed as papillary thyroid carcinoma would prompt surgical removal of all remaining thyroid tissue (i.e., completion thyroidectomy) and adjuvant radioactive iodine therapy. With recommended change in nomenclature to noninvasive follicular tumor with papillary-like features, conservative management (e.g., lobectomy without radioactive iodine therapy) should be advocated.
 - Cytogenetics and molecular genetics:
 - Initial studies showed adenomatoid nodules to be polyclonal.
 - Subsequent studies have shown that at least some adenomatoid nodules are monoclonal with cytogenetic abnormalities, aneuploidy, and oncogenic mutations to support a neoplastic origin.
 - Such findings complicate differentiation of non-neoplastic (dominant) adenomatoid nodule from neoplastic follicular adenoma.

Differential Diagnosis

- Follicular adenoma (Table 27-2):
 - Differentiation essentially based on arbitrary findings, including:
 - Adenoma:
 - Single lesion
 - Completely encapsulated
 - Dissimilar cytomorphology to surrounding parenchyma
 - Compression of surrounding parenchyma

TABLE 27-2 Adenomatoid Nodules Versus Follicular Adenoma

Feature	Adenomatoid Nodules	Follicular Adenoma
Number	Multiple	Solitary
Capsule	Poor encapsulation; a capsule may be present but it does not completely encapsulate mass; in association with retrogressive changes fibrosis may envelop lesion but appears irregular of variable thickness, including marked thickening within and around lesion(s)	Well-developed, completely surrounding mass; appears rather uniform in thickness and appearance
Adjacent thyroid gland	No compression of surrounding gland	Compression of surrounding gland
Growth as compared to rest of the thyroid gland	Comparable growth pattern in adjacent gland	Different growth pattern in adjacent gland
Appearance as compared with the rest of the thyroid gland	Variable cellularity similar to those outside nodules	Uniform cellularity dissimilar to remainder of gland
Degenerative changes	Frequently present	May be present but not common
Clonality	Polyclonal cell population; studies have shown that at least some adenomatoid nodules are monoclonal with cytogenetic abnormalities, aneuploidy and oncogenic mutations to support a neoplastic origin	Monoclonal cell population

TABLE 27-3 Adenomatoid Nodules Versus Papillary Thyroid Carcinoma

Features	Adenomatoid Nodules	Papillary Carcinoma
Papillae	Simple	Complex
Nuclei	<ol style="list-style-type: none"> 1. Round and regular 2. Dense chromatin (hyperchromatic) 3. Linear polarity along basal aspect of cell 4. Nuclei are not crowded or overlap 5. Nuclear grooves and “inclusions” may be present 	<ol style="list-style-type: none"> 1. Enlarged with irregularities in size and shape 2. Dispersed to optically clear chromatin pattern 3. Disorganized orientation of nuclei without linear polarity of the nuclei, which are haphazardly located within the cells 4. Nuclear crowding and overlapping 5. Nuclear grooves 6. Intranuclear inclusions
Fibrosis	Variable and irregular in appearance; may be markedly thickened in and around the follicles	Intratumoral, irregular in appearance and more dense (fibromatosis-like)
Calcifications	Dense deposits lacking any specific form (i.e., lamination or concentric rings) usually in fibrotic (acellular) foci and within the media of vessels	Laminated or having concentric rings (psammoma bodies) and seen in association with the neoplastic cellular infiltrate and in the connective tissue of the parenchyma

- Adenomatoid nodules:
 - Multiple lesions
 - Lack of capsule or complete encapsulation
 - Similar cytomorphology to surrounding parenchyma
 - No compression of surrounding parenchyma
- In any given case distinction between adenomatoid nodule (dominant or multiple) from adenoma (multiple albeit uncommon) or arising in setting of adenomatoid nodules can be problematic.
- From practical standpoint this differentiation is between benign lesions so that therapy and prognosis are essentially similar.
- Follicular carcinoma:
 - See Histology above.
- Papillary thyroid carcinoma, conventional type, and follicular variant (Table 27-3)

Treatment and Prognosis

- Patients with asymptomatic nontoxic goiter(s) do not need to undergo any therapy:
 - Management with periodic serum TSH measurement and ultrasound assessment considered reasonable
- Surgery is preferred treatment for symptomatic nodules:
 - Surgery should be as conservative as possible, including resection of mass lesion(s) with sparing of the remaining thyroid.

- Total thyroidectomy may be required in those patients with:
 - Multifocal, bilateral nodules
 - Large intrathoracic lesions causing moderate or severe compressive symptoms
 - For large lesions with low radioactive iodine uptake that usually require extremely high radioactive iodine therapy for successful treatment
- Thyroid hormone replacement initiated after total or near total thyroidectomy
- Radioiodine therapy (^{131}I therapy) can be used for ablation of adenomatoid nodules:
 - Option for patients:
 - With contraindications for surgery (e.g., advanced age with associated comorbidities)
 - Who reject surgery
 - Who have had prior surgery or radiation to neck, making surgical procedures more difficult
 - Nodules are relatively radioresistant and higher doses are required in treating adenomatoid nodules.
 - Larger nodules require higher radioiodine dose for ablation.
 - Risks associated with this form of treatment may include radiation exposure of entire thyroid with possible:
 - Increase risk of developing cancer
 - Hypothyroidism
- Prognosis in uncomplicated cases is excellent.
- No increased risk of developing cancer in setting of adenomatoid nodules

Dyshormonogenetic Goiter (DG)

(Figs. 27-79 through 27-81)

Definition: Inherited or inborn errors of thyroid metabolism resulting in overstimulation (hyperplasia) of thyroid gland.

- Numerous causes of inborn errors of thyroid metabolism (Box 27-10), all of which result in a deficient amount of circulating thyroid hormone, which leads to a loss in negative feedback to pituitary gland which, in turn, leads to hypersecretion of thyroid-stimulating hormone (TSH) causing continuous stimulation and hyperactivity of thyroid gland

Clinical

- Rare:
 - 1 in 30,000 to 50,000 live births
- Too few cases to make any definitive statements regarding mode of inheritance but appears that autosomal recessive inheritance is much greater than autosomal dominant inheritance



Fig. 27-79. Dyshormonogenetic goiter.

Total thyroidectomy specimen showing an enlarged thyroid gland with nodules and degenerative changes, including cyst formation, fibrosis, and hemorrhage.

BOX 27-10 Inherited Metabolic Disorders of Thyroid Metabolism Resulting in Dyshormonogenetic Goiter

- Unresponsiveness to thyroid-stimulating hormone (TSH)
 - Iodide transport failure
 - Defective peroxidase activity
 - Deficient hydrogen peroxide activity:
 - Receptor abnormality
 - Iodide organification or Pendred syndrome (familial deaf-mutism and goiter)
 - Defective iodotyrosyl coupling and iodothyronine synthesis
 - Defective thyroglobulin:
 - Impaired synthesis (absence or synthesis of abnormal thyroglobulin)
 - Defective transport
 - Defective iodotyrosine
 - Other:
 - Nodular goiter with intense thyroid calcification
 - Familial absence of the thyroid gland (athyreosis)
-
- More common in women than in men; occurs over wide age range from neonates to sixth decade with median of 16 years of age:
 - Most cases develop prior to third decade.
 - No racial or ethnic predilection
 - Thyroid abnormalities seen in disorders of thyroid hormonogenesis include:
 - Goitrous thyroid and hypothyroidism
 - Pituitary gland defects result in hypothyroidism but not a goiter
 - Clinical presentation (signs and symptoms) dependent on severity of the error:
 - Severe defect:
 - Presentation in early life (neonatal period) with (congenital) hypothyroidism, goiter, mental

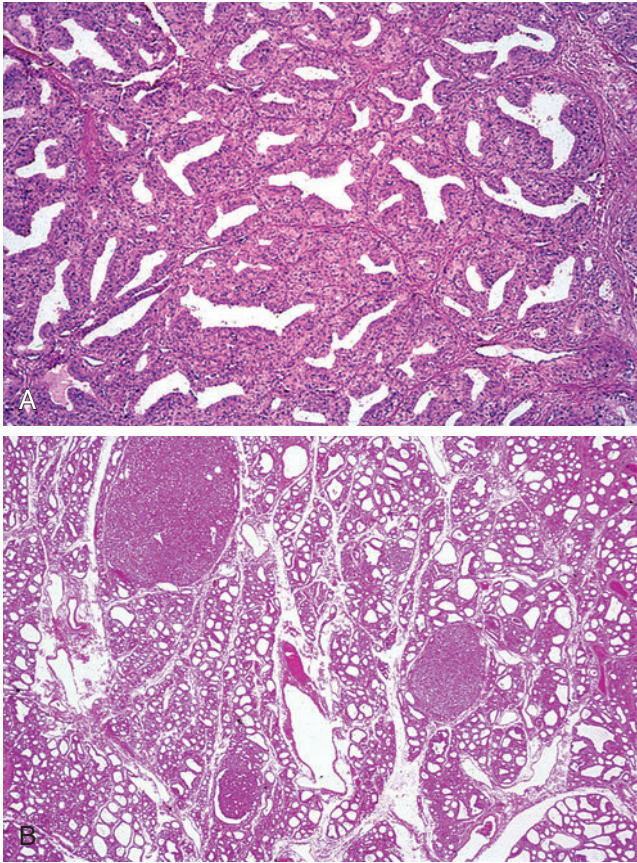


Fig. 27-80. Dyshormonogenetic goiter.

A, Diffusely hyperplastic thyroid including the presence of papillary hyperplasia with minimal to absent colloid and increased cellularity. **B**, Multiple nodules characterized by increased cellularity with decreased to absent colloid. In both illustrations there is an absence of histologically normal thyroid parenchyma as well as an absence of an associated lymphocytic cell infiltrate.

retardation, and growth abnormalities (cretinism)

- Mild or less severe defect:
 - Presentation in adolescence or adult life with goiter and minimal evidence of thyroid dysfunction; patients may be euthyroid
- Extrathyroid malformations may be present, including:
 - Urogenital malformations
 - Cardiac abnormalities on echocardiography
 - Features of dysmorphism in form of high-arched palate, low-set ears, and microcephaly
- Laboratory evaluation for patient suspected of having an inborn error of thyroid metabolism is complex and extensive and follows a sequential flowchart depending on findings of any one or more test results.

- Among tests that may be performed and evaluated for thyroid dyshormonogenesis include:
 - T_4 and T_3 concentration
 - Thyroid-stimulating hormone (TSH)
 - Thyroxine-binding globulin (TBG)
 - Thyrotropin releasing hormone (TRH): assessment of hypothalamic-pituitary function
 - Radioiodine uptake and scanning
 - Thyroglobulin antibodies (if present, the patient may have an autoimmune thyroiditis)
 - Hearing test:
 - Sensorineural deafness in presence of goiter and hypothyroidism diagnostic of Pendred syndrome
 - Origin for congenital nerve deafness unknown
 - Radioiodine kinetic studies for labeled urinary monoiodotyrosine (MIT) and diiodotyrosine (DIT):
 - Defective iodotyrosine deiodination characterized by release of MIT and DIT in degradation of thyroglobulin in process of recovery of its thyroid hormones
 - Surgical excision for histologic analysis
- Diagnosis of an inborn error of thyroid metabolism can be made in utero by ultrasonography and the measurement of TSH in amniotic fluid.
- Most cases of thyroid dysgenesis are sporadic and of unknown cause:
 - There may be a family history of goiter.

Pathology

NOTE: Irrespective of underlying cause, pathologic changes (gross and microscopic) seen are essentially the same.

Gross

- Enlarged thyroid gland that in some cases may weigh up to 600 g
- Glands are (multi)nodular with associated fibrosis, which may encapsulate individual nodules.
- In addition to fibrosis, other secondary (degenerative) changes may include:
 - Cyst formation, hemorrhage, and, less commonly, calcification

Histology

- Diffuse process with absence of any normal appearing thyroid tissue
- Thyroid is characterized by nodularity, fibrosis, and marked follicular hyperplasia with prominent papillarity (simple not complex), hypercellularity, and decreased to absent colloid.
 - Microfollicular, trabecular, macrofollicular, solid, and microcystic growth patterns can be seen.

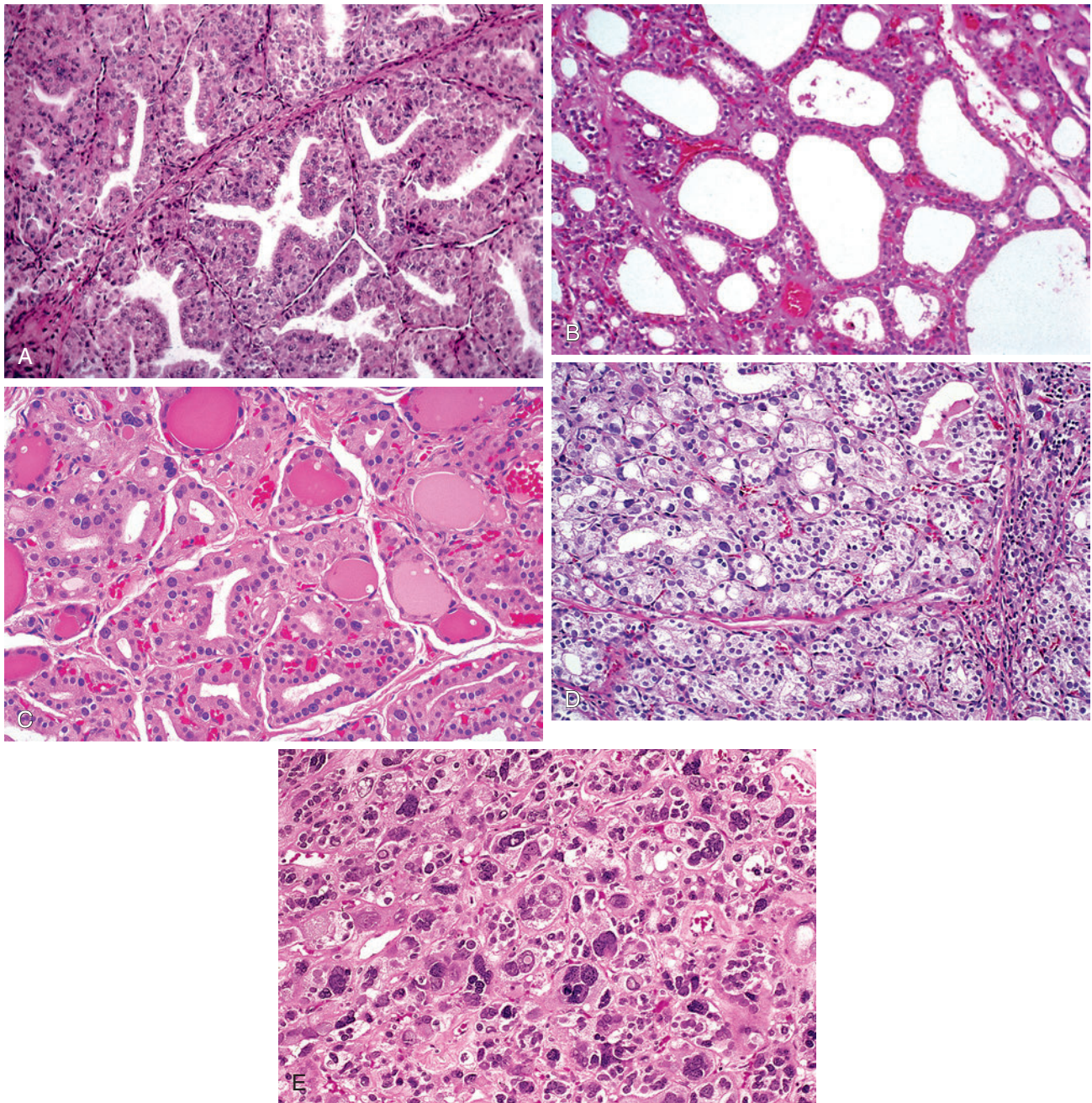


Fig. 27-81. Dyshormonogenetic goiter.

Dyshormonogenetic goiter is characterized by **(A)** papillary hyperplasia and absence of colloid; **(B)** variably dilated follicles including micro- and macrofollicles devoid of colloid; **(C)** follicular growth including identifiable colloid-filled follicles but other follicles without colloid; **(D)** nodular appearance with nodules separated by fibrosis and minimal to absent colloid formation. Note the variegated cytomorphology in figures **C** and **D**, including cells with relatively bland nuclei and other areas in which there is nuclear pleomorphism; **(E)** severe cytologic atypia, including hypercellularity with marked nucleomegaly, hyperchromasia, and intranuclear inclusions.

- In any one gland, all of above features can be present, creating a variegated appearance at low magnification.
- Follicular epithelial cells of nodules include cells with round to oval nuclei, coarse nuclear chromatin pattern, eosinophilic to clear cytoplasm, and basal orientation of nuclei within the cell.
- Marked cytologic atypia in internodular thyroid tissue commonly present, including:
 - Bizarre nuclei with nucleomegaly and hyperchromasia
 - Mitotic activity and/or necrosis not present
- Fibrosis consisting of thick, acellular bands seen throughout gland
 - Fibrosis may completely encircle (“encapsulate”) the nodules.
 - Presence of nodules surrounded by fibrosis may suggest a follicular neoplasm (adenoma or carcinoma).
 - Fact that entire thyroid gland is histologically abnormal may assist in diagnosis and in differentiating from follicular adenoma or carcinoma
- Despite presence of prominent papillarity, nuclear features do not conform to those seen in papillary thyroid carcinoma.
- A benign lymphocytic cell infiltrate may be present.
- Myxoid change may be present.
- Malignant thyroid tumors (papillary thyroid carcinoma or follicular carcinoma) may develop in setting of dys hormonogenetic goiter; features that may assist in diagnosis include:
 - For papillary thyroid carcinoma:
 - Characteristic architectural and/or cytomorphic features, including complex (not simple) papillary growth, elongated or twisted appearing follicles, enlarged nuclei with irregularities in size and shape, dispersed to optically clear-appearing nuclear chromatin, margination of the chromatin along nuclear membrane, crowding and overlapping nuclei, loss of basal polarity of nuclei, nuclear grooves, and nuclear (eosinophilic) inclusions
 - For follicular carcinoma:
 - Somewhat more problematic in “encapsulated” nodules of dys hormonogenetic goiter may appear to have foci of “invasive” growth into capsule
 - Presence of angioinvasion and/or metastasis would be diagnostic of follicular carcinoma.
 - No definitive cytologic features that can be used in differentiating dys hormonogenetic goiter from follicular carcinoma
- Histochemistry:
 - Periodic acid-Schiff (PAS) can be used to identify colloid in cases with areas in which colloid production is minimal to absent.

- Immunohistochemistry:
 - Thyroglobulin and TTF-1 reactivity
 - Absence of calcitonin or neuroendocrine markers (e.g., chromogranin, synaptophysin)

Differential Diagnosis (Table 27-4)

- Diffuse hyperplasia (Graves disease)
- Adenomatoid nodules
- Papillary thyroid carcinoma
- Follicular thyroid carcinoma
- Medullary thyroid carcinoma

Treatment and Prognosis

- Surgery (partial or total thyroidectomy) may be necessary for patients with obstructive or pressure symptoms, or in those patients suspected of having a malignant neoplasm.
- Nonsurgical (medical) treatment is same as that for any hypothyroid patient and includes thyroid hormone replacement:
 - Intra-amniotic injections of thyroxine in fetus with fetal goiter detected by routine ultrasound in early pregnancy (gestational week 18) and fetal hypothyroidism (TSH >100 mU/l) suspected of having DG reported to have beneficial effects as evidenced by reduction in growth of goiter was reduced and reduction of elevated amniotic TSH levels over course of pregnancy
- Due to generalized pituitary insufficiency, patients may develop adrenal crisis if unmonitored medical treatment is given.
- Prognosis especially for those patients with mild disease is excellent.
- In patients with severe forms of disease (congenital goiters and cretinism), mental and growth retardation may occur.
 - In these patients, early detection with early medical management is essential for normal development of nervous system and in preventing permanent mental retardation.

Amyloid Goiter (Figs. 27-82 and 27-83)

Definition: Symptomatic mass or clinically detectable thyroid enlargement due to amyloid deposition.

- Amyloid deposits represent extracellular accumulation of fibrillar proteins, which are identified in association with a variety of clinical settings and occurring in a variety of tissue sites.
- Amyloidosis may manifest in several forms, including:
 - Systemic amyloidosis (primary and secondary)
 - Multiple myeloma-associated amyloidosis
 - Localized or solitary amyloidosis
 - Familial amyloidosis

TABLE 27-4 Dyshormonogenetic Goiter and Histologic Simulators

	Dyshormonogenetic Goiter	Graves Disease (Untreated)	Papillary Carcinoma (Classic Type)	Adenomatoid Nodules (Nodular Goiter)
Gland involvement	Diffuse; thyroid is hyperplastic; no normal thyroid; increased nodularity	Diffuse; thyroid is hyperplastic; no normal thyroid	Limited in extent; multifocal; intervening thyroid tissue is normal	Multiple nodules; intervening thyroid tissue is normal
Cellularity	Hypercellular throughout the gland	Hypercellular throughout the gland	Variable cellularity but typically more cellular than surrounding thyroid	Variably cellular from hypo- to hypercellular
Architecture	Microfollicular, trabecular, macrofollicular, solid and microcystic with prominent papillarity; papillae are present throughout the gland; papillae are usually simple in appearance but may be complex, are often broad rather than narrow, and have a fibrovascular stroma	Diffuse follicular hyperplasia; prominent papillary architecture; lobular architecture retained; papillae are present, typically are simple in appearance but may be complex, and are often broad rather than narrow, with a fibrovascular stroma	Multiple growth patterns: papillary, follicular (micro- and macrofollicular), solid, trabecular; papillary growth limited to neoplastic proliferation; narrow papillae have a complex growth with fibrovascular stroma	Variable-sized follicles widely dilated; retrogressive changes may include the presence of papillae
Colloid	Scant to absent	Minimal to absent; scalloping is present	Present; darker (inspissated) appearing	Abundant; watery in appearance
Cytomorphology (follicular epithelial cells)	Variably appearing epithelial cells with round to oval nuclei, coarse chromatin, eosinophilic to clear cytoplasm; basal orientation of the nuclei; severe cytologic atypia is commonly present and includes bizarre nuclei with nucleomegaly and hyperchromasia in parenchyma and less often in nodules	Columnar cells; enlarged nuclei, amphophilic cytoplasm, indistinct cell borders; nuclei are round and regular with coarse chromatin arranged along the basal aspect of the cell	Enlarged nuclei; irregularities in size and shape; haphazardly located in cell; dispersed to optically clear chromatin; nuclear crowding and overlapping; nuclear grooves and intranuclear round and eosinophilic inclusions; nondescript cytoplasm	Flattened cells, round and regular nuclei with a dense chromatin; nuclei are linearly oriented along basal aspect of cell; nuclear grooves; "inclusions" may be present, appearing clear and bubbly, and are artifacts of tissue processing
Fibrosis	Marked fibrosis; fibrosis accentuates nodularity	Minimal to absent fibrosis in the untreated patient or in a patient without long-standing disease; when present, fibrosis is irregular and often creates a nodular appearing gland	Intratumoral; dense irregular bands	Variable and irregular in appearance; result of retrogressive changes

Clinical

- Very rare occurrence
 - Most common setting in which amyloid is seen occurs in the thyroid is in association with medullary thyroid carcinoma.
- Amyloid deposition in thyroid can occur as part of both primary and secondary systemic amyloidosis:
 - More commonly seen as part of secondary systemic amyloidosis:
 - In this setting, amyloid is usually found at autopsy rather than resulting in symptomatic mass.
- Predisposing disorders associated with secondary systemic amyloidosis involving thyroid include:
 - Chronic inflammatory diseases: infections (chronic osteomyelitis, pulmonary tuberculosis, chronic bronchitis with bronchiectasis, chronic peritonitis), rheumatoid arthritis, familial Mediterranean fever
 - Neoplasms including Hodgkin disease, others
- In symptomatic amyloid goiter, clinical presentation includes nontender, rapidly enlarging neck mass that may be associated with dysphagia, dyspnea, and hoarseness.

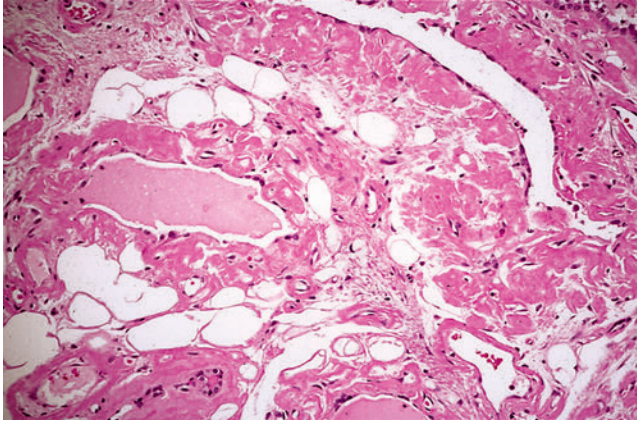


Fig. 27-82. Amyloid goiter.

The amyloid deposition is eosinophilic, acellular, and amorphous in appearance and almost completely replaces the thyroid parenchyma. Elongated thyroid follicles lined by attenuated follicular epithelial cells are seen, one of which still retains colloid material (*left of center*).

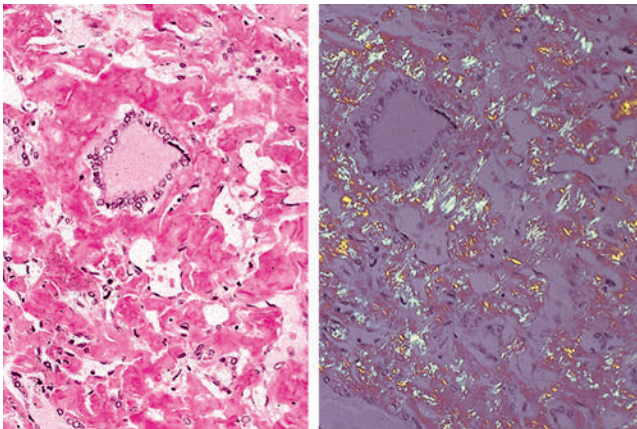


Fig. 27-83. Amyloid goiter.

Left panel, Light microscopic appearance of amyloid including deposition of acellular and amorphous eosinophilic material surrounding a colloid-filled follicle. *Right panel*, Congo red stain showing characteristic apple-green birefringence.

- Patients are euthyroid and thyroid dysfunction is not generally present, however:
 - Amyloid deposition may be so extensive as to result in hypothyroidism.
 - May rarely be associated with hyperthyroidism

Pathology

Fine-Needle Aspiration Biopsy

- Aspirated material contains few cells and small fragments of cyanophilic material (amyloid).
- Amyloid is congophilic.

Gross

- Enlarged glands with nodular to diffuse appearance weighing from 25 to 300 g
- Cut surface is white to tan with a rubbery to firm consistency.

Histology

- Diffuse amyloid deposition is usually seen but focal (nodular) deposits may occur.
- Amyloid appears as extracellular eosinophilic, acellular, and amorphous material.
- In diffuse deposition, amyloid is evenly distributed throughout gland replacing thyroid parenchyma.
- In nodular deposition, amyloid is focally seen and remainder of gland is essentially unremarkable.
- Degree of amyloid deposition may vary from moderate to extensive.
- Amyloid is seen in perifollicular and interfollicular locations compressing follicles.
- In areas of amyloid deposition, residual follicles vary in appearance from elongated with normal colloid content to slit-like atrophic follicles without colloid.
 - Follicular epithelial cells generally appear as flat single cells.
 - Squamous metaplasia may be seen.
- Amyloid deposition seen around vascular spaces (“angiocentric”) and, less often, within walls of vascular spaces:
 - Vascular-related amyloid does not result in any functional compromise of involved vascular space.
- Additional associated findings may include:
 - Chronic lymphocytic thyroiditis
 - Foreign body type giant cell reaction
 - Areas of mature fat
- Histochemistry:
 - Stains for amyloid (Congo red, crystal violet, thioflavin-T) are positive:
 - Apple-green birefringence seen under polarized light with Congo red staining
- Immunohistochemistry:
 - Positive reactivity with amyloid A (AA) antibody
 - Calcitonin and chromogranin reactivity are not seen.
- Electron microscopy:
 - Nonbranching fibrils varying in size from 50 to 150 Å in diameter

Differential Diagnosis

- Amyloid stroma in medullary thyroid carcinoma
- Amyloid may be mistaken for fibrous tissue; latter may be seen in association with many thyroid diseases.

Treatment and Prognosis

- Treatment in symptomatic patients is thyroidectomy (partial or total).
- Prognosis in relationship to amyloid deposition of thyroid gland is excellent:
 - However, patient deaths may occur due to specific organ failure secondary to amyloid deposition (cardiac, renal, or hepatic).
- Prognosis in relationship to amyloid deposition occurring in the setting of medullary thyroid carcinoma correlates to that associated with medullary thyroid carcinoma (see Chapter 28).

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Neoplasms of the Thyroid Gland

CLASSIFICATION OF NEOPLASMS OF THE THYROID GLAND

See [Box 28-1](#).

BOX 28-1 Classification of Thyroid Gland Neoplasms

Follicular Epithelial Origin

Benign

- Follicular adenoma and variants

Malignant

- Follicular carcinoma and variants
- Papillary carcinoma and variants
- Poorly differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Others:
 - Squamous cell carcinoma
 - Mucoepidermoid carcinoma
 - Tumors with thymic-like differentiation

C-Cell Origin

- Medullary thyroid carcinoma

Mixed Follicular and C-Cell Origin

- Mixed medullary and follicular carcinoma
- Mixed medullary and papillary carcinoma

Nonepithelial Tumors

Benign

- Paraganglioma
- Teratoma

• Mesenchymal tumors:

- Benign peripheral nerve sheath tumor
- Granular cell tumor
- Hemangioma
- Leiomyoma
- Solitary fibrous tumor
- Others

Malignant

• Malignant lymphoproliferative lesions:

- Non-Hodgkin malignant lymphoma
- Plasmacytoma
- Hodgkin lymphoma
- Others

• Sarcomas:

- Angiosarcoma
- Follicular dendritic cell sarcoma
- Leiomyosarcoma
- Others

Secondary Tumors

GENERAL CONSIDERATIONS

- Thyroid cancer is the most common endocrine malignancy but represents 1.4% to 4.6% of all new human cancers diagnosed in the United States.
- Incidence of thyroid carcinoma in United States has increased rapidly since 1980:
 - More refined/sophisticated detection methods including radiologic imaging (ultrasound, CT, MRI) contribute to increase in incidence.
 - Sharpest increase is in diagnosis of papillary thyroid carcinoma, particularly papillary microcarcinoma but also follicular variant of papillary thyroid carcinoma.
- Percentage of cancer deaths (mortality rate) due to thyroid cancer is low (less than 0.4% in women and in men):
 - In contrast to increase in incidence, changes in mortality rates have been much smaller, likely resulting from:
 - Improved treatment
 - Increased incidence primarily in early stage papillary carcinoma
- Clinically apparent thyroid nodules occur in fairly large percentage of the population (up to 10%):
 - Many of these nodules are probably benign.
 - Differential diagnosis of any thyroid nodule includes a malignant thyroid neoplasm.
- Demographics:
 - In general, thyroid tumors are more common in women than in men and occur in all ages ranging from the young (children in the first and second decades of life) to elderly adults.
- Risk factors for development of thyroid cancer include:
 - Radiation exposure:
 - Causes thyroid carcinoma primarily by direct effects on DNA
 - Primarily associated with external radiation

- Internal (^{131}I) radiation therapy used safely for diagnostic and therapeutic purposes associated with small increase risk of thyroid carcinoma incidence
 - Risk factors associated with radiation-induced thyroid tumors include:
 - Amount of radiation exposure
 - Young age at exposure to radiation
 - High serum thyroglobulin levels
 - Genetic predisposition:
 - Only 5% of follicular cell-derived thyroid carcinomas are a component of a familial cancer syndrome.
 - Familial follicular cell-derived tumors or non-medullary thyroid carcinoma encompass a heterogeneous group of diseases classified into two distinct groups:
 - Syndromic-associated tumors occur in syndromes in which nonmedullary thyroid carcinomas are predominant tumor encountered, including:
 - Phosphatase and tensin (PTEN)-hamartoma tumor syndrome/Cowden syndrome
 - Familial adenomatous polyposis/Gardner syndrome
 - Carney complex type 1, Werner syndrome, Pendred syndrome
 - Other syndromes, such as McCune-Albright syndrome, Peutz-Jeghers syndrome, and ataxia-telangiectasia syndrome, may be associated with development of follicular cell-derived tumors but link is less established than above syndromes.
 - Nonsyndromic tumors occur in tumor syndromes in which thyroid involvement is minor component, including:
 - Familial follicular cell-derived tumor syndromes or nonsyndromic tumors:
 - Non-medullary thyroid carcinomas are major findings, including:
 - Pure familial papillary thyroid carcinoma with or without oncocytic cytoplasmic change; familial papillary thyroid carcinoma with papillary renal cell carcinoma; familial papillary thyroid carcinoma with multinodular goiter; familial nonmedullary (papillary) thyroid carcinoma type 1
 - Familial adenomatous polyposis (FAP) syndrome, including its subtype Gardner syndrome:
 - Autosomal dominant inheritance with mutations in *APC* gene (5q21)
 - Characterized by multiple adenomatous polyps of the large intestine, multiple osteomas of the skull and mandible, cutaneous keratinous cysts, and soft tissue tumors (e.g., fibromatosis)
- Associated with an increased risk of papillary thyroid carcinoma (PTC):
 - Thyroid carcinoma occurs in up to 12% of patients
 - Tend to occur at early age
 - Histologically, include PTC, cribriform-morular variant, and solid variant
- Phosphatase and tensin homolog (PTEN)-hamartoma tumor syndrome, including Cowden disease (multiple hamartoma syndrome):
 - Autosomal dominant inheritance
 - Germline mutation of *PTEN* gene (10q23.2)
 - Characterized by multiple hamartomas, mucocutaneous lesions, including trichilemmomas, acral keratoses, and oral mucosal papillomas
 - Associated with increased risk of follicular epithelial cell lesions/tumors, including:
 - Adenomatoid nodules accounting for 75% of thyroid abnormalities in this setting
 - PTC and follicular carcinomas may also occur.
- Other familial disorders with specific gene mutations associated with thyroid carcinoma include:
 - Carney complex:
 - Germline mutation *PRKR1 α* (17q22-24)
 - Follicular carcinoma and papillary carcinoma
 - Werner syndrome:
 - Germline mutation *WRN* (8p11-22)
 - Follicular carcinoma, papillary carcinoma, undifferentiated (anaplastic) thyroid carcinoma
 - Pendred syndrome
 - Mutation of Pendred syndrome (*PDS*) gene (*SLC26A4* gene on chromosome 7q31) encodes amino acid protein pendrin shown to function as iodide/chloride transporter
 - Goitrous thyroid
- Familial nonmedullary thyroid carcinoma (FNMTc):
 - Originate from follicular cells of thyroid gland accounting for more than 90% of all thyroid cancers
 - Approximately 3% to 10% of FNMTcs are of familial origin defined as two or more affected first-degree relatives with NMTC in the absence of other known familial syndromes.
 - Greater than 85% of thyroid tumors in non-syndromic FNMTc are papillary thyroid carcinoma followed by follicular thyroid carcinoma (approximately 10%); poorly differentiated and undifferentiated (anaplastic) thyroid carcinomas represent approximately 5%.

- Compared to sporadic NMTC, FNMTC:
 - Presents at younger age
 - Associated with higher incidence of multifocal disease, extrathyroidal extension, and nodal metastasis
 - Multiple endocrine neoplasia syndrome:
 - Linked to development of C-cell-related lesions/neoplasms
 - See Section 10.
- Dietary factors:
 - Iodine:
 - In iodine-deficient diets (endemic goiter areas), follicular thyroid carcinoma more common
 - In iodine-sufficient diets, papillary thyroid carcinoma more common
- Pre-existing thyroid diseases:
 - Thyroid carcinoma often preceded by other thyroid abnormalities, including:
 - Adenomatoid nodules
 - Lymphocytic thyroiditis
 - Graves disease
 - Remains uncertain whether patients with above abnormalities are at increased risk for developing thyroid carcinoma
- Hormonal and reproductive factors:
 - Thyroid carcinoma occurs more commonly in women than in men.
 - Differences between genders in thyroid cancer incidence declines with age.
 - Increasing parity may increase risk of thyroid carcinoma.
 - Thyroid carcinoma reported to occur more often among women who are older when they first give birth.
 - Small increase in risk of thyroid carcinoma with increasing age at menopause
 - Other suggested risk factors for thyroid carcinoma in women are:
 - Exogenous estrogens, including oral contraceptives
 - Lactation-suppressant drugs
 - Postmenopausal estrogen therapy
 - Fertility drugs (e.g., clomiphene, progesterone)
- Clinical findings:
 - Most patients with benign thyroid nodules/tumor and carcinomas present with asymptomatic thyroid nodule.
 - Clinical findings related to risk of carcinoma in thyroid nodule include:
 - Age:
 - Overall most patients with thyroid carcinoma are middle age.
 - Thyroid nodule is more likely to be carcinoma in patients under 20 years and in patients over 65 years of age.
 - Gender:
 - Men are more apt to have malignant thyroid tumors than women.
 - Family history of thyroid cancer or syndrome associated with thyroid cancer
 - History of childhood head and neck therapeutic irradiation, total body irradiation, or exposure to ionizing radiation
 - History of other cancer:
 - Kidney, breast, lung, and melanoma
 - Sudden or rapid enlargement of thyroid or of long-standing thyroid nodule(s) with or without pain:
 - Most likely represents hemorrhage into a cystic nodule:
 - Occurs in benign and malignant nodules
 - Hallmark presentation for some thyroid malignant tumors, including undifferentiated (anaplastic) carcinoma and malignant lymphoma
 - Large nodule with distortion of structures of upper neck and mediastinum and/or tracheal compression with difficulty breathing:
 - Can occur in association with benign thyroid nodules but presence of these symptoms raises concern for a malignant thyroid lesion, although most malignant thyroid tumors are asymptomatic
 - Hoarseness and/or vocal cord paralysis:
 - Most commonly related to laryngeal-based disease (benign or malignant) but can be associated with infiltration of recurrent laryngeal nerve by thyroid cancer
- Physical examination:
 - Number of nodules:
 - Although not always true, multiple nodules more likely to be benign, whereas solitary nodules more likely to be malignant
 - Hard and fixed thyroid mass:
 - More likely to be malignant
 - Ipsilateral cervical adenopathy:
 - May indicate metastasis from an (ipsilateral) thyroid malignant tumor clinically overt or occult
- Laboratory testing:
 - Most patients with thyroid cancer are euthyroid.
 - Serum thyroglobulin:
 - Often elevated in patients with papillary and follicular carcinoma:
 - May be elevated in association with follicular adenoma so does not necessarily allow for distinguishing benign and malignant thyroid follicular neoplasms.
 - Not typically elevated in medullary thyroid carcinoma and undifferentiated (anaplastic) thyroid carcinoma

- Useful in monitoring patients following treatment (surgery and radioactive iodine) for papillary or follicular carcinoma as elevated levels may indicate recurrence or metastasis.
- Serum calcitonin:
 - Elevated levels represent diagnostic feature that may occur in medullary thyroid carcinoma
- Germline RET proto-oncogene mutation testing:
 - Indicated in patients with thyroid nodule and family history of medullary thyroid carcinoma or potential diagnosis of multiple endocrine neoplasia (MEN) type II syndrome
- Radiologic imaging:
 - Ultrasonography:
 - Thyroid ultrasound used in patients with palpable nodules (with or without elevated TSH) to:
 - Determine presence of single discrete nodule or multiple nodules
 - Demonstrate anatomic location of nodule in thyroid (anterior versus posterior) as well as composition (cystic versus solid)
 - Assess nodule(s) size
 - Thyroid malignancies tend to:
 - Be hypoechogenic (particularly marked hypoechogenicity)
 - Be solid
 - Have infiltrative or microlobulated margins
 - Show presence of microcalcifications
 - Be taller than wide shaped when measured in transverse view
 - However, no single feature or combination of sonographic features is sufficiently sensitive to be the sole screening test for thyroid cancer.
 - Thyroid nodule may be considered benign when:
 - Purely cystic
 - Spongiform appearing (>50% of nodule volume occupied by microcystic spaces)
 - On basis of thyroid sonographic imaging features, nodule appearance can be classified as:
 - Low risk for malignancy:
 - Tend to be purely cystic or spongiform
 - Noninfiltrative borders
 - Intermediate risk for malignancy:
 - Predominantly solid, hypo- or iso- to hyperechoic
 - Noncalcified
 - Regular margins
 - High risk for malignancy:
 - Hypoechoic
 - Microcalcifications
 - Infiltrative or microlobulated margins
 - Radionuclide imaging
 - Thyroid scintigraphy using ^{123}I or $^{99\text{m}}\text{Tc}$ pertechnetate
 - Incidence of carcinoma higher for hypofunctioning “cold” nodules than for hyperfunctioning (“hot”) nodules
 - “Hot” nodules are almost always benign
- Fine-needle aspiration biopsy (FNAB)
 - Represents an extremely useful initial approach in diagnosis of thyroid mass
 - Quick and inexpensive with minimal complications
 - Thyroid nodules are one of most common indications for neck FNAB.
 - Presurgical diagnosis via FNAB prevents unneeded surgery for benign, nonprogressive lesions and helps to triage patients with a neoplasm for appropriate procedure.
 - Diagnostic sensitivity and specificity reported to be high, greater than 90%
 - Standardization and interpretation of thyroid cytology greatly improved by widespread adoption of Bethesda reporting system (Table 28-1), which classifies biopsies in six-tiered system as well as including implied risk of malignancy and associated usual management (Table 28-2)
 - Post-FNAB histologic changes may create diagnostic problems in the evaluation of tissue sections, including presence of features raising concern for malignancy, including:
 - Pseudoinvasion, necrosis, papillary architecture, cytologic atypia
 - See Chapter 29.
- Intraoperative consultation (frozen section diagnosis):
 - Use of intraoperative frozen sections in diagnosis of thyroid tumors has decreased with increasing use of FNAB.
 - See Chapter 29.
- Histologic types of thyroid neoplasms:
 - Majority of thyroid tumors are of follicular epithelial cell origin and include:
 - Follicular adenoma and variants thereof
 - Follicular carcinoma and variants thereof
 - Papillary carcinoma and variants thereof
 - Less common are C-cell-derived medullary thyroid carcinoma
 - Nonepithelial neoplasms of thyroid are uncommon:
 - Most common nonepithelial thyroid neoplasm is malignant lymphoma.
 - Rarely, primary mesenchymal tumors as well as metastases to thyroid gland occur.
 - Frequency of malignant thyroid neoplasms include:
 - Papillary carcinoma: approximately 80% to 85%
 - Follicular carcinoma: approximately 10% to 15%

TABLE 28-1 Bethesda System for Reporting of Thyroid Cytopathology: Diagnostic Categories

Category	Diagnoses	Findings	Frequency of Diagnosis
I	Nondiagnostic or unsatisfactory	Cyst fluid only; virtually acellular specimen; other (obscuring blood, clotting artifact, etc.)	<15%
II	Benign	c/w: • Benign follicular nodule (e.g., ANs) • CLT • Granulomatous (subacute) thyroiditis	30% to 75%
III	Atypia of undetermined significance or follicular lesion of undetermined significance	Contain cells with architectural and/or nuclear atypia not sufficient to be classified as suspicious for follicular neoplasm, suspicious for malignancy, or malignant but show atypia more marked than benign lesions	<10%
IV	Follicular neoplasm or suspicious for follicular neoplasm	Specify if oncocyctic (Hürthle) cell type	~5%
V	Suspicious for malignancy	Suspicious for: PTC; MTC; metastatic carcinoma; lymphoma	<5%
VI	Malignant	PTC; PDTC; MTC; UC; SCC; carcinoma with mixed features; metastatic carcinoma; NHL	~5%

~, Approximately; c/w, consistent with; ANs, adenomatoid nodules; CLT, chronic lymphocytic (Hashimoto) thyroiditis; MTC, medullary thyroid carcinoma; NHL, non-Hodgkin lymphoma; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; SCC, squamous cell carcinoma; UC, undifferentiated (anaplastic) carcinoma.

From Ali SZ, Cibas EA, editors: *The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes*, New York, 2010, Springer.

TABLE 28-2 Bethesda System for Reporting of Thyroid Cytopathology: Risk of Malignancy and Recommended Clinical Management

Bethesda Classification	Risk of Malignancy	Recommended Management
Nondiagnostic or unsatisfactory (Bethesda I)	N/A	Repeat FNA with ultrasound guidance
Benign (Bethesda II)	0 to 3%	Clinical follow-up
Atypia of undetermined significance, follicular lesion of uncertain significance (Bethesda III)	5% to 15%	Repeat FNA
Follicular neoplasm, suspicious for follicular neoplasm (Bethesda IV)	15% to 30%	Surgical lobectomy
Suspicious for malignancy (Bethesda V)	60% to 75%	Near total thyroidectomy or surgical lobectomy
Malignant (Bethesda VI)	>95%	Near total thyroidectomy

From Ali SZ, Cibas EA, editors: *The Bethesda system for reporting thyroid cytopathology: definitions, criteria and explanatory notes*, New York, 2010, Springer.

- Medullary carcinoma: <5%
- Poorly differentiated thyroid carcinoma: <2%
- Undifferentiated (anaplastic) thyroid carcinoma: <2%
- Malignant lymphoma: <5%
- Immunohistochemistry of thyroid neoplasms
 - Majority of thyroid cancers are differentiated carcinomas of follicular epithelial cell origin diagnosed on morphologic grounds.
 - Immunohistochemical staining can be important and at times essential in confirming specific diagnosis.
 - Table 28-3 includes an overview of more common antibodies that may be used in diagnosis of the more common thyroid neoplasms.
- Molecular genetics of thyroid tumors (Table 28-4):
 - Papillary thyroid carcinomas have activating mutations of genes coding for proteins, which signal along the mitogen-activated protein kinase pathway (MAPK).
 - Papillary thyroid carcinomas commonly have three genetic alterations, including:
 - RET/PTC rearrangements
 - BRAF point mutations
 - RAS point mutations
 - Mutations in RET, BRAF, and RAS genes found in approximately 70% of all papillary thyroid carcinomas but rarely overlap in same tumor
 - RET (rearranged during transfection) protooncogene:

TABLE 28-3 Antibodies Used in Diagnosis of Thyroid Neoplasia

Antibody	FA	FTC	PTC	MTC	UTC	PDTC
Thyroglobulin	+	+	+	–	–	+*
TTF-1 (N)	+	+	+	+	–	+
PAX8 (N)	+	+	+	+	+	+
Calcitonin	–	–	–	+	–	–
NE markers	–	–	–	+	–	–
CD56	+	+	R/A	+	–	–
CK (AE1/AE3)	+	+	+	+	±	+

CK, Cytokeratin; FA, follicular adenoma; FTC, follicular thyroid carcinoma; N, nuclear; NE markers, synaptophysin and chromogranin; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; R/A, reduced to absent; TTF-1, thyroid transcription factor 1; UTC, undifferentiated thyroid carcinoma.

*Typically very focal limited to abortive or small follicles containing colloid or limited to isolated cells as paranuclear globules or vacuoles.

TABLE 28-4 Common Genetic Alterations in Thyroid Neoplasia

Tumor Type	Affected Genes	Prevalence
Follicular adenoma	<i>RAS</i> <i>PAX8/PPARγ</i> translocation	20% to 40% 5% to 20%
Follicular carcinoma	<i>RAS</i> <i>PAX8/PPARγ</i> translocation <i>PIK3CA</i> mutation <i>PTEN</i>	30% to 50% 20% to 50% 5% to 10% 5% to 10%
Papillary carcinoma, classical	<i>BRAF</i> <i>RET/PTC</i> translocation <i>RAS</i> <i>TRK</i>	30% to 70% 20% to 40% 0 to 10% 0 to 10%
Papillary carcinoma, follicular variant	<i>RAS</i> <i>PAX8/PPARγ</i> translocation <i>RET/PTC</i> translocation <i>BRAF</i>	25% to 45% 0 to 30% 5% to 10% 5% to 10%
Poorly differentiated carcinoma	<i>RAS</i> <i>TP53</i> <i>B-catenin</i> (CTNNB1) <i>BRAF</i> <i>PIK3CA</i> mutation <i>AKT1</i> mutation	20% to 50% 15% to 40% 0 to 25% 5% to 15% 10% to 20% 5% to 10%
Undifferentiated (anaplastic) carcinoma	<i>TP53</i> <i>B-catenin</i> (CTNNB1) <i>RAS</i> <i>BRAF</i> <i>PIK3CA</i> mutation <i>PTEN</i> mutation	50% to 80% 5% to 65% 10% to 50% 10% to 40% 5% to 25% 5% to 20%
Medullary carcinoma Sporadic Familial	<i>RET</i> , somatic <i>RET</i> , germline mutation	50% >95%

- Rearrangements of *RET* gene, known as *RET/PTC* rearrangements, occur in papillary thyroid carcinoma (PTC).
- *RET/PTC* rearrangement implicated in early stages of PTC representing early event in development of PTC
- Several types of *RET/PTC* identified differing according to 5' partner gene involved in rearrangement
 - Two most common rearrangement types are:
 - *RET/PTC1*: typically found in classic PTC, papillary microcarcinomas
 - *RET/PTC3*: more common than the other fusion proteins in solid and radiation-induced PTCs, especially in children exposed to the radiation fallout from the Chernobyl accident
- Uncommon to rare in follicular variant of PTC
- Germline mutations present in virtually all patients with familial forms of medullary thyroid carcinoma, including:
 - MEN-2A
 - MEN-2B
 - Familial medullary thyroid carcinoma
- Somatic mutations of *RET* codon 918 occur in approximately 50% of sporadic medullary thyroid carcinomas.
- B-RAF proto-oncogene, serine/threonine kinase (*BRAF*) mutation:
 - Belongs to RAF family of protein kinases important components of the mitogen-activated protein kinase (MAPK) signaling pathway mediating cell growth, differentiation, and survival
 - Spectrum of mutations include point mutations, small in-frame deletions or insertions, and chromosomal rearrangement.
 - V600E is most common mutation (98% to 99%) and involves nucleotide 1799, resulting in valine-to-glutamate substitution at residue 600 (V600E).
 - Mutations of *BRAF* gene found in 40% to 45% of PTCs
 - Occur early in development of PTC based on presence in papillary microcarcinomas
 - Among thyroid tumors *BRAF* mutations restricted to:
 - Papillary thyroid carcinoma:
 - Classic type
 - Papillary microcarcinomas
 - Tall cell variant
 - Poorly differentiated thyroid carcinomas
 - Undifferentiated (anaplastic) thyroid carcinoma arising from thyroid papillary carcinoma.

- Uncommon to rare in follicular variant of PTC
- Not found in follicular carcinoma and benign thyroid nodules
- Reported to serve as prognostic marker for PTC associated with more aggressive features including:
 - Tumor recurrence
 - Extrathyroidal extension
 - Metastatic disease (regional, distant)
 - Advanced tumor stage (AJCC III/IV)
- Purported aggressive behavior of *BRAF*-associated PTCs not universally reported
- Rat sarcoma (*RAS*) oncogene mutations:
 - Found in benign and malignant thyroid neoplasms, suggesting *RAS* activation may be an early step in thyroid tumor development
 - 3 *RAS* genes prominent in cancer pathogenesis, including:
 - Neuroblastoma *RAS* viral oncogene homolog (*N-RAS*)
 - Kirsten rat sarcoma viral oncogene homolog (*K-RAS*)
 - Harvey rat sarcoma viral oncogene homolog (*H-RAS*)
 - Found in all types of follicular cell-derived tumors:
 - Prevalence includes *N-RAS* > *H-RAS* > *K-RAS*
 - *RAS* mutations found in:
 - 40% to 50% follicular carcinomas:
 - Lower incidence of oncocytic variant
 - 20% to 40% follicular adenomas:
 - Lower incidence of oncocytic variant
 - 10% to 20% PTCs:
 - Virtually all follicular variants of PTC
 - Also found in 20% to 50% of poorly differentiated thyroid carcinoma and 10% to 50% of undifferentiated (anaplastic) thyroid carcinoma
- Other molecular genetic findings in thyroid neoplasms:
 - Peroxisome proliferator-activated receptor γ (*PAX8/PPAR γ*) gene rearrangement:
 - Nuclear receptors that bind DNA as heterodimers with retinoid X receptors
 - Shown to play important role in regulating genes involved in adipocytic differentiation and lipid metabolism
 - Result in recurrent translocation t(2;3)(q13;p25) leading to fusion of thyroid transcription factor *PAX8* and *PPAR γ* genes
 - *PAX8/PPAR γ* rearrangements involved in thyroid cancer found in:
 - 20% to 50% of conventional FTC: ~5% of oncocytic carcinomas
 - 5% to 20% of follicular adenomas
 - 1% to 5% follicular variant of PTC
 - 0 to 1% of classic PTC
 - Thyroid tumors with *PAX8/PPAR γ* rearrangement do not usually carry any *RAS* mutation, suggesting that the development of FTC involves two independent pathways associated with either *PAX8/PPAR γ* translocation or *RAS* mutation
 - Tend to be present in:
 - Younger-age patients
 - Smaller tumors
 - Tumors more likely to be angioinvasive
- Telomerase reverse transcriptase (*TERT*) gene mutations:
 - Telomeres are the terminal portion of chromosomes that protect chromosome integrity by preventing their degradation and uncontrolled fusion and breaking cycles with other chromosomes
 - Telomerase (telomere terminal transferase) is an RNA-dependent reverse transcriptase complex that maintains telomere length allowing for cell replication and extending the life span of the cell
 - *TERT* is the enzyme protein core encoded by the *TERT* gene and is expressed in thyroid tumors (but is not normally expressed in thyroid tissue).
 - Found in 12% of papillary thyroid cancers and 14% of follicular thyroid cancers
 - Found to significantly correlate with older age at diagnosis
 - Demonstrated in thyroid cancers particularly prevalent in aggressive, less differentiated thyroid cancers, including:
 - Tall cell variant-PTC, poorly differentiated thyroid cancer, undifferentiated (anaplastic) thyroid cancer, and *BRAF* V600E mutation-positive PTC
 - Shown to strongly correlate with poorer outcome in differentiated thyroid tumors
 - Prognostic value of *TERT* mutations reported to be significantly stronger than that of *BRAF* (V600E)
 - *TERT* protein by immunohistochemical staining found to be more expressed in neoplastic than in normal tissues and to display different cellular localization, suggesting it could contribute to thyroid cancer progression by mechanisms taking place in cytoplasm
- Phosphatidylinositol 3-kinase (PI3K)/AKT (AKT) signaling pathway
 - Plays important role in regulation of cell survival, proliferation, and migration

- Activating mutations in *RAS*, *PIK3CA*, and *AKT* genes or inactivating mutations in *PTEN* tumor suppressor gene can inappropriately stimulate signaling pathway.
- Mutations in signaling pathway occurs in:
 - 5% to 10% of (differentiated) follicular carcinomas
 - More common in poorly differentiated thyroid carcinoma and undifferentiated (anaplastic) thyroid carcinoma harboring: *PIK3CA* mutation (10% to 20%) and *AKT1* mutation (5% to 10%)
 - *PIK3CA* and *AKT1* mutations frequently present in undifferentiated (anaplastic) thyroid carcinoma coexisting with *BRAF* and *RAS* mutations
- Late event in thyroid carcinogenesis:
 - Higher prevalence in advanced thyroid cancer and undifferentiated (anaplastic) thyroid carcinoma
- β -catenin:
 - Ubiquitously expressed cytoplasmic protein
 - Inappropriate stabilization followed by nuclear translocation proposed as important step in oncogenesis
 - *CTNNB1* gene encodes β -catenin
 - Somatic mutations in exon 3 reported in:
 - 25% of poorly differentiated thyroid carcinoma
 - 60% of undifferentiated (anaplastic) thyroid carcinoma
 - Rare in (well) differentiated thyroid cancers
 - Oncogenic signaling through β -catenin occurs in the cribriform morular variant of PTC in the setting of familial adenomatous polyposis with germline *APC* mutations and in sporadic cases.
- Tumor protein 53 (TP53) tumor suppressor gene
 - Most commonly mutated tumor suppressor gene in human cancer
 - Transcriptional activator involved in cell cycle progression:
 - Ability to arrest cell cycle and activate program cell death confers significant to TP53 in determining cell survival
 - Inactivating point mutations of TP53 tumor suppressor gene highly prevalent in poorly differentiated thyroid carcinoma and undifferentiated (anaplastic) thyroid carcinoma
 - Not present in (well) differentiated thyroid cancers
 - Represent late event in progression and dedifferentiation of thyroid cancer
- Micro-RNAs (miRNAs or miRs):
 - Belong to class of small noncoding messenger RNA that have emerged as potent regulators of a variety of biologic processes, including oncogenesis
 - Act as posttranscriptional regulators of gene expression and are constantly deregulated in human cancer; found downregulated in lung, colon, and prostate cancer
 - Increasingly implicated in regulating malignant progression of cancer
 - Involved in thyroid cell proliferation and migration validating role in downregulation in thyroid carcinogenesis
 - MiR-221 and miR-222 found to be deregulated in human papillary thyroid carcinomas; involved in cell proliferation through inhibition of cell cycle regulator, p27kip1, in human papillary carcinomas
 - miRs may regulate fundamental aspects of the PTC phenotype, i.e., signaling, differentiation, invasion and metastasis, by fine tuning gene expression
 - Increased role in determining thyroid cancer phenotype serving as important diagnostic tool and useful as class identifiers especially in context of follicular thyroid carcinoma, papillary thyroid carcinoma, and anaplastic thyroid carcinoma
 - Cancer-relevant miRs include oncomiRs (miR-21 and miR-146b) and tumor suppressor miRs (let-7 family, miR-204, and miR-375).
 - Increased expression of miR-21 associated with known aggressive form of PTC (tall cell variant) and may be a critical event in pathogenesis
 - OncomiRs miR-221 and miR-222 reported to play role in PTC aggressiveness; associated with less differentiated tumors
 - miRNAs and their target genes could be targeted for novel therapeutics
- Molecular classification
 - The Cancer Genome Atlas (TCGA) project:
 - Comprehensive multiplatform analysis of nearly 500 PTCs (excluding clinically aggressive thyroid cancers including poorly and undifferentiated carcinomas)
 - Integrated genomic characterization of papillary thyroid carcinoma (PTC)
 - Refine classification of PTC into molecular subtypes and associate them with clinically relevant parameters
 - PTC is MAPK-driven cancer that has two mutually exclusive drivers with distinct signaling consequences, including:

- *BRAF* V600E-like tumors include classic PTC with papillary architecture and characteristic nuclear features (whether invasive or noninvasive); gene expression profile shows relatively less evidence of thyroid differentiation with lower expression levels of thyroid differentiation scores (TDS) genes; used for all infiltrative lesions despite follicular architecture that may predominate
 - *RAS*-like tumors include encapsulated or circumscribed (noninvasive) tumors with follicular architecture and nuclear atypia (hallmarks characteristic of follicular variant of PTC); gene expression profile that resembles normal thyroid (high TDS scores); genetics similar to follicular adenoma and follicular carcinoma (not part of the TCGA project analysis).
- Reclassification of follicular variant (FV) of PTC is inevitable with recent recommended by panel of expert thyroid pathologists to replace FVPTC with alternative nomenclature such as “Noninvasive follicular tumor [NIFT] with papillary-like features.” See later under FVPTC.
- Treatment for thyroid cancer:
 - Surgery is preferred treatment for vast majority of thyroid tumors:
 - Extent of surgery varies to include:
 - Lumpectomy:
 - Removal of a nodule/mass alone with minimal surrounding thyroid tissue
 - Generally not recommended for removal of thyroid tumors
 - Partial thyroidectomy:
 - Removal of nodule/mass with larger margin of surrounding thyroid tissue
 - Unacceptable in management of thyroid cancer
 - Isthmusectomy:
 - Removal of tumor within isthmus to include a margin of surrounding thyroid tissue
 - Lobectomy or hemithyroidectomy:
 - Removal of thyroid lobe with or without isthmus
 - Subtotal thyroidectomy:
 - Complete resection of one lobe and isthmus and partial removal of contralateral lobe
 - Bilateral subtotal thyroidectomy:
 - Significant portion of both lobes removed
 - Near total thyroidectomy:
 - Removal of all thyroid tissue except for 1 gram remnant on one side typically preserved to protect adjacent parathyroid tissue or to avoid distal recurrent laryngeal nerve dissection; such a remnant must be anodular and away from cancer focus
 - Total thyroidectomy:
 - Removal of entire thyroid gland; advantages of total thyroidectomy include association with higher survival rate for larger lesions (greater than 1.5 cm); association with lowest recurrence rate; improved sensitivity of serum thyroglobulin as marker for persistent or recurrent disease; allows for utilization of radioactive iodine to treat persistent or recurrent disease; reduction in (unlikely) possibility of residual tumor in contralateral lobe transforming to an anaplastic carcinoma
 - Surgical complications may include:
 - Recurrent laryngeal nerve paralysis
 - In hands of expert thyroid surgeon risk is low (e.g., 1% to 2%)
 - Risk increases (e.g., 6% to 8%) in nonexpert thyroid surgeons
 - Hypoparathyroidism:
 - May be a significant problem in patients following bilateral or total thyroidectomy
 - Rates of temporary hypoparathyroidism (calcium levels <8.0 mg/dl within 6 months after thyroidectomy) reported to be 17% to 40%
 - Rates of permanent hypoparathyroidism range from 1.2% to 6.5%.
 - Risk of hypoparathyroidism increases with invasive cancers; when lymph node dissection is performed with thyroidectomy; linked to experience of surgeon
 - Lymph node dissection:
 - Cervical lymph nodes divided into levels I through VI and grouped into central and lateral compartments
 - See Section 4 for more detailed discussion of anatomy of cervical neck lymph nodes.
 - Surgical treatment of cervical lymph nodes in thyroid carcinoma remains subject of debate:
 - Node dissection indicated when there are palpable nodes and/or radiographically suspicious or positive lymph nodes
 - Selective neck dissection designed to remove regional lymph nodes involved by tumor or at risk for metastasis
 - Central compartment neck dissection includes tissue from hyoid bone to mediastinum and from one jugular vein to the other jugular vein:
 - Lateral deep jugular area is carefully examined (palpated) for disease.
 - In presence of palpable lymph nodes laterally lymphadenectomy to include levels II, III, IV is performed.

- Further, evaluation of the lymph nodes accompanying the inferior thyroid artery into the posterior triangle of the neck is indicated in the presence of palpable nodes, dissection of level V nodes is performed.
- Submandibular triangle usually is not included in the dissection because thyroid cancer rarely metastasizes to the submandibular triangle.
- In presence of cervical nodal metastasis and in patients with aggressive disease, imaging to include the parapharyngeal space and base of skull is indicated; because standard neck dissections do not allow for dissection of lymph nodes in these areas, if significant adenopathy of these regions is visualized, then appropriate techniques for nodal dissection of these sites should be planned and performed in addition to the standard cervical node dissection.
- Radioactive iodine therapy (^{131}I):
 - Thyroid ablation with ^{131}I used in treatment of differentiated thyroid carcinoma:
 - ^{131}I destroys residual microscopic (metastatic) thyroid cancer.
 - Facilitates identification of metastatic foci by radioactive iodine scanning
 - Used in treatment of distant metastasis with best results seen in patients who are under 40 years of age at time of their metastasis and whose metastatic foci concentrate ^{131}I
 - Poorer outcomes seen in patients over 40 years of age at time of their metastasis, have extensive metastatic disease, poorly differentiated tumors, and/or tumors that do not take up ^{131}I
 - Utility of radioactive iodine therapy is negated in presence of a normally situated thyroid gland proper because the latter would concentrate radioactive iodine rather than the planned intent for this therapy to destroy residual cancer outside the confines of thyroid gland proper.
 - Reasonably safe procedure
 - Potential complications may include:
 - Usually involve organs known to concentrate iodine, including salivary glands causing sialadenitis, loss or change in taste, xerostomia; eyes causing xerophthalmia, epiphora; gonads causing transient reductions in fertility; serious life-threatening complications are rare but may include acute bone marrow failure, reduced pulmonary function, second primary malignancy (e.g., leukemia, solid tumors)
- External irradiation:
 - May be used postoperatively in patients with differentiated thyroid carcinoma with or without metastasis
- Chemotherapy:
 - Generally has limited role in treatment of thyroid cancers; most often used in conjunction with other modes of therapy (surgery and radiation) in treatment of poorly differentiated or undifferentiated (anaplastic) carcinomas
- Thyroid hormone therapy:
 - Differentiated thyroid carcinomas contain functional thyroid stimulating hormone (TSH) receptors that are more abundant in follicular carcinoma than papillary carcinoma.
 - TSH stimulates growth of differentiated thyroid carcinoma.
 - In theory, suppression of TSH receptors with suppressive doses of thyroxine may result in tumor regression.
- Prognosis:
 - Prognosis with more common types of thyroid cancers is good with best overall survival rates associated with papillary carcinoma.
 - Important prognostic factors include:
 - Presence or absence of extrathyroidal extension
 - Presence or absence of metastatic disease: in lymph nodes, presence or absence of extranodal extension
 - Age and gender of patient
 - Pathologic features including histology, tumor size, presence or absence of encapsulation
- Follow-up:
 - There is no standard protocol in follow-up of patients with thyroid cancer.
 - In general, scintiscan should be done within 3 months following initial therapy with reexamination at 1 year.
 - Disease-free patients then have whole-body radioactive iodine scans at 3 and 5 years.
 - Recurrent tumor is treated with radioactive iodine.
 - Serum thyroglobulin measurement
 - Reliable biomarker for well-differentiated thyroid follicular epithelial cell-derived cancer recurrence
 - Specific and sensitive marker
 - Shown to have poor accuracy for predicting malignancy in follicular neoplasms with oncocytic cells
 - Serum calcitonin measurement:
 - Used to follow patients with residual or metastatic medullary thyroid carcinoma

TABLE 28-5 TNM Classification of Thyroid Carcinomas

Primary Tumor (T)	
<i>Note:</i> all categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification).	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension limited to thyroid
T1a	Tumor 1 cm or less, limited to the thyroid
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
T4a	Moderately advanced disease Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Very advanced disease Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
All anaplastic carcinomas are considered T4 tumors.	
T4a	Intrathyroidal anaplastic carcinoma
T4b	Extrathyroidal anaplastic carcinoma with gross extrathyroid extension
Regional Lymph Nodes (N)	
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph node (Level VII)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From Edge SB, et al: *AJCC cancer staging manual*, ed 7, New York, 2010, Springer, p 89.

Pathologic staging (p): Correspond to the T (pT), N (pN), and M (pM) categories.

Residual tumor is designated as R: *RX*, Residual tumor cannot be assessed; *R0*, no residual tumor, *R1*, microscopic residual tumor, *R2*, macroscopic residual tumor.

Additional descriptors: “m” suffix indicates the presence of multiple primary tumors in a single site [pT(m)NM]; “r” prefix indicates recurrent tumor when staged after a disease-free interval [rTNM]; “a” prefix indicates stage determined at autopsy [aTNM].

CLINICAL STAGING OF THYROID CARCINOMA

- Clinical staging of thyroid tumors is determined by physical examination, thyroid imaging, or endoscopic examination:
 - Inspection and palpation of thyroid gland and cervical neck
 - Imaging studies include radioisotope thyroid scans, ultrasonography, CT scan, MRI scan.
 - Endoscopic evaluation includes indirect laryngoscopy to evaluate vocal cord motion.
- TNM classification of thyroid gland cancers (Table 28-5) must include all information obtained in clinical staging plus patient demographics (i.e., age and gender) and information gathered on pathologic evaluation (i.e., fine-needle aspiration biopsy, gross and microscopic evaluation) including:
 - Cancer type (e.g., papillary or follicular carcinoma versus medullary carcinoma versus undifferentiated [anaplastic] carcinoma)

TABLE 28-6 Clinical Staging

Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and undifferentiated (anaplastic) carcinoma.				Medullary Carcinoma (All Age Groups)			
Papillary or Follicular (Differentiated)				Stage I	T1	N0	M0
<i>Under 45 years</i>				Stage II	T2	N0	M0
					T3	N0	M0
Stage I	Any T	Any N	M0	Stage III	T1	N1a	M0
Stage II	Any T	Any N	M1		T2	N1a	M0
<i>45 Years and Older</i>					T3	N1a	M0
Stage I	T1	N0	M0	Stage IVA	T4a	N0	M0
Stage II	T2	N0	M0		T4a	N1a	M0
Stage III	T3	N0	M0		T1	N1b	M0
	T1	N1a	M0		T2	N1b	M0
	T2	N1a	M0		T3	N1b	M0
	T3	N1a	M0		T4a	N1b	M0
Stage IVA	T4a	N0	M0	Stage IVB	T4b	Any N	M0
	T4a	N1a	M0	Stage IVC	Any T	Any N	M1
	T1	N1b	M0	Anaplastic Carcinoma			
	T2	N1b	M0	All anaplastic carcinomas are considered Stage IV.			
	T3	N1b	M0	Stage IVA	T4a	Any N	M0
	T4a	N1b	M0	Stage IVB	T4b	Any N	M0
Stage IVB	T4b	Any N	M0	Stage IVC	Any T	Any N	M1
Stage IVC	Any T	Any N	M1				

From Edge SB, et al: *AJCC cancer staging manual*, ed 7, New York, 2010, Springer, pp 87-88.

- Primary tumor size (T)
- Regional lymph node involvement (N)
- Distant metastasis (M)

NOTE: Pathologic staging (p): correspond to the T (pT), N (pN), and M (pM) categories

- Clinical staging of thyroid gland cancers, including papillary or follicular carcinoma, medullary carcinoma, and undifferentiated (anaplastic) carcinoma is detailed in [Table 28-6](#).

BENIGN FOLLICULAR EPITHELIAL NEOPLASMS

FOLLICULAR ADENOMA (FA) (Figs. 28-1 through 28-6)

Definition: Benign encapsulated tumor with evidence of follicular cell differentiation showing growth pattern and cytomorphology different from surrounding thyroid parenchyma, but lacking features of papillary thyroid carcinoma.

- Whether clonality is a part of definition of an adenoma in contrast to adenomatoid nodules is controversial because clonality has been shown to be present in a large percentage (70%) of dominant adenomatoid nodules in setting of nodular goiter.

Clinical

- Affects women more than men; occurs over a wide age range but is most common in the fifth to sixth decades of life

- Clinical presentation is usually that of a painless neck (thyroid) mass; duration of symptoms varies from months to years.
- Most often solitary and limited to one part of the thyroid lobe but may involve the entire lobe:
 - Uncommonly, multiple adenomas may be present in a single gland.
- Patients are usually euthyroid; serum thyroglobulin may be raised but clinical evidence of hyperthyroidism is rarely seen.
- Radiology:
 - Thyroid imaging (^{123}I or $^{99\text{m}}\text{technetium}$):
 - Most often “cold” or hypofunctional or poorly functional nodule
 - May be hyperfunctioning (“hot”) nodule:
 - Tend to be more cellular than hypofunctioning (“cold”) adenoma

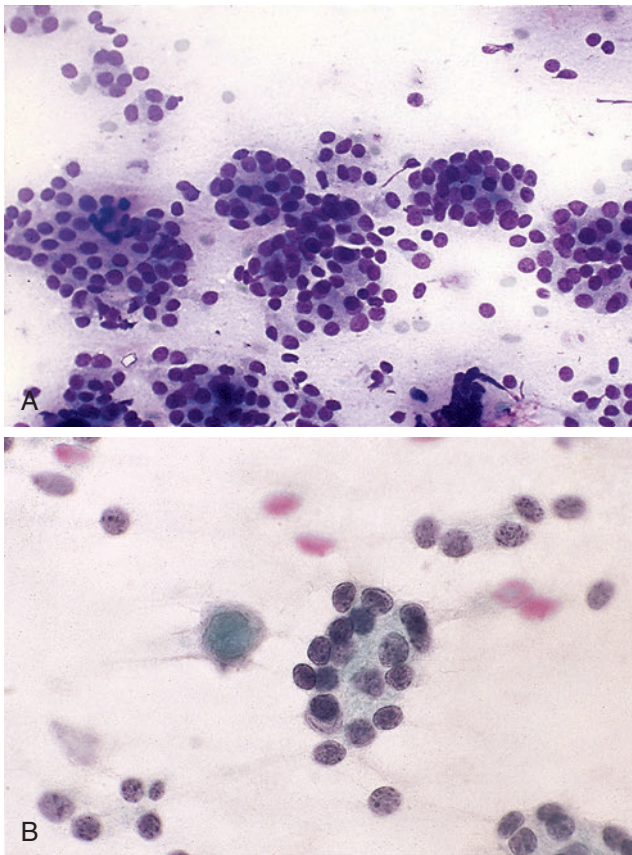


Fig. 28-1. Fine-needle aspiration biopsy (FNAB), follicular adenoma.

A, Smears of follicular neoplasm are typically much more cellular than adenomatoid nodules and have a preponderance of small follicular structures. Colloid is scanty or absent in more cellular follicular neoplasms (Diff-Quik stain). **B**, Syncytial grouping of the cells in this small follicle with extruded fragment of dense colloid. The opaque chromatin pattern and round nuclear contours are typical of a follicular proliferation and contrast to features seen in association with papillary thyroid carcinoma (Papanicolaou stain). The FNAB diagnosis was “follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV).” A lobectomy was performed and the lesion proved to be a follicular adenoma.

- Sometimes associated with hyperthyroidism (toxic or Plummer adenoma)
- No specific etiologic factors associated with development of FA

Pathologic Features

Fine-Needle Aspiration Biopsy

- Often FNAB diagnosis is “follicular neoplasm, suspicious for follicular neoplasm (Bethesda IV),” which informs treating physician that a neoplasm is present requiring surgical removal (e.g., lobectomy)

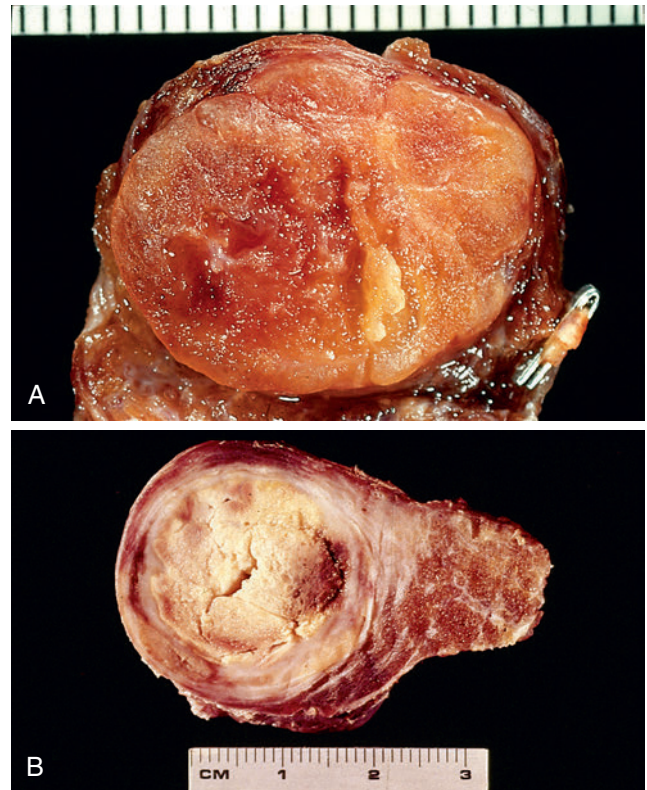


Fig. 28-2. Follicular adenomas.

A, Follicular adenoma appearing as a solitary, circumscribed to thinly encapsulated lesion with tan-brown and glistening appearance. **B**, Follicular adenoma with post-FNAB retrogressive changes including necrosis, hemorrhage, and cyst formation.

- Features associated with a follicular neoplasm that contrast with those of a (cellular) adenomatoid nodule or other lesions include:
 - Syncytial groups with or without distinct microfollicles; microfollicular or trabecular growth
 - Cellular smears
 - Increased cellularity
 - Scanty colloid, which is usually dense and in follicular lumina
 - Uniform cells with round nuclei, inconspicuous nucleoli, and ill-defined cell borders
 - Nuclear chromatin is opaque to coarsely granular and usually evenly distributed
 - Cytoplasmic features vary from scant to oxyphilic.
 - Absence of nuclear features diagnostic for papillary thyroid carcinoma

Gross

- Solitary encapsulated mass:
 - Capsule varies in thickness but usually is thin.
 - Generally completely envelops tumor

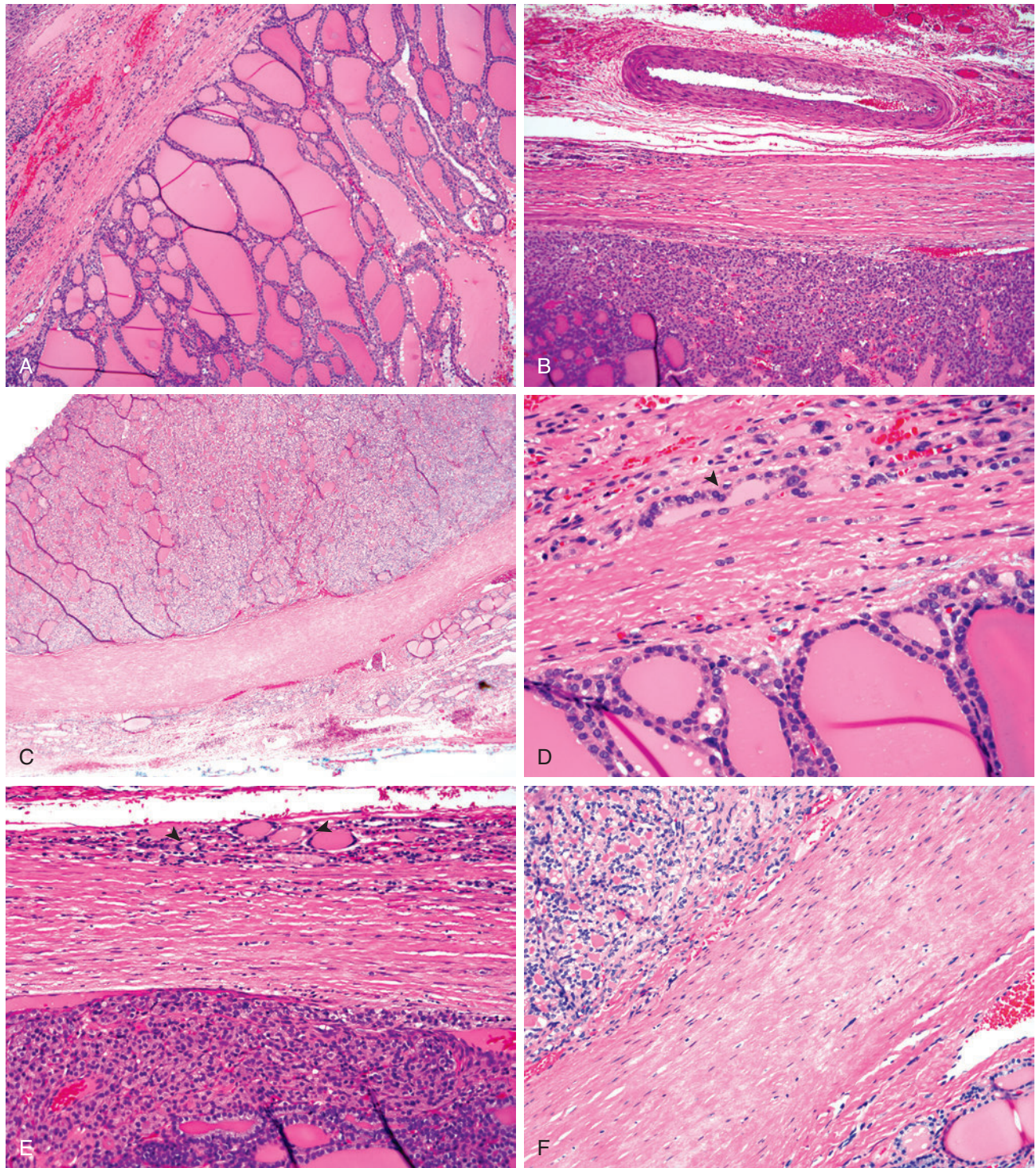


Fig. 28-3. Follicular adenoma.

The hallmark of a follicular adenoma is its encapsulation and absence of invasive growth and/or nuclear features diagnostic for papillary thyroid carcinoma. The presence of a complete capsule encircling the tumor is a feature that separates an adenoma from an adenomatoid nodule. The capsule may vary from **(A)** thin to **(B)** moderately thick to **(C)** thick.

D through **F**, In all instances, the capsule appears relatively uniform in thickness with linear/parallel arrangement of fibers lacking thicker and thinner areas and disorganization in arrangement of its fibers as might be seen in reactive fibrosis. The non-neoplastic thyroid tissue adjacent to the tumor is compressed (*arrowheads* in **D** and **E**).

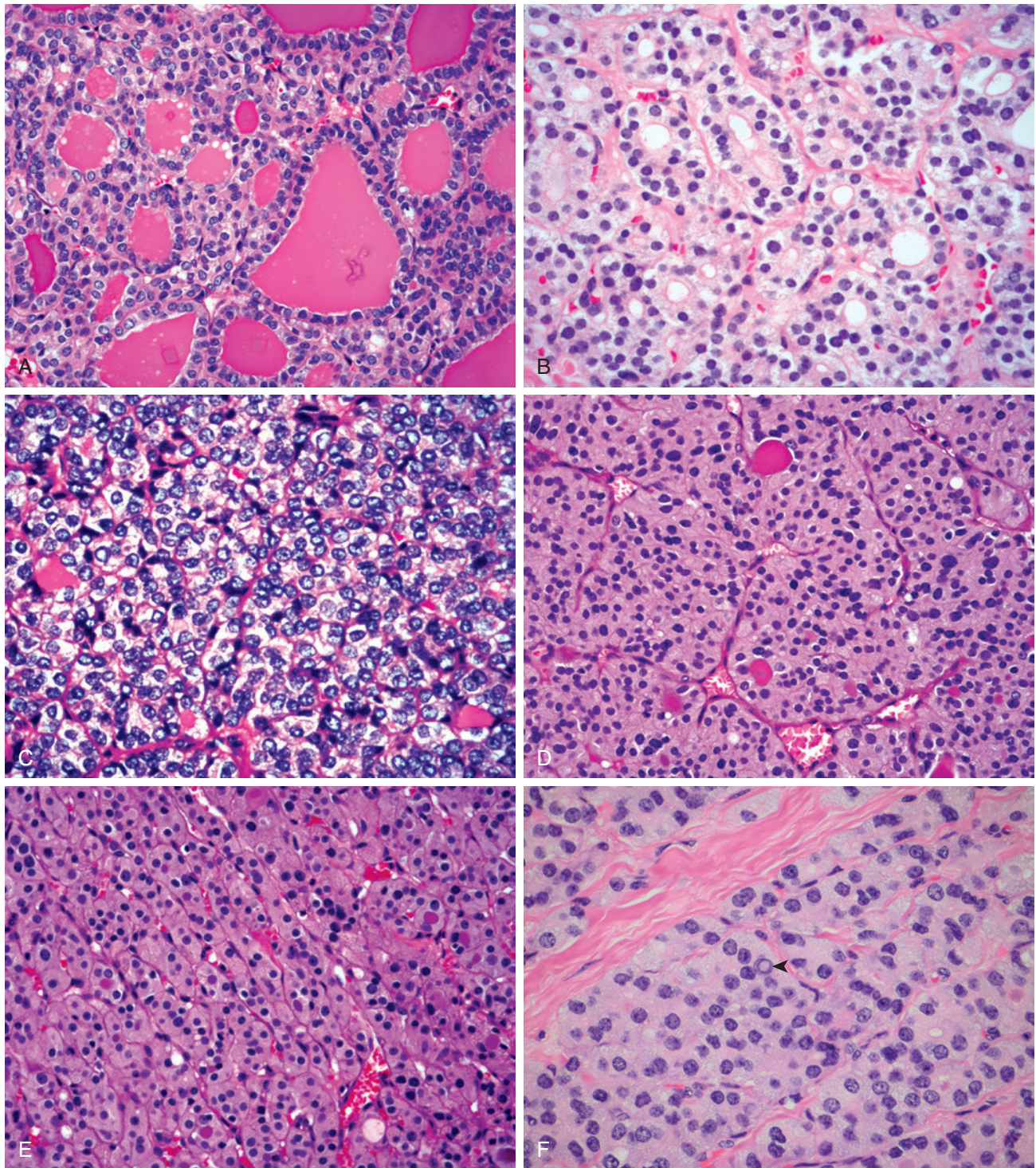


Fig. 28-4. Follicular adenoma.

Growth patterns may include (A) normocellular, (B) microfollicular, (C) solid, (D) organoid/insular, and (E) trabecular. The lesional cells are composed of round to oval nuclei with coarse nuclear chromatin and smooth nuclear contours. F, Rarely, intranuclear inclusions (*arrowhead*) typically associated with papillary thyroid carcinoma can be seen in other thyroid lesion types including follicular adenomas. In D through F, the cells show granular eosinophilic cytoplasm but not as brightly eosinophilic as seen in oncocyctic cells.

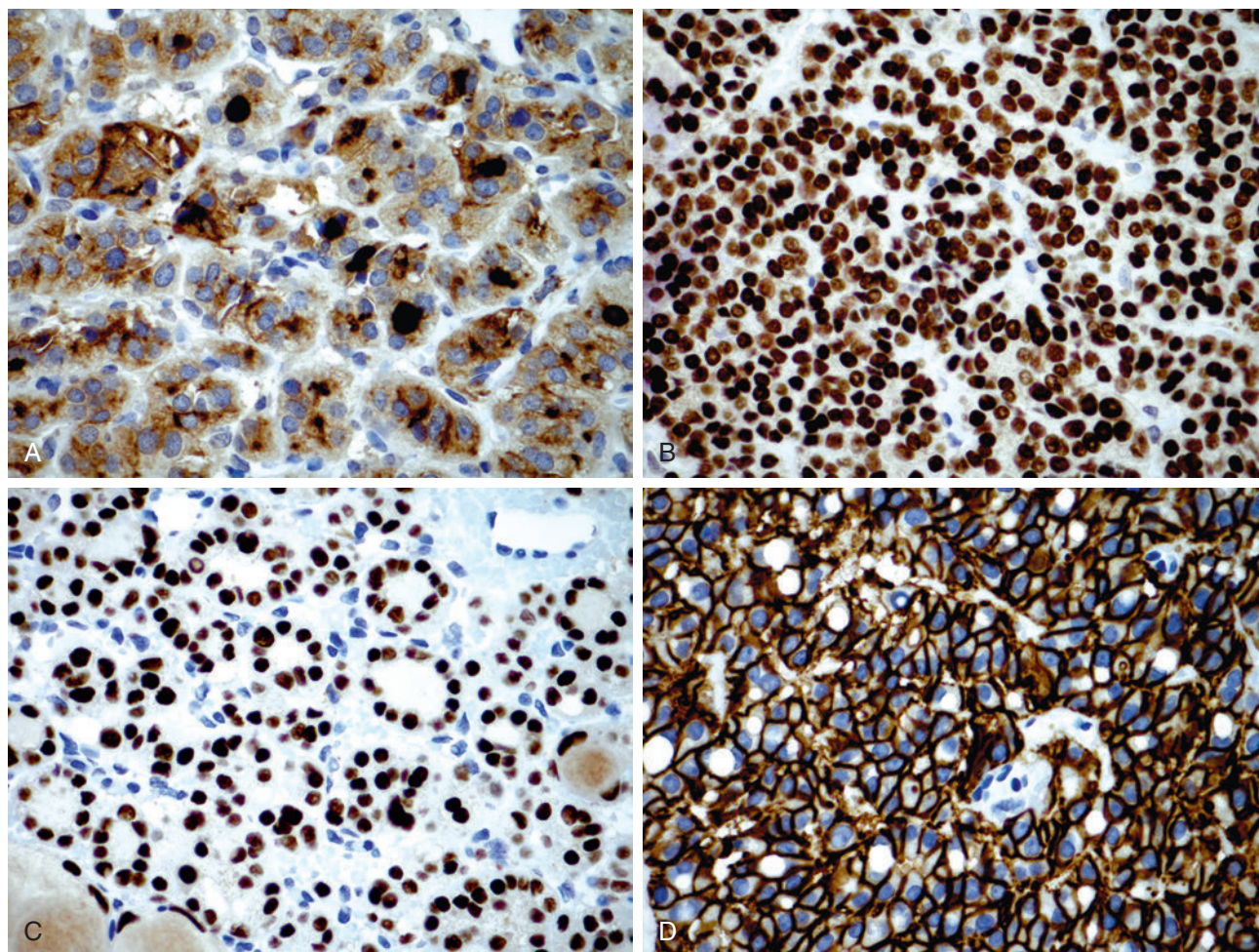


Fig. 28-5. Follicular adenoma, immunohistochemical staining.

Immunohistochemical staining in follicular adenomas include reactivity for **(A)** thyroglobulin, **(B)** TTF-1 (nuclear), **(C)** PAX8 (nuclear), and **(D)** CD56 (membranous).

- Vary in size but generally measure <3 cm; larger tumors measuring more than 10 cm can be seen
- Pale tan to brown to orange (oncocytic)
- Solid with a rubbery to firm consistency and a homogeneous appearance except in the presence of retrogressive changes, which may include:
 - Hemorrhage, fibrosis, cyst formation, calcification, and infarction

Histology

- Encapsulated tumors without evidence of capsular and/or vascular invasion:
 - Generally fibrous capsule completely envelops tumor
 - Capsule is composed of fibrous tissue, within which small to medium-size vascular spaces and smooth muscle bundles may be seen.
 - Capsule is generally thin and clearly demarcated from neoplasm on one side and uninvolved thyroid tissue on the other side, which is usually compressed and may be atrophic.
- Capsule may vary in thickness from thin and regular to thick and irregular but tends to retain relative uniformity in thickness, enveloping the lesion without wide variations in thickness.
- Typically envelops lesion, remaining peripheral to and not within lesion
- Markedly thickened capsule should engender ample sampling to include tumor-to-capsule-to-parenchymal interface to exclude possible presence of an invasion that may confer a diagnosis of carcinoma.
- Composed of relatively uniform-appearing colloid-filled follicles with varying growth patterns that may include:
 - Normofollicular (simple)
 - Macrofollicular (colloid)
 - Microfollicular (fetal)

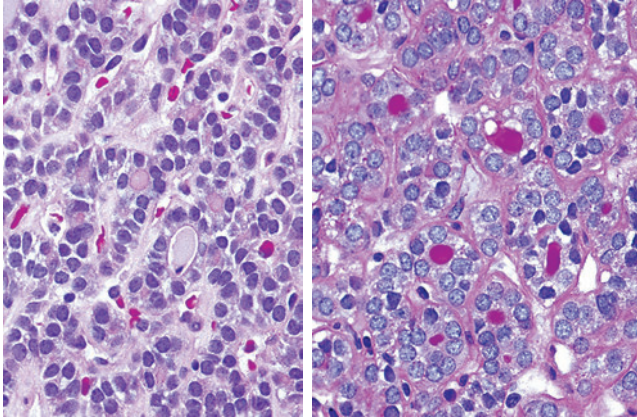


Fig. 28-6. Staining for colloid.

(Left) This cellular tumor was encapsulated without evidence of invasive growth or features of papillary thyroid carcinoma. Colloid is present but may not be readily appreciated on hematoxylin and eosin stains. (Right) Periodic acid Schiff (PAS) staining assists in highlighting the presence of colloid.

- Solid (embryonal)
- Trabecular (embryonal)
- Organoid (cell nests) and/or insular:
 - Presence of insular growth pattern does not convey a diagnosis of poorly differentiated (“insular”) thyroid carcinoma:
 - Requisite criteria for poorly differentiated thyroid carcinoma includes presence of increased mitotic activity and necrosis with or without invasion; see later in chapter for discussion on poorly differentiated thyroid carcinoma
- In general, follicular adenomas usually show single architectural pattern but may show an admixture of patterns:
 - Although not pathognomonic, a neoplasm with a variety of growth patterns should raise suspicion for papillary thyroid carcinoma.
- Cellularity and cytologic appearance of follicular adenoma varies from tumor to tumor and even within the same tumor:
 - Neoplastic cells are generally uniform with defined cell borders.
 - Nuclei tend to:
 - Be round to oval with coarse to hyperchromatic nuclear chromatin, smooth (rounded) nuclear contours, absent to inconspicuous nucleoli, and a variable amount of amphophilic to eosinophilic cytoplasm:
 - Granular eosinophilic cytoplasm may be present not as brightly eosinophilic as present in oncocytic (Hürthle) cells
- In association with granular eosinophilic cytoplasm nuclei may be enlarged with vesicular-appearing nuclei and some irregularities in size and shape, but nuclear chromatin tends to remain coarse and overall findings do not reach level of papillary thyroid carcinoma.
 - Align along basal aspect of cell.
 - Eosinophilic nuclear (pseudo)inclusions may rarely be present.
- Colloid-filled follicles are generally readily apparent but in some instances may be difficult to identify.
 - Periodic acid Schiff (PAS) stains assist in identifying presence of colloid.
- Follicular adenomas are well vascularized, and stromal component includes small to large vascular spaces:
 - Neoplastic cells can be seen within stromal vascular spaces but any neoplastic foci in vascular spaces within the tumor itself do not qualify as a carcinoma.
- Rare mitotic figures can be seen:
 - Presence of increased mitotic activity (>3-5 mitoses per 10 high power fields) and necrosis should be of concern and raise suspicion for a carcinoma.
- Degenerative stromal changes may uncommonly be seen and not as frequently found as in adenomatoid nodules:
 - Papillary or pseudopapillary architecture may be present but cytomorphologic (i.e., nuclear) findings associated with papillary thyroid carcinoma are not present.
 - Term papillary adenoma has been used for such lesions but the use of this designation should be avoided.
- Immunohistochemistry:
 - Thyroglobulin, thyroid transcription factor-1 (TTF-1, nuclear), and PAX8 (nuclear) positive
 - Cytokeratins (AE1/AE3, CK7, CK8, CK18) positive
 - CK19 negative
 - CD56 positive (membranous)
 - Calcitonin, synaptophysin, chromogranin negative
- Cytogenetics and molecular genetics:
 - RAS mutation in 20% to 40%:
 - Lower incidence in follicular adenoma, oncocytic type
 - PAX-PPAR γ translocation in 5% to 20%
 - Absence of:
 - RET/PTC translocation
 - BRAF mutation
 - PTEN mutation
 - PIK3CA/AKT pathway mutation

TABLE 28-7 Follicular Adenoma versus Adenomatoid Nodule

Feature	Follicular Adenoma	Adenomatoid Nodules
Number	Solitary	Multiple
Capsule	Well-developed, completely surrounding mass; appears rather uniform in thickness and appearance	Poor encapsulation; a capsule may be present but it does not completely encapsulate mass; in association with retrogressive changes fibrosis may envelop lesion but appears irregular of variable thickness, including marked thickening within and around lesion(s)
Adjacent thyroid gland	Compression of surrounding gland	No compression of surrounding gland
Growth as compared to the rest of the thyroid gland	Different growth pattern in adjacent gland	Comparable growth pattern in adjacent gland
Appearance as compared to the rest of the thyroid gland	Uniform cellularity dissimilar to remainder of gland	Variable cellularity similar to those outside nodules
Degenerative changes	May be present but not common	Frequently present
Clonality	Monoclonal cell population	Polyclonal cell population; studies have shown that at least some adenomatoid nodules are monoclonal with cytogenetic abnormalities, aneuploidy, and oncogenic mutations to support a neoplastic origin

Differential Diagnosis

- Adenomatoid nodule (Table 28-7)
- Follicular carcinoma:
 - Differentiating features separating follicular adenoma from follicular carcinoma is presence of invasion, including capsular invasion and/or vascular invasion:
 - See [Follicular Carcinoma](#) later in chapter for detailed discussion of vascular and capsular invasion.
 - Features in an adenoma raising concern for a possible diagnosis of carcinoma include:
 - Thickened fibrous capsule
 - Increased mitotic activity and/or necrosis
 - Diffuse nuclear atypia
 - No known molecular test at present assisting in differentiating follicular adenoma from follicular carcinoma
- Papillary thyroid carcinoma
- Medullary thyroid carcinoma

Treatment and Prognosis

- Conservative surgery (lobectomy) is preferred treatment.
- No recurrences or metastases

HISTOLOGIC TYPES OF FOLLICULAR ADENOMAS (Box 28-2)

- Generally, histologic variants of follicular adenoma do not confer on a given neoplasm any difference in

BOX 28-2 Histologic Types of Follicular Adenomas

- Follicular adenoma, oncocytic (Hürthle cell)
- Hyalinizing trabecular adenoma (paraganglioma-like)
- Follicular adenoma with atypical features
- Follicular adenoma, clear cell
- Follicular adenoma, signet ring cell
- Follicular adenoma with intracellular fat droplets
- Mucinous follicular adenoma (follicular adenoma with mucinous stroma)
- Follicular adenoma with spindle cell metaplasia
- Follicular adenoma with papillary architecture
- Follicular adenoma with bizarre nuclei
- Follicular adenoma with mesenchymal cell components
- Hyperfunctioning adenoma (toxic or “hot” adenoma)

clinical parameters or biologic behavior as compared to conventional types of follicular adenomas.

Follicular Adenoma, Oncocytic Type (Figs. 28-7 through 28-9)

Definition: Follicular epithelial cell-derived neoplasm dominated by presence of mitochondria-rich cells (i.e., oncocytes, oxyphilic cells) without evidence of invasion or metastasis.

- Terminology derived from the Greek word meaning “swollen”
- Results from increase in mitochondrial content of a cell
 - By light microscopy, an oncocytic cell is one that has a prominent granular eosinophilic-appearing cytoplasm.

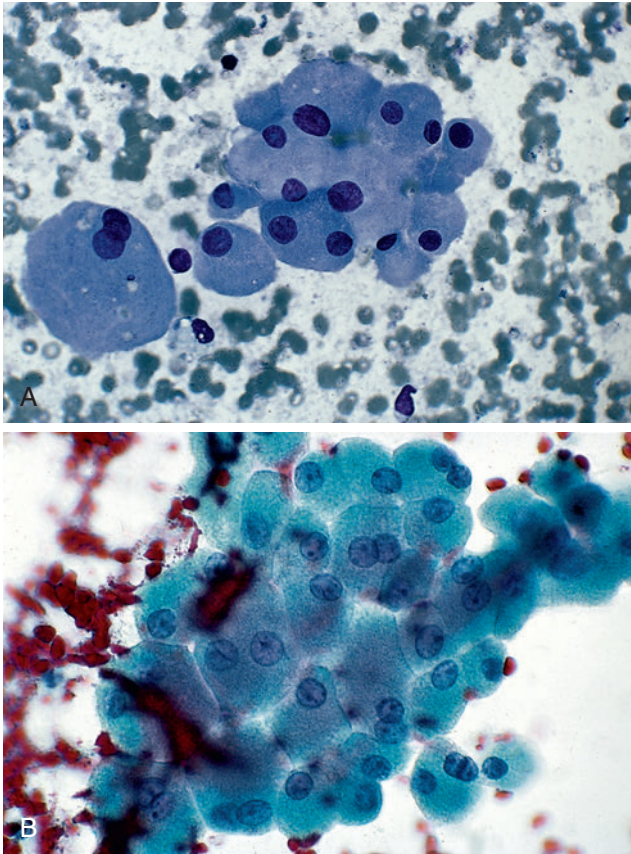


Fig. 28-7. Fine-needle aspiration biopsy (FNAB), follicular adenoma, oncocytic type.

A, The cells are large with abundant granular cytoplasm appearing gray-blue (Diff-Quik). Note the low nuclear-cytoplasmic ratio. Very cellular oncocytic follicular neoplasms have little or no colloid; the cells tend to form small loosely cohesive groups or shed singly.

B, Papanicolaou stained smear shows oncocytic features manifested as cytoplasmic granularity. The cytoplasm is usually more abundant than in nononcocytic follicular cells. The nuclei are round, with readily apparent nucleoli. The FNAB diagnosis was “follicular neoplasm or suspicious for a follicular neoplasm, oncocytic (Hürthle) cell type (Bethesda IV).” A lobectomy was performed and the lesion proved to be a follicular adenoma.

- Should be distinguished from cells with cytoplasmic eosinophilia, which:
 - Has eosinophilic appearance of cytoplasm in hematoxylin and eosin stain (H&E)-stained sections but lacks granularity and bright pink appearance of oncocytic cells
- Oncocytic change in thyroid gland not restricted to follicular cells as it can also occur in:
 - Neoplastic C-cells (i.e., oncocytic medullary thyroid carcinoma [MTC])

Synonyms: Hürthle cell adenoma; oncocytic adenoma; oxyphilic cell adenoma; Askanazy cell adenoma

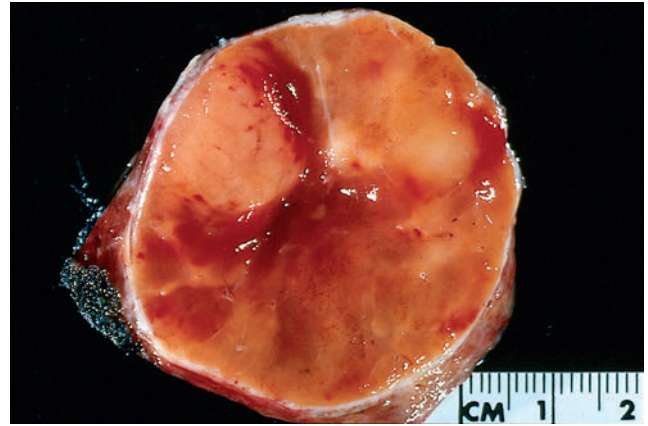


Fig. 28-8. Follicular adenoma, oncocytic type.

The tumor is completely encapsulated and characterized by an orange color.

BOX 28-3 Thyroid Lesions with Oncocytic Cells

Non-Neoplastic Lesions

- Nodular goiter (adenomatoid nodules)
- Chronic lymphocytic (Hashimoto) thyroiditis
- Graves disease
- Postradiation
- Aging

Neoplasms

- Follicular adenoma variants
- Follicular carcinoma variants
- Papillary carcinoma variants
- Medullary carcinoma
- Undifferentiated (anaplastic) thyroid carcinoma

- Hürthle originally described the cell that is now felt to represent parafollicular cell or C-cell of ultimobranchial derivation and not the oncocyte; description of oncocyte attributed to Askanazy
- Use of designation oncocytic (Hürthle, oxyphilic) is purely descriptive, indicative of a type of change in a cell and NOT indicative of any specified biologic behavior in a thyroid tumor
- Too often, assumption made that diagnosis of “Hürthle cell neoplasm” qualifies tumor as malignant, essentially being synonymous with a follicular carcinoma:
 - Erroneous assumption as oncocytic cell changes can be seen in non-neoplastic and neoplastic (benign and malignant) thyroid lesions (Box 28-3).

Clinical

- Similar demographics, clinical presentation, treatment, and biology to “conventional” follicular adenoma

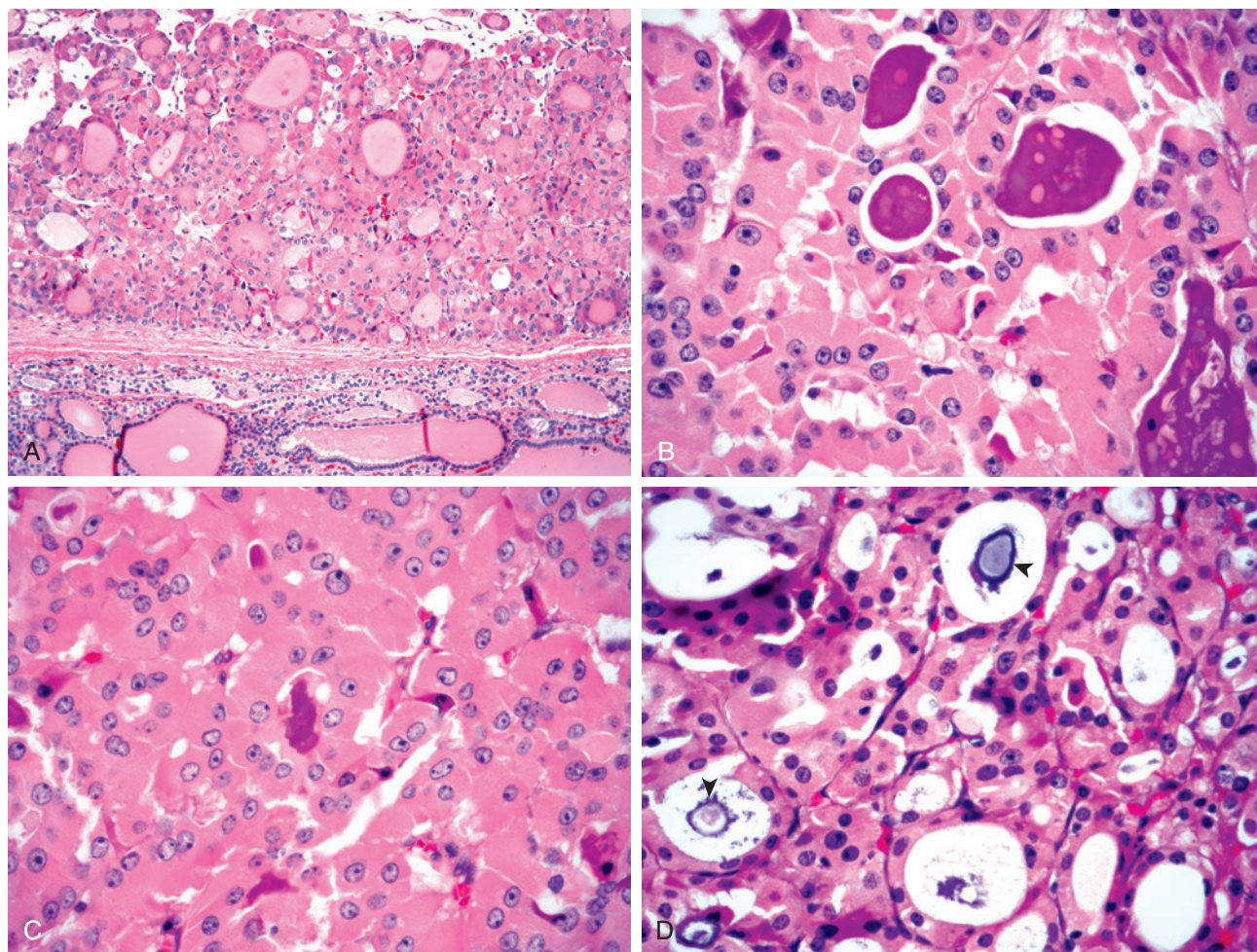


Fig. 28-9. Follicular adenoma, oncocytic type.

A, Thinly encapsulated tumor. **B** and **C**, Lesional cells are characterized by the presence of abundant eosinophilic granular-appearing cytoplasm. Nuclear enlargement is present but in spite of the nuclear enlargement the nuclei remain round to oval with dispersed nuclear chromatin and enlarged eosinophilic nucleoli. A variable amount of colloid is present. **D**, Colloid may calcify and simulate the appearance of psammoma bodies (*arrowheads*).

- Serum thyroglobulin measurement reliable biomarker for thyroid cancer recurrence but shown to have poor accuracy for predicting malignancy in follicular neoplasms with oncocytic cells

Pathologic Features

Fine-Needle Aspiration Biopsy

- FNAB diagnosis is “follicular neoplasm or suspicious for a follicular neoplasm, oncocytic (Hürthle) cell type (Bethesda IV),” which informs treating physician that a neoplasm is present requiring surgical removal (e.g., lobectomy)
- Smears or aspirates dominated by enlarged oval to polygonal cells, often in sheets, that have abundant, granular-appearing cytoplasm:
- Nuclei tend to be enlarged, round to oval, eccentrically located with prominent eosinophilic nucleoli.

- Binucleated cells can be seen.
- Nuclear chromatin tends to be coarse.
- Colloid is minimal to absent.

Gross

- Similar to “conventional” follicular adenoma except that oncocytic cell change imparts distinct bright orange to brown coloration
- Vary in size and may be quite large (>4 cm):
 - Large size may correlate to presence of malignant neoplasm (follicular carcinoma, oncocytic type) but does not uniformly correlate to malignancy.

Histology

- Similar histologic features as “conventional” follicular adenoma:
 - Encapsulated tumors

- Capsule may vary in thickness.
 - No capsular and/or vascular invasion
- Growth patterns may include:
 - Follicular
 - Microfollicular
 - Solid
 - Trabecular
 - Organoid
 - Papillary architecture
 - May be focal or extensive
 - Prominent/extensive papillary growth may be seen as a retrogressive phenomenon occurring spontaneously or following fine-needle aspiration biopsy
 - Nuclear characteristics diagnostic for papillary carcinoma absent
- Characterized by presence of cells with abundant eosinophilic granular-appearing cytoplasm
 - Cytoplasmic margins often distinctly seen
- Presence of oncocyctic cytoplasm often causes nuclear enlargement but in spite of nuclear enlargement nuclei tend to remain rather uniform-appearing round to oval with coarse to granular to vesicular-appearing chromatin and presence of distinct (centrally located) eosinophilic nucleoli
 - Nuclear grooves and nuclear (pseudo)inclusion may be identified.
 - Presence of such features not diagnostic for papillary thyroid carcinoma and can be seen in benign thyroid lesions/neoplasms
- Clear cell change may be seen:
 - May be juxtaposed or intermixed with oncocyctic cells
 - Caused by swelling of mitochondria
- Colloid:
 - May be readily apparent or limited in extent
 - May calcify including concentric laminations, suggesting presence of psammoma bodies and a possible diagnosis of papillary thyroid carcinoma:
 - Typically located within lumens, not usual location in papillary thyroid carcinomas
 - Cytomorphologic (i.e., nuclear) features not those of papillary thyroid carcinoma
- Oncocyctic cells owing to oxygen-sensitive nature of mitochondria more readily undergo retrogressive changes either spontaneously or following traumatic event such as post-fine-needle aspiration biopsy; such alterations may include:
 - Infarction
 - Necrosis
 - Hemorrhage (recent and remote in form of hemosiderin-laden macrophages)
 - Papillary architecture
 - Cyst formation
 - Fibrosis
 - Calcifications
- Term Hürthle cell neoplasm of uncertain malignant potential has been ascribed to those tumors showing worrisome but inconclusive features of malignancy, including:
 - Smaller cells with high nuclear-to-cytoplasmic ratio
 - Increased mitotic activity
 - Because these tumors have uniformly followed a benign clinical course this terminology is not advocated and designation of follicular adenoma, oncocyctic type is preferred.
- Histochemistry:
 - Stains for mitochondria may be positive and include:
 - Phosphotungstic acid hematoxylin (PTAH): red staining
 - Novelli stain: dark purple staining
- Immunohistochemistry:
 - Cytokeratins, thyroglobulin, and TTF-1 positive:
 - Thyroglobulin reactivity less intense than in nononcocyctic follicular cells
 - Chromogranin, synaptophysin, and calcitonin negative
 - Low proliferation indices (less than 5%) by KI67 (MIB-1) staining
- Electron microscopy:
 - Oncocyctic cells are packed with mitochondria.
 - Mitochondrial abnormalities can be seen, including quantitative and qualitative (size, shape, content) changes.
- Cytogenetics and molecular genetics:
 - RET/PTC rearrangements may be present:
 - Questionable relevance relative to diagnosis and classification
 - May reflect very low rearrangement level using highly sensitive detection method or tumor heterogeneity
 - Additional findings reported include:
 - Large deletions of mitochondrial DNA (mtDNA), mutations of mtDNA genes coding for oxidative phosphorylation (OXPHOS) proteins, and mutations of nuclear genes coding also for mitochondrial OXPHOS proteins
 - Such mitochondrial alterations lead to energy production defects in Hürthle cell tumors:
 - Increased proliferation of mitochondria may reflect compensatory mechanism for such defects and is associated with overexpression of factors involved in mitochondrial biogenesis
 - Mitochondrial abnormalities also thought to play a major role in predisposition for necrosis instead of apoptosis, which seems to be blocked in most Hürthle cell tumors

Differential Diagnosis

- Follicular carcinoma, oncocytic type:
 - Diagnosis of follicular carcinoma, oncocytic type made in presence of capsular or vascular invasion
 - In absence of invasive growth, features found in an encapsulated follicular neoplasm (including the oncocytic follicular adenoma) that may increase concern for malignancy include:
 - Increased cellularity in particular at the tumor-to-capsule-to-stromal interface
 - Smaller cells with increased nuclear-to-cytoplasmic ratio
 - Increased mitotic activity
 - Necrosis either individual cell or confluent foci
- Papillary thyroid carcinoma (PTC):
 - Usual type:
 - Does not have oncocytic cytoplasm but nuclear enlargement and to some degree nuclear clearing seen in follicular adenoma, oncocytic type may be mistaken for PTC
 - Tall cell type:
 - Some authorities consider tall cells to be variant of oncocytic.
- Medullary thyroid carcinoma, oncocytic type:
 - Oncocytic change in thyroid gland not restricted to follicular cells because it can also occur in neoplastic C-cells (i.e., oncocytic medullary thyroid carcinoma [MTC]):
 - Immunohistochemical staining for calcitonin, neuroendocrine markers present in MTC and absent in follicular epithelial cell tumors
 - Immunohistochemical staining for thyroglobulin and TTF1 present in oncocytic follicular adenoma and absent in MTC

Treatment and Prognosis

- Conservative surgery (lobectomy) is preferred treatment and considered curative.

Hyalinizing Trabecular Adenoma/Tumor

(Figs. 28-10 and 28-11)

Definition: Encapsulated follicular epithelial-derived tumor with trabecular growth pattern and presence of prominent intratrabecular hyalinization located in cytoplasm of lesional cells and in extracellular space.

Synonym: Paraganglioma-like adenoma of thyroid (PLAT)

Terminology

- Controversy among authorities whether hyalinizing trabecular adenoma should be considered variant of papillary thyroid carcinoma (PTC) based on:
 - Occurrence of hyalinizing trabecular adenoma in the setting of lymphocytic thyroiditis or in patients

with a history of radiation therapy, two settings more typically seen in association with papillary thyroid carcinoma

- Co-existence with typical thyroid papillary carcinoma
- Presence of HTA-like foci in typical thyroid papillary carcinoma
- Overlapping nuclear features shared with PTC
- Demonstration of *RET/PTC* translocation in percentage of cases
- Occasional presence of nodal metastasis showing pattern of growth similar to hyalinizing trabecular adenoma
- Weighing in favor for categorization as adenoma includes:
 - Overwhelming majority of solitary encapsulated thyroid lesions showing feature of hyalinizing trabecular adenoma behave as benign neoplasms
 - *BRAF* mutations a finding present in PTCs not reported in hyalinizing trabecular adenoma
 - Micro (mi)-RNAs known to be upregulated in PTC were downregulated in hyalinizing trabecular adenoma
- At present, most authorities view hyalinizing trabecular adenoma as a benign neoplasm but given similarities to papillary carcinoma designation hyalinizing trabecular tumor recommended

Clinical

- Affects women more than men; occurs over a wide age range from the third through eighth decades of life
- Clinical presentation is that of an asymptomatic neck mass.
- May occur in any portion of the thyroid gland
- Radiology:
 - Thyroid imaging (^{123}I or $^{99\text{m}}\text{technetium}$): “cold” nodule; may appear as a “hot” nodule
- Etiology unknown:
 - Several cases reported following radiation exposure

Pathologic Features

Fine-Needle Aspiration Biopsy

- Cohesive aggregates radially oriented around hyaline material
- Cells with abundant cytoplasm and low nuclear-to-cytoplasmic ratio
- Intranuclear cytoplasmic inclusions, nuclear grooves, and nuclear overlapping are common (best seen with the Papanicolaou method):
 - Cytoplasmic yellow bodies useful cytomorphologic indicator of hyalinizing trabecular adenoma; see details under microscopic description below

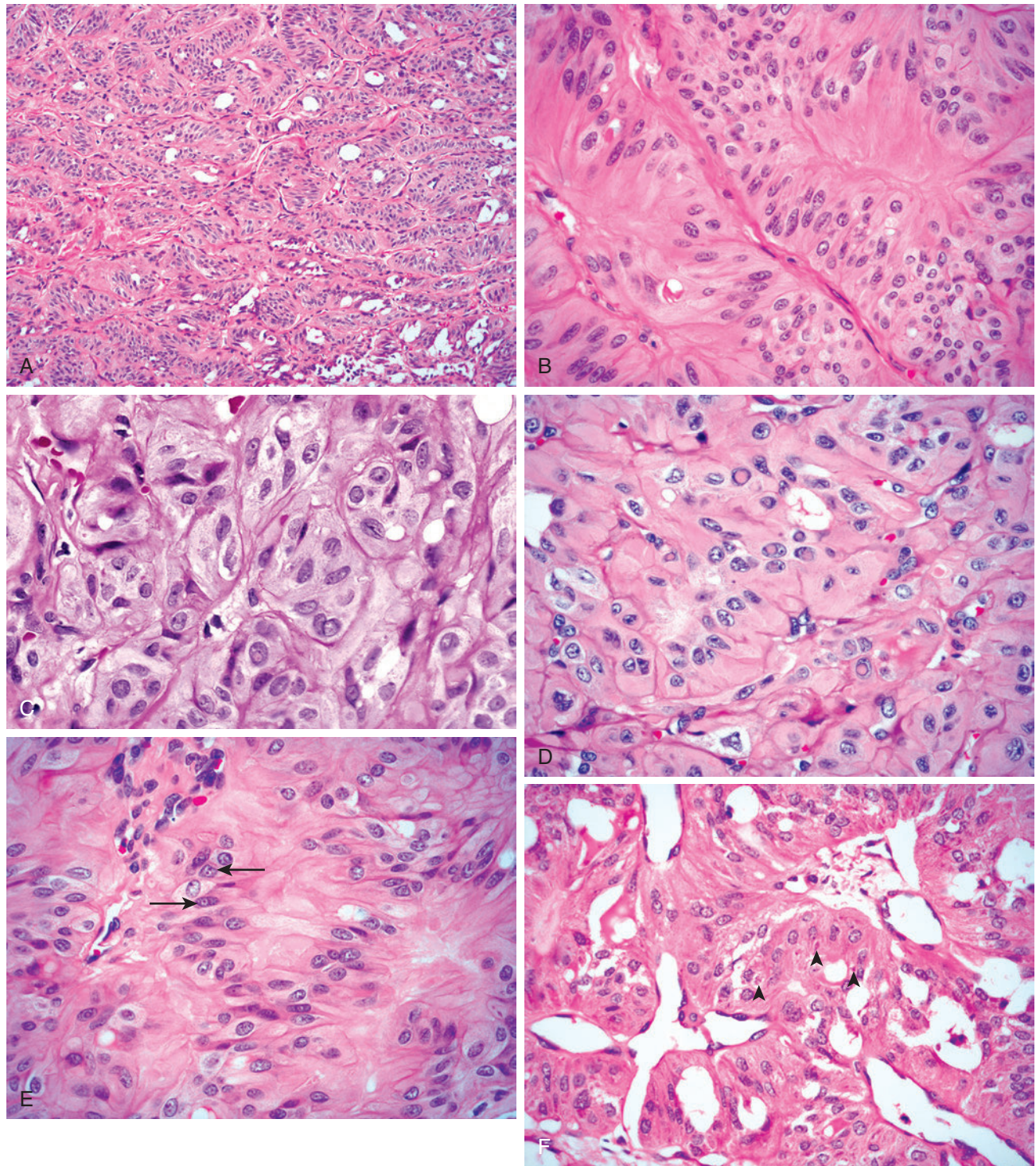


Fig. 28-10. Hyalinizing trabecular adenoma/tumor.

Tumor characterized by **(A)** trabecular and organoid (cell nest; paraganglioma-like) growth pattern with fibrovascular stroma (paraganglioma-like) and prominent hyalinization; numerous variably sized cystic spaces are characteristically present; **(B)** elongated cells that may be oriented perpendicular to the fibrovascular stroma; **(C)** oval to elongated nuclei with irregularities in size and shape, nuclear grooves, and finely dispersed nuclear chromatin; **(D)** eosinophilic nuclear (pseudo) inclusions that may be numerous in any given case; **(E)** perinucleolar halos (*arrows*); and **(F)** yellow bodies (*arrowheads*) often located close or adjacent to and indenting nuclei (paranuclear) appearing surrounded by clear halo.

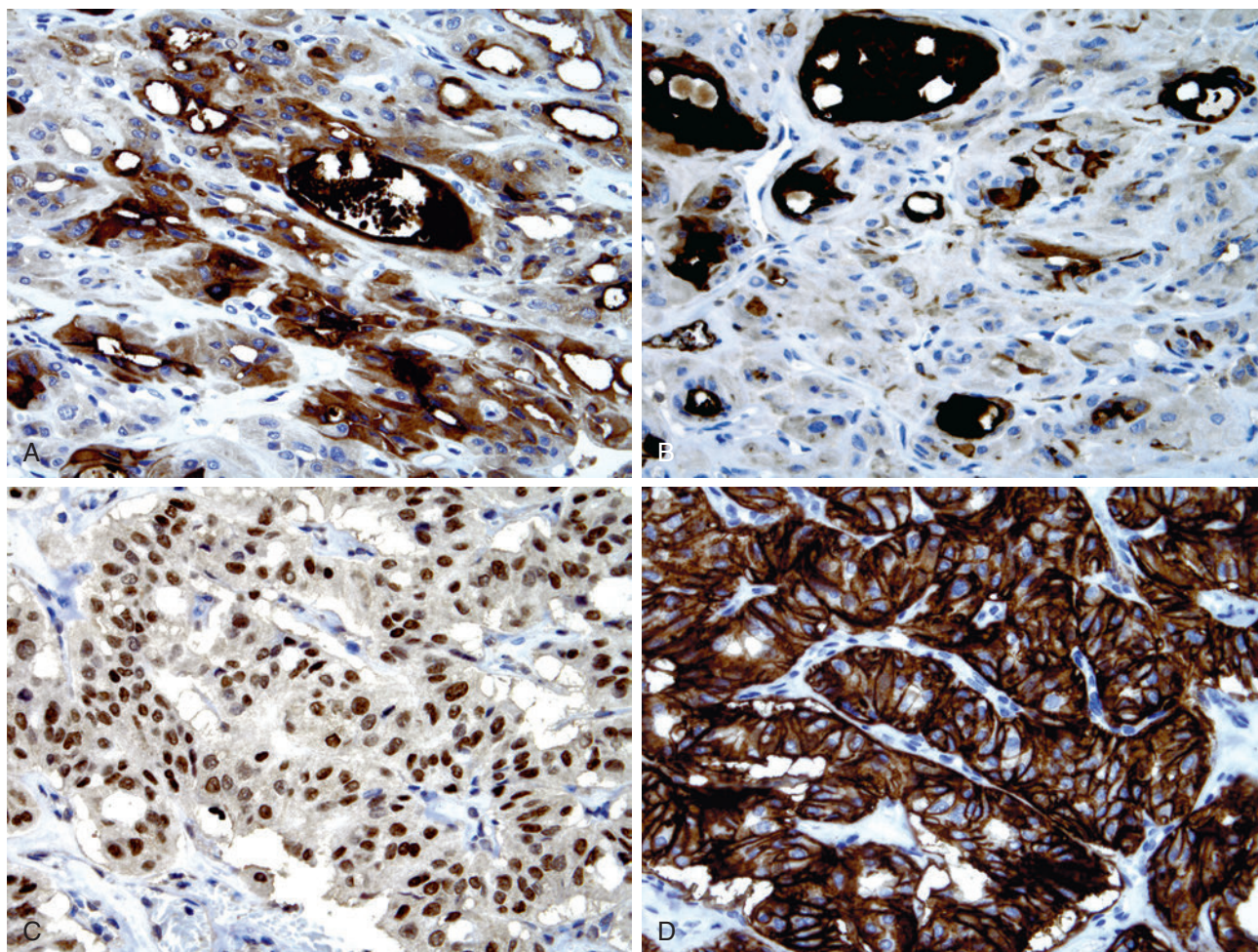


Fig. 28-11. Hyalinizing trabecular adenoma/tumor, immunohistochemical staining.

Immunohistochemical staining in hyalinizing trabecular adenoma/tumor includes **(A)** thyroglobulin with staining of lesionsal cells as well as follicles and cysts but **(B)** may be limited to follicles and microcysts with minimal to absent staining of the lesionsal cells; **(C)** TTF-1 (nuclear staining) and **(D)** MIB-1 (Ki67) (membranous).

- May be present but uncommon in papillary thyroid carcinoma and in follicular adenomas (including oncocytic variant)
- Diff-Quik–stained smears highlighted the hyaline material (metachromatic), perinucleolar clearing, and cytoplasmic bodies.
- Overall features may suggest papillary thyroid carcinoma or even medullary thyroid carcinoma but combination of a bloody background, radially oriented cohesive cells, cells with abundant cytoplasm, nuclei with very frequent cytoplasmic inclusions and grooves, and presence of hyalin should suggest hyalinizing trabecular adenoma.

Gross

- Well-circumscribed, single, solid, encapsulated or circumscribed tumor measuring from 1 to 5 cm in diameter but usually less than 2.5 cm
- Cut surface shows tendency to appear lobulated.

Histology

- Circumscribed to encapsulated tumor characterized by trabecular to organoid growth with fibrovascular stroma:
 - Trabeculae may appear coiled.
 - Lobulated growth can be seen.
- Presence of prominent extracellular and intracellular hyalinization
- Follicle formation is minimal or absent:
 - Tumor has little colloid formation.
- Characteristically, microcysts and larger cystic spaces are seen:
 - Possibly represent abortive follicle formation
- Cells are elongated and sharply outlined oriented perpendicular to fibrovascular stroma.
- Nuclei are round, oval, or elongated with
 - Nuclear grooves
 - Eosinophilic nuclear (pseudo)inclusions

- Perinucleolar halos:
 - Represent giant lysosomes as seen by electron microscopy
- Cytoplasm is finely granular with acidophilic, amphophilic, or clear appearance.
- Cytoplasmic yellow bodies common and frequent finding representing very useful finding in FNAB or in surgical pathology material in diagnosis:
 - On H&E staining, appear as solid, round, pale yellow cytoplasmic inclusions surrounded by clear halo
 - Are refractile with a microvacuolated or granular substructure
 - Located close to the nucleus (paranuclear) sometimes indenting the nucleus resulting in semilunar deformity of nucleus (nuclear molding); rarely, may be intranuclear
 - Positive staining with PAS, GMS, alcian blue-PAS, Sudan black B
 - Ultrastructurally, cytoplasmic intermediate filaments, myelinosomes with parallel whorled and stacked membranes (“fingerprint” bodies), swollen mitochondria and huge membrane-limited organelles composed of disrupted membranes and microtubules, vesicles, and myelinosomes with “fingerprint” bodies; the organelles may occupy a semilunar depression in the nucleus.
 - Yellow bodies are consistent with giant lysosomes.
 - Yellow bodies are uncommon but may be identified in other thyroid neoplasms, including papillary carcinoma, follicular carcinoma, follicular adenoma or carcinoma with oncocytic cells
- Calcifications including calcified colloid and/or psammoma body-like formations can be seen.
- Chronic lymphocytic thyroiditis is often found in surrounding thyroid gland.
- Occasional mitotic figure may be identified
- Histochemistry:
 - Hyalinized foci may suggest presence of amyloid but staining for amyloid including Congo red is negative.
- Immunohistochemistry:
 - Thyroglobulin and TTF-1:
 - Thyroglobulin may be limited to follicles and microcysts.
 - TTF-1 (nuclear staining) present in lesional cells
 - Unique cell membrane and cytoplasmic granular immunoreactivity for MIB-1 (Ki67):
 - Present with some monoclonal antibodies but not polyclonal antibodies suggesting this staining is artifactual
 - Calcitonin, chromogranin, synaptophysin negative
 - Galectin-3 expression may be present:

- Variable expression; seen in some but not all cases and when present is never as intense as might be present in papillary thyroid carcinoma

- Until recently HBME-1 negative but immunoreactivity reported with staining of lesional cells and intratrabecular hyaline matrix material identified
- CD56 reactivity (membranous) may be present.
- Discrepant results reported for high-molecular-weight cytokeratins and CK19
- Cytogenetics and molecular genetics:
 - Presence of *RET/PTC* somatic translocations with similar (or greater) frequency to that of thyroid papillary carcinoma.
 - Absence of *BRAF* mutation
 - Micro (mi)-RNAs known to be upregulated in PTC not found in hyalinizing trabecular adenoma

Differential Diagnosis

- Other thyroid lesions/neoplasms with trabecular growth and hyalinization:
 - Adenomatoid nodules
 - Lymphocytic thyroiditis
- Papillary thyroid carcinoma
- Medullary thyroid carcinoma
- Paraganglioma

Treatment and Prognosis

- Conservative surgery (lobectomy or subtotal thyroidectomy)
- Excellent prognosis following surgical removal

Additional Notes

- Hyalinizing trabecular neoplasms with minimally invasive growth have been identified and termed.

Hyalinizing Trabecular Carcinoma

- Considered to be malignant counterparts of hyalinizing trabecular adenoma:
- Extremely rare:
 - Some cases reported may in fact represent cribriform-morular variant of papillary thyroid carcinoma that may be associated with familial-adenomatous polyposis (FAP)
 - Measure from 2.5 to 4 cm
 - Histology is identical to that hyalinizing trabecular adenoma except there is capsular and/or vascular invasion.
 - These minimally invasive tumors are biologically low grade.
- Conservative surgical removal is indicated with close follow-up.

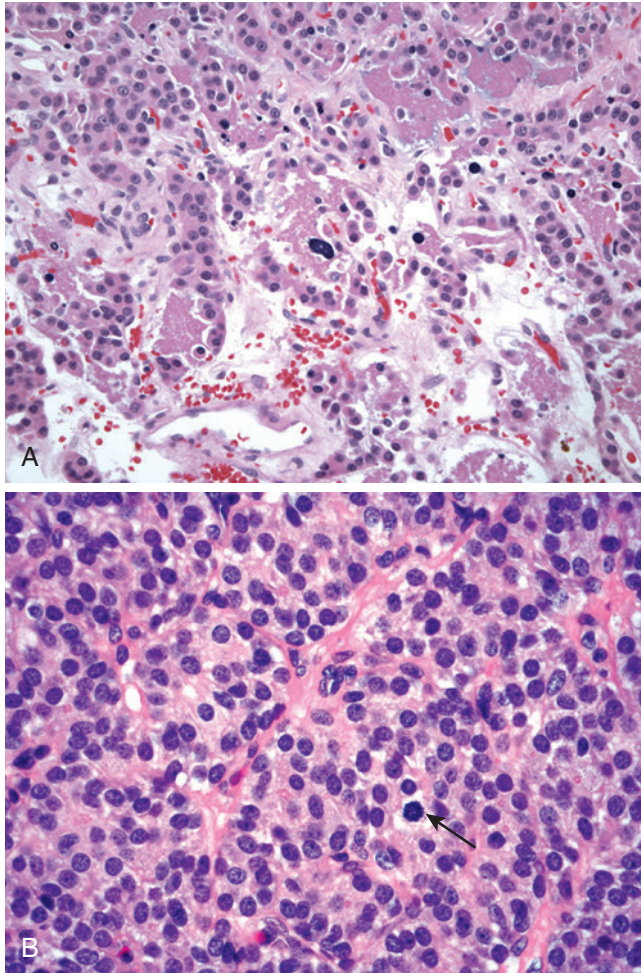


Fig. 28-12. Atypical follicular adenoma.

Follicular adenoma with atypical features may include tumors with (A) necrosis and nuclear atypia; (B) increased mitotic activity (arrow). In such tumors definitive features for carcinoma including invasive growth and/or nuclear features diagnostic for papillary thyroid carcinoma are absent.

Follicular Adenoma with Atypical Features (Fig. 28-12)

Definition: Any encapsulated follicular neoplasm that lacks features for papillary thyroid carcinoma but shows histologic features suspicious for a more aggressive neoplasm (i.e., carcinoma) without definitive evidence of either capsular or vascular space invasion.

Synonyms: Atypical follicular adenoma; follicular tumor/neoplasm of uncertain malignant potential; well-differentiated (follicular) tumor of uncertain malignant potential

Clinical

- Demographics and clinical presentation similar to those of (typical) follicular adenoma

Pathology

- Macroscopic and FNAB features similar to those of (typical) follicular adenoma
- Histologic features that raise possibility of a potentially more aggressive follicular neoplasm (i.e., carcinoma) and that may be considered as “atypical” include:
 - Increased mitotic activity in absence of necrosis:
 - Benign endocrine organ neoplasms generally are amitotic, and presence of mitoses raises concern for possibility of a malignant tumor.
 - However, as an isolated finding increased mitotic activity is not indicative of malignancy.
 - In presence of necrosis consideration for a possible diagnosis of poorly differentiated thyroid carcinoma should be entertained (see under Malignant Neoplasms)
 - Necrosis (in absence of previous FNAB):
 - Presence of coagulative type necrosis considered potentially worrisome features for carcinoma (even more so than mitotic activity)
 - Pronounced cellular proliferation with diffuse nuclear atypia
 - Categorization of a tumor as being atypical or of uncertain biologic behavior may include encapsulated follicular tumors in which tumor extends only to inner half of its capsule but falling short for definitive evidence of capsular invasion, which would allow diagnosis of follicular carcinoma
- Classification of an encapsulated follicular tumor showing equivocal cytomorphologic features for papillary thyroid carcinoma or limited foci diagnostic for papillary thyroid carcinoma remains controversial:
 - If extent of change is significant/widespread (to date there is no clear definition of what constitutes “significant” or “widespread”) then diagnosis of encapsulated (noninvasive) papillary thyroid carcinoma, follicular variant, can be made although recent recommendation is to replace the term “follicular variant of PTC” with “noninvasive follicular tumor with papillary-like features.” (See under PTC in malignant neoplasms.)
 - If nuclear features are equivocal and there is no invasion, then such a tumor can be termed as an atypical adenoma.
 - If features are equivocal but there is definitive evidence of invasion, then tumor can be diagnosed as carcinoma:
 - In such circumstances specific designation of type of carcinoma (i.e., papillary versus follicular) is academic because treatment should be similar.
 - Depending on one’s level of confidence following designations can be used for a neoplasm

with invasive growth but equivocal cytomorphologic features:

- Carcinoma, favor papillary thyroid carcinoma, follicular variant
- Carcinoma, favor follicular carcinoma, minimally invasive
- Well-differentiated carcinoma, not otherwise specified
- In follicular neoplasm considered to be atypical (or in any encapsulated thyroid neoplasm with questionable features for malignancy) most critical issue is adequate and appropriate sectioning to evaluate tumor-capsule-thyroid parenchymal interface for evidence of invasive growth:
 - Guideline to number of sections considered adequate to exclude the presence of invasion include:
 - For a tumor measuring <6 cm = submit entire tumor
 - For a tumor measuring 6 cm = submit at least 10 blocks
 - For a tumor measuring >6 cm = submit one additional block per centimeter of tumor
- Cytogenetics and molecular genetics:
 - Telomerase reverse transcriptase (TERT) promoter mutations (C228T and C250T) found in many malignancies, including in thyroid carcinomas, may be present in atypical follicular adenoma (and less commonly in “usual” follicular adenoma).
 - May occur as early genetic event in thyroid follicular tumors that have not developed malignant features on routine histopathologic workup

Differential Diagnosis

- Follicular carcinoma, minimally invasive
- Adenomatoid nodules
- Papillary thyroid carcinoma, follicular variant

Treatment and Prognosis

- Treatment is surgical removal (similar to usual types of follicular adenomas):
 - Surgery is conservative in extent limited to the affected portion(s) of the thyroid gland (lobectomy or subtotal thyroidectomy).
 - Prognosis is excellent.
 - Long-term follow-up shows atypical follicular adenomas to behave in a benign course.

FOLLICULAR ADENOMAS CLASSIFIED BY CELL TYPE OR GROWTH PATTERN

- All have similar demographics, clinical presentation, treatment, and biology as “conventional” follicular adenomas.

Follicular Adenoma with Clear Cells

(Figs. 28-13 and 28-14)

- Predominantly or exclusively composed of cells with clear (empty) to finely granular-appearing cytoplasm:
 - Clear-appearing cytoplasm may be due to:
 - Massively dilated mitochondria appearing as intracytoplasmic vesicles on electron microscopy
 - Intracytoplasmic glycogen, lipid, or mucin accumulation
 - Intracytoplasmic thyroglobulin deposition:
 - Intracellular thyroglobulin accumulation may be related to effects of thyroid stimulating hormone (TSH) causing increased thyroglobulin deposition within cell cytoplasm due to inability of cell to release or excrete it.
 - Clear cell change may be closely linked to oncocytic cell change representing “end-stage” cytoplasmic changes of a tumor that once was predominantly oncocytic.
- Nuclei are centrally situated, are small, round, and regular with hyperchromasia with or without sharp cell outlines.
- Growth pattern is usually follicular but may include trabecular or solid growth.
- Colloid-containing follicles may be absent or only focally identified; periodic acid Schiff (PAS) is helpful in identifying the presence of colloid.
- Histochemistry:
 - Diastase-sensitive, PAS-positive intracytoplasmic material
- Immunohistochemistry:
 - Thyroglobulin, TTF-1 (nuclear), and PAX8 (nuclear) positive but may be focal and of limited intensity
 - Calcitonin and neuroendocrine cell markers (chromogranin and synaptophysin) negative
 - CD10, renal cell carcinoma (RCC) antibody, carbonic anhydrase IX (CAIX), PAX2, PAX8 negative

Differential Diagnosis

- Metastatic renal cell carcinoma (Table 28-8)
- Follicular carcinoma with clear cells
- Papillary thyroid carcinoma
- Parathyroid lesions
- Medullary thyroid carcinoma with clear cells

Follicular Adenoma with Signet Ring Cells (Fig. 28-15)

Synonym: Signet ring cell adenoma

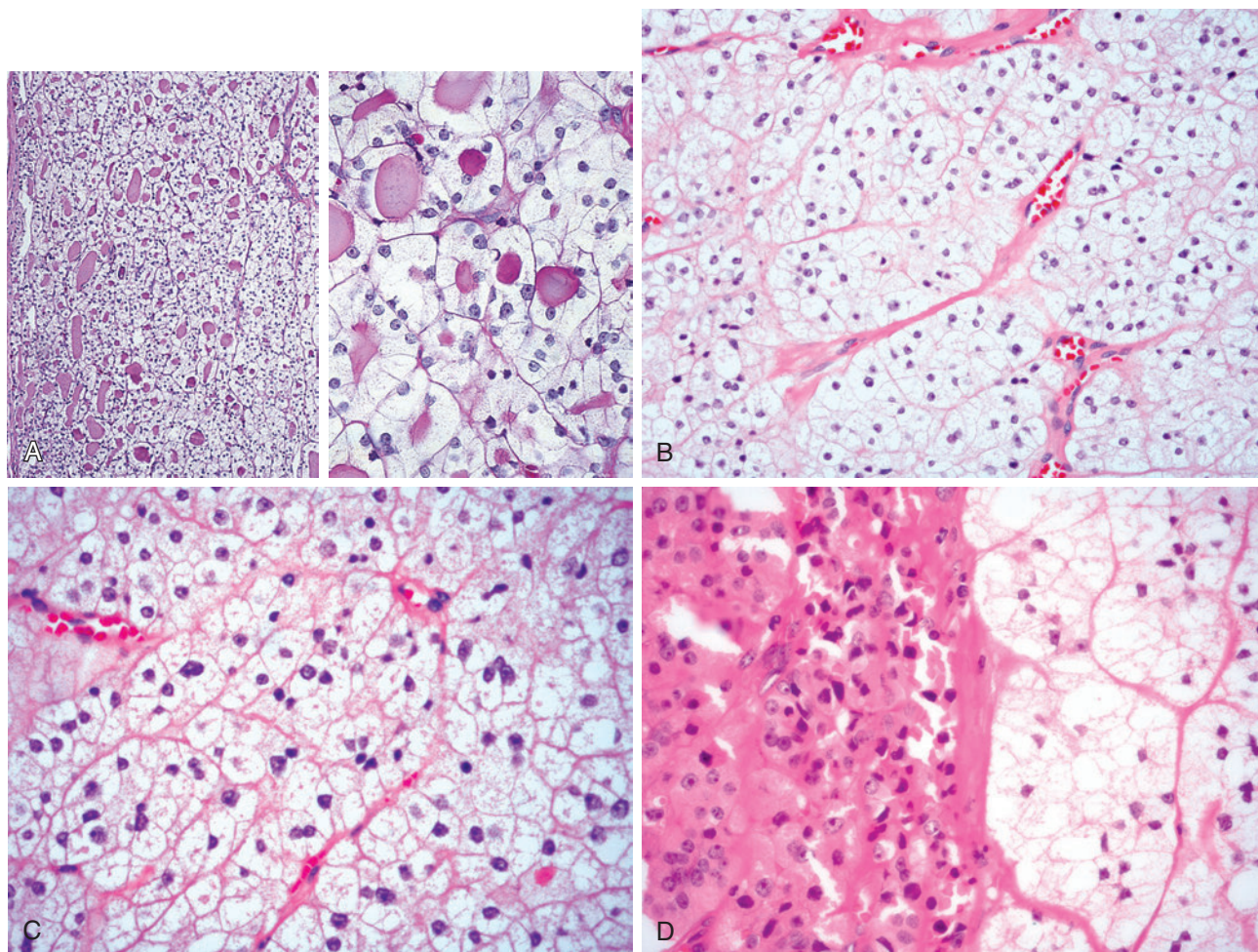


Fig. 28-13. Follicular adenoma with clear cells.

A, Left, Solitary encapsulated thyroid tumor with a nested growth and readily apparent colloid-filled follicles; **right,** colloid-filled follicles with small round to oval hyperchromatic nuclei and characteristic clear cytoplasm. **B and C,** In this example there is no evident colloid formation, potentially raising concern for a possible diagnosis of metastatic renal cell carcinoma. Immunohistochemical staining (see next image) confirms the diagnosis of a follicular adenoma with clear cells. **D,** Juxtaposition of cells with clear cytoplasm (*right side*) and cells with oncocytic cytoplasm (*left side*). Clear cell change may be closely linked to oncocytic cell change representing “end-stage” cytoplasmic changes of a tumor that once was predominantly oncocytic.

Pathology

Fine-Needle Aspiration

- Signet ring cells are round to oval, with large cytoplasmic vacuoles and hyperchromatic, eccentric nuclei.
- Colloid in the background may be scanty.

Histology

- Characterized by cells that have large intracytoplasmic vacuoles that result in eccentric displacement of cell nucleus creating a signet ring appearance:
 - Cytoplasm appears clear to acidophilic to finely granular.
- Nuclei are hyperchromatic and flattened or semi-lunar in appearance but may retain a rounder appearance.
- Growth pattern is microfollicular and nested; colloid is readily apparent.
- Histochemistry:
 - Diastase-resistant, PAS-positive intracytoplasmic material
 - Mucicarmine and alcian blue may be positive.
 - Thyroglobulin is a sialic acid-containing glycoprotein, and therefore thyroglobulin will stain with periodic acid Schiff (PAS) and acid mucin stains (e.g., alcian blue at pH 2.5, sulfomucin).

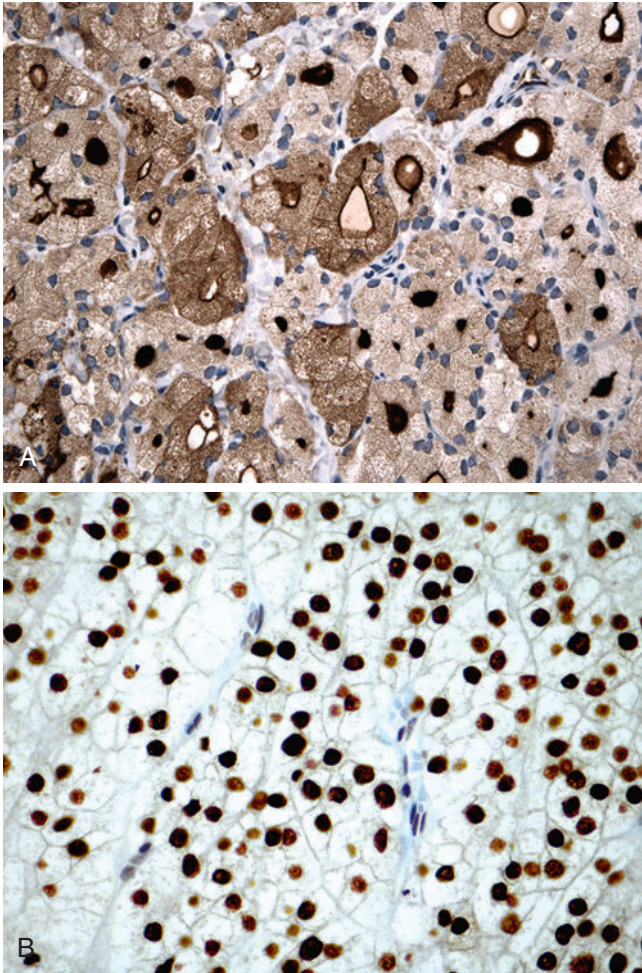


Fig. 28-14. Immunohistochemical staining in follicular adenoma with clear cells.

Immunohistochemical staining in a follicular adenoma with clear cell change includes **(A)** thyroglobulin (strong staining of colloid and granular cytoplasmic staining); **(B)** TTF-1 (nuclear). Such findings differentiate a follicular adenoma with clear cells from metastatic renal cell carcinoma.

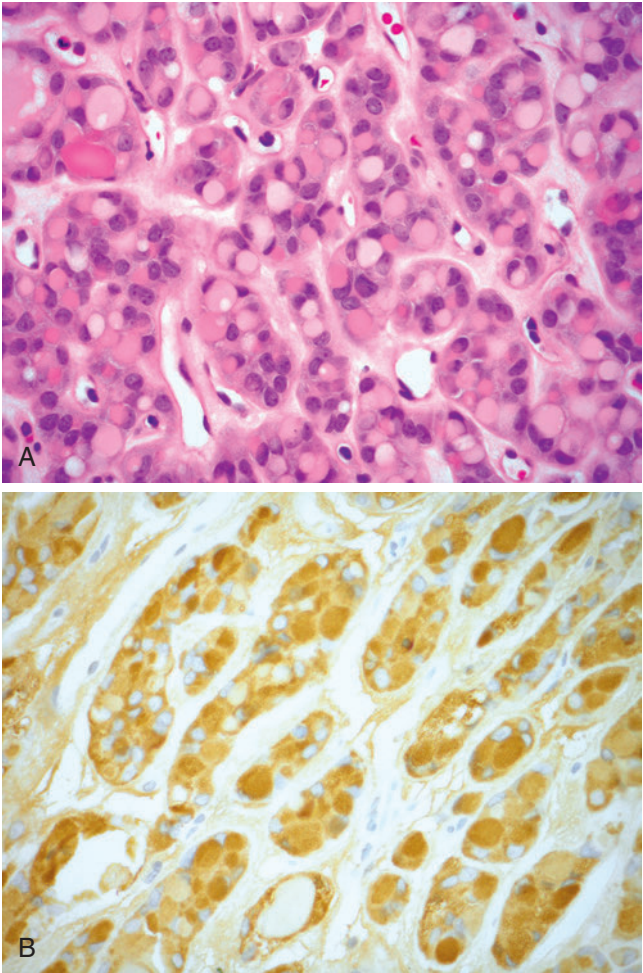


Fig. 28-15. Follicular adenoma with signet ring cells.

A, Characteristically the cells have large intracytoplasmic vacuoles resulting in eccentric displacement of nucleus and creating a signet ring appearance; cytoplasm appears acidophilic to eosinophilic. **B**, Thyroglobulin reactivity is present.

TABLE 28-8 Follicular Tumors with Clear Cells versus Metastatic Renal Cell Carcinoma

Features	Follicular Adenoma/Carcinoma with Clear Cells	Metastatic Renal Cell Carcinoma
Luminal secretion	Colloid; will be PAS positive	No colloid; red blood cells; pseudofollicles
Nested growth with fibrovascular stroma	Present	Present
Cytoplasm	Foamy appearing	Clear with distinct cell borders
Nuclear	Round; dispersed or coarse chromatin	Small, round, hyperchromatic
Glycogen (diastase-sensitive, PAS-positive)	Yes, but colloid will be diastase resistant	Yes; intensely positive
IHC findings	Thyroglobulin, TTF-1, PAX8 positive; CD10, RCC, CAIX, PAX2 negative	Thyroglobulin, TTF-1 negative CD10, RCC, CAIX, PAX2, PAX8 positive

CAIX, Carbonic anhydrase IX; IHC, immunohistochemistry; RCC, renal cell carcinoma antibody; TTF-1, thyroid transcription factor 1.

- Mucicarmine, a stain for neutral mucins, is positive but usually weakly positive:
 - Mucicarminophilia seen in the signet ring cells is attributed to intracytoplasmic thyroglobulin accumulation.
- Immunohistochemistry:
 - Strong thyroglobulin reactivity is present:
 - Intense thyroglobulin immunoreactivity correlates to intracytoplasmic thyroglobulin deposition that, in turn, gives cell its signet ring appearance.
 - Intracellular thyroglobulin accumulation may be related to effects of thyroid-stimulating hormone (TSH), causing increased thyroglobulin deposition within cell cytoplasm due to inability of cell to release or excrete it.
 - Weak thyroglobulin staining may be present in a given example.
 - TTF-1 and PAX8 (nuclear) immunoreactive
 - Calcitonin and neuroendocrine cell markers (chromogranin and synaptophysin) are negative.

Differential Diagnosis

- Metastatic adenocarcinoma (lung, gastrointestinal tract)

Follicular Adenoma with Intracellular Fat Droplets (Fig. 28-16)

Synonym: Lipid-rich adenoma

- Follicular adenoma with fat is extremely rare.
- Fat in follicular epithelial cells may occur as a result of aging.

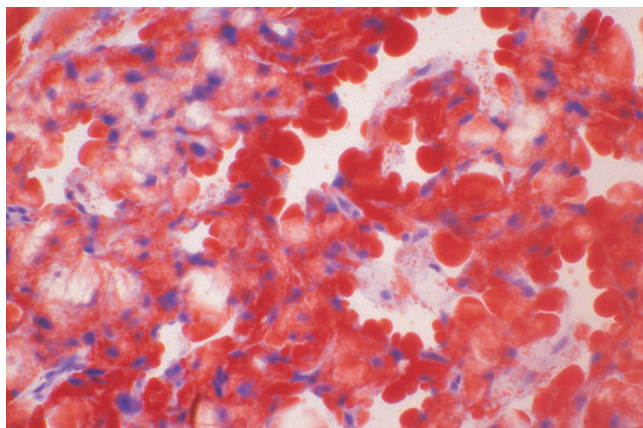


Fig. 28-16. Lipid-rich cell adenoma.

Oil red O stain for fat is positive. This tumor was characterized by cells with small to medium-sized intracytoplasmic vesicles that resulted in indentation of the centrally situated nucleus.

- Characterized by cells that have small to medium-sized intracytoplasmic vesicles that result in indentation of centrally situated nucleus.
- Histochemistry:
 - Oil red O or other fat stains will be positive.
- Immunohistochemistry:
 - Thyroglobulin and TTF-1 positive

Differential Diagnosis

- Thyrolipoma

Mucinous Follicular Adenoma or Follicular Adenoma with Mucinous Stroma (Fig. 28-17)

- Characterized by presence of abundant extracellular basophilic-appearing mucin
- Growth patterns include microcystic, reticular, or multicystic

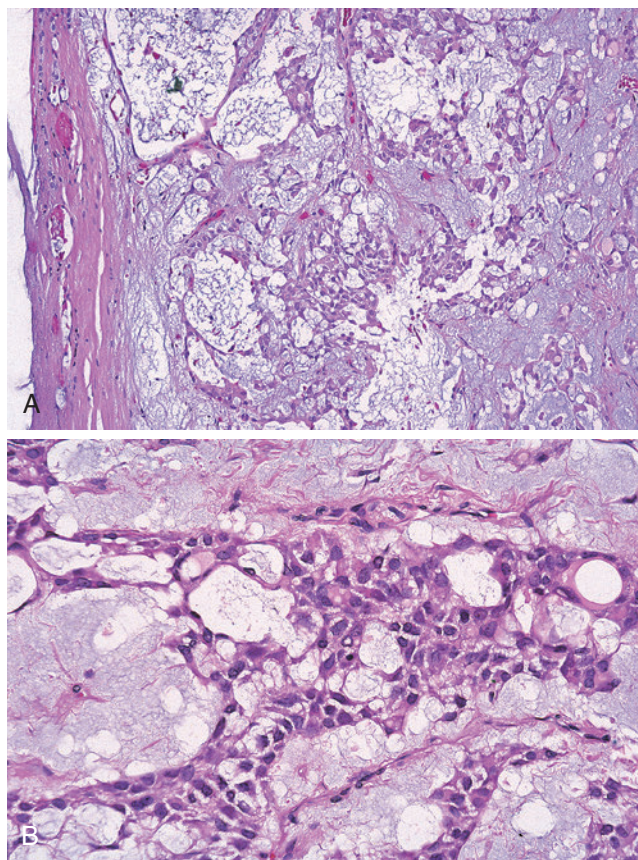


Fig. 28-17. Follicular adenoma with mucinous stroma.

A, B, Encapsulated tumor showing variable cellularity characterized by presence of abundant extracellular basophilic-appearing mucin. The growth patterns include microcystic and reticular. The cells were thyroglobulin positive (not shown).

- Mucinous pools may be present.
- Signet ring cells may be identified.
- Extracellular mucin stains with alcian blue and colloidal iron but not with mucicarmine and DPAS
- Tumor cells positive for thyroglobulin and negative for calcitonin, CEA, galectin-3, HBME-1, and CK19
- Considered a degenerative phenomenon

Additional Alterations in Follicular Adenomas

- Follicular adenoma with spindle cell metaplasia (Fig. 28-18)
 - Variably seen in a given tumor:
 - May be focal or more diffuse
 - Short fascicles, storiform, or whorling growth
 - Bland cytomorphology lacking significant pleomorphism, mitotic activity, necrosis, or invasive growth
 - No cytomorphologic features diagnostic of papillary thyroid carcinoma
 - Immunoreactivity for:
 - Thyroglobulin, TTF-1, PAX8, and cytokeratin
 - Low proliferation indices (MIB1 or Ki67)
 - Spindle cell metaplasia can also be seen in adenomatoid nodules, follicular carcinoma, papillary thyroid carcinoma, and medullary thyroid carcinoma.
- Follicular adenoma with papillary architecture (Fig. 28-19)
 - Referred to as follicular adenoma with papillary hyperplasia or papillary adenoma
 - These lesions:
 - Have a tendency to occur in children and adolescents
 - Have papillae that often are wider as compared to the more narrower-appearing papillae seen in papillary thyroid carcinoma
 - Despite papillary architecture lack cytomorphology of papillary thyroid carcinoma
 - Have a benign biologic course
- Follicular adenoma bizarre nuclei (Fig. 28-20)
 - Presence of scattered bizarre hyperchromatic and pleomorphic nuclei in an otherwise usual follicular adenoma
 - Nuclear changes referred to as endocrine atypia
 - Cells are immunoreactive for thyroglobulin, TTF-1 (nuclear), and PAX8 (nuclear)
 - Negligible to low proliferation rate by Ki67 staining
- Follicular adenoma with mesenchymal cell components (Fig. 28-21)
 - Associated mesenchymal components may include:
 - Lipomatous stroma (thyrolipoma, adenolipoma)
 - Cartilage (chondroid metaplasia)
 - Bone (chondroid and osseous metaplasia)
 - Smooth muscle
 - Fibrous tissue
- Post-FNAB-infarcted follicular adenoma:
 - Infarction may be partial or complete.
 - Infarction may compromise histology, making recognition of nature of lesion difficult.
 - Infarction appears as coagulative necrosis with associated hemorrhage and a variable amount of inflammatory cells
 - With time, granulation tissue and macrophages may be present.
 - Peripheral rim of residual, viable tumor may be present, which may show marked reactive nuclear atypia.
 - In infarcted foci, architectural pattern of lesion is retained despite cellular necrosis.
 - PAS staining for colloid may be helpful in recognizing lesion as a follicular epithelial neoplasm.
 - Antigenicity of tumor often is retained, including cytokeratin and thyroglobulin reactivity.
 - Tumors with cytoplasmic oxyphilia due to high content of oxygen-sensitive mitochondria are more easily traumatized, potentially resulting in infarction and additional retrogressive changes.
- Hyperfunctioning adenoma (toxic or “hot” adenoma)
 - Rare occurrence
 - Associated with symptoms of hyperthyroidism due to autonomous production of thyroxine
 - “Hot” appearance on radioactive iodine scanning
 - Histologically shows hyperplastic foci with papillary growth with follicles lined by tall cuboidal cells
 - Histology reminiscent of that seen in Graves disease

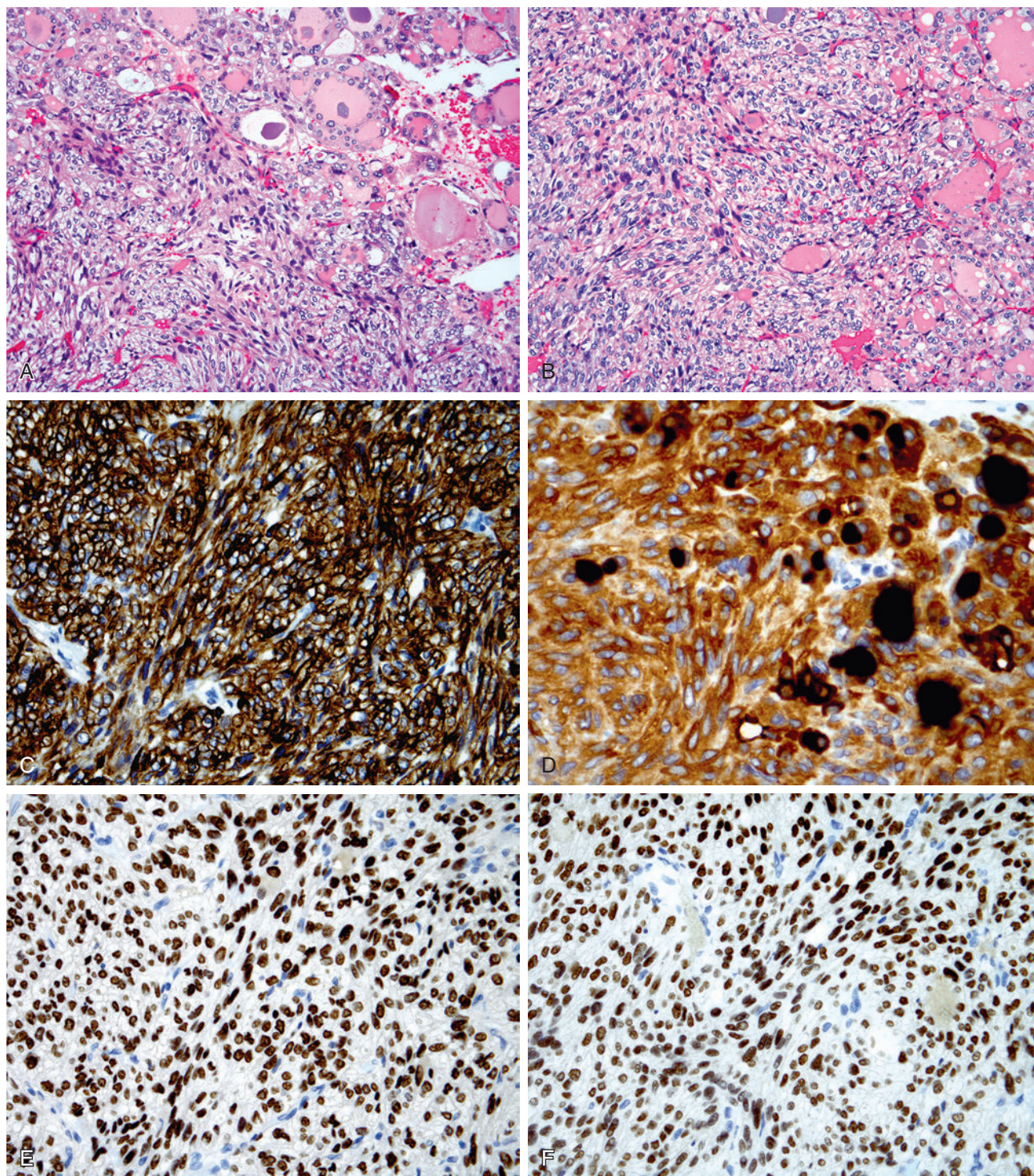


Fig. 28-18. Follicular adenoma with spindle cells.

A, This encapsulated tumor showed foci of follicular adenoma (*upper right*) adjacent to areas composed of spindle-shaped cells with storiform growth and no evidence of colloid and/or follicular epithelial cell differentiation. **B**, Intimate admixture of colloid-filled thyroid follicles and spindle cells lacking evidence of follicular cell derivation is seen. Immunohistochemical staining shows the spindle cells to be reactive for **(C)** cytokeratin (AE1/AE3), **(D)** thyroglobulin, **(E)** TTF-1 (nuclear), and **(F)** PAX8 (nuclear).

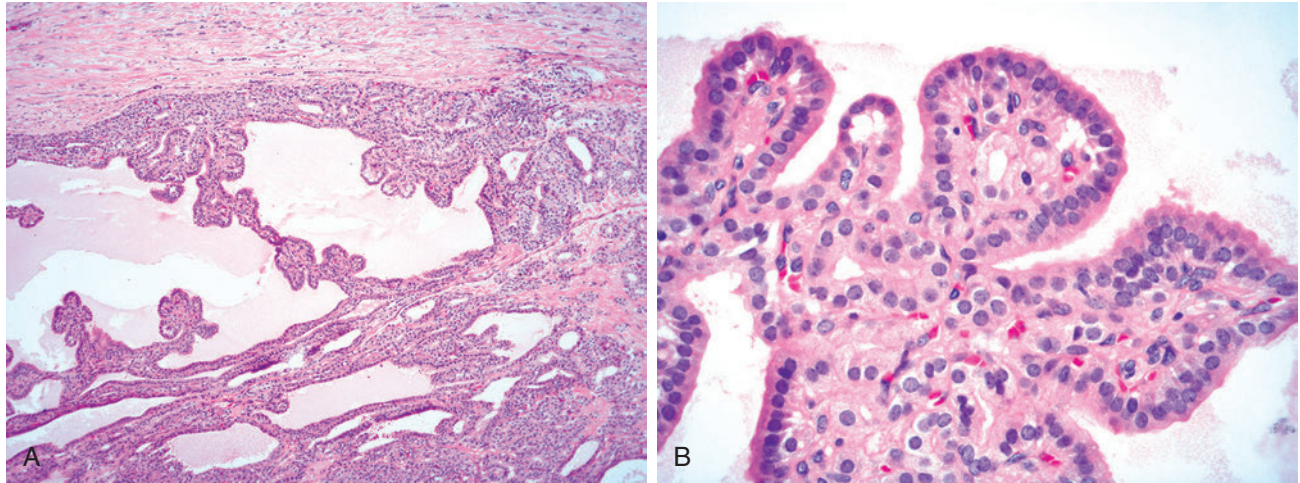


Fig. 28-19. Follicular adenoma with papillary architecture.

A, Encapsulated follicular neoplasm with foci of papillary architecture. **B**, The nuclei are small, round to oval with coarse nuclear chromatin and aligned along the basal aspect of the cells lacking nuclear features diagnostic for papillary thyroid carcinoma. The papillae tend to be wider than the narrower appearance of papillae typically seen in papillary thyroid carcinoma.

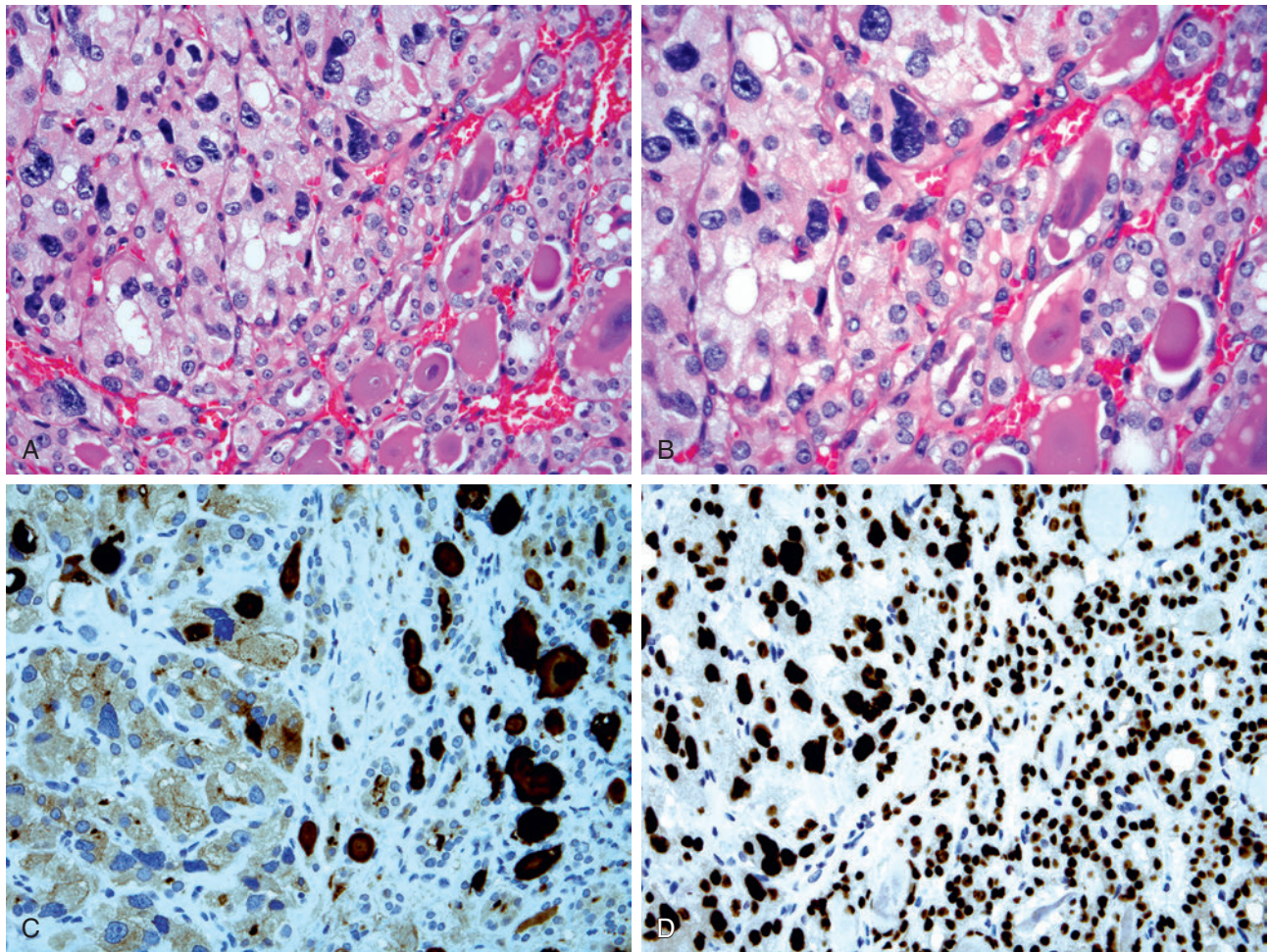


Fig. 28-20. Follicular adenoma with nuclear atypia (endocrine atypia).

A and **B**, Focal areas of follicular adenoma showing the presence of bizarre hyperchromatic and pleomorphic nuclei. Such nuclear changes are referred to as endocrine atypia. The fact that these changes are focal and not diffuse and lacking other features that may raise concern for malignancy (e.g., necrosis, mitotic activity, invasion) should allow for a diagnosis of a benign (reactive) proliferation. Typical and bizarre cells are immunoreactive for **(C)** thyroglobulin and **(D)** TTF-1 (nuclear).

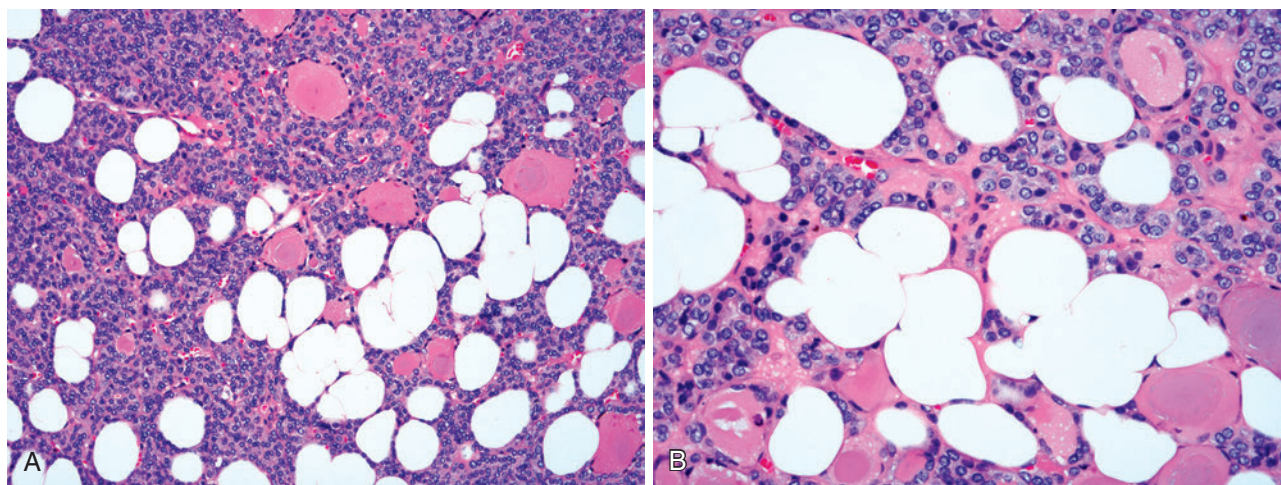


Fig. 28-21. Follicular adenoma with mesenchymal components.

A, B, In this example mature adipose tissue is intimately admixed with the adenoma (thyrolipoma; adenolipoma). Other mesenchymal components that can be seen in follicular adenomas may include cartilage, bone, smooth muscle, and fibrous tissue (not shown).

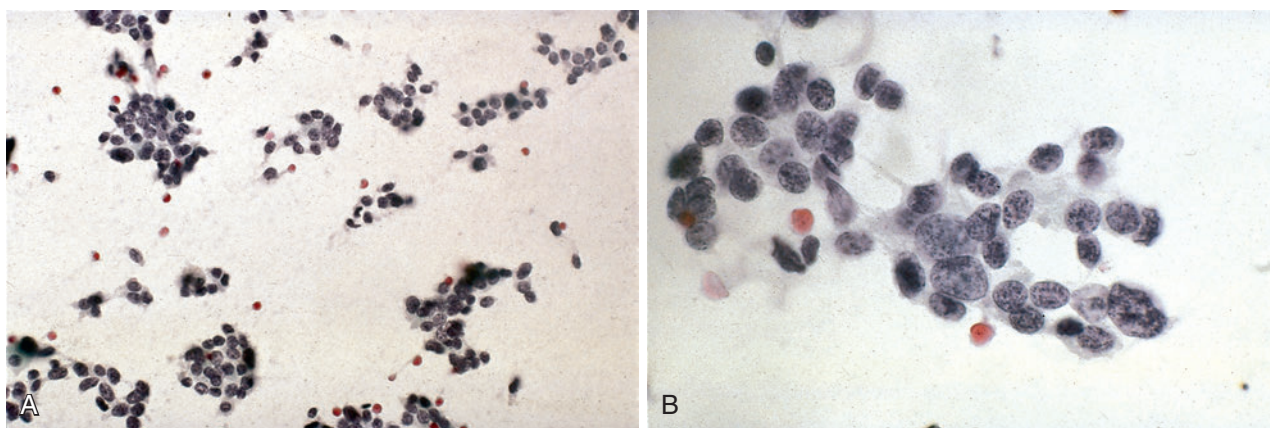


Fig. 28-22. Fine-needle aspiration biopsy of a solitary, solid thyroid mass.

A, The aspirate is cellular with absent colloid. Small cell clusters with syncytial configuration are present, as are isolated cells. A microfollicular pattern is focally present. **B,** Cells are monomorphic, enlarged with uniform, round to oval nuclei with evenly distributed, finely granular (coarse) chromatin, small to inconspicuous nucleoli, and pale to clear cytoplasm with indistinct cell margins. Anisokaryosis and anisochromatosis can be seen. The FNAB diagnosis was “follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV). A lobectomy was performed and the lesion proved to be a follicular carcinoma.

MALIGNANT FOLLICULAR EPITHELIAL NEOPLASMS

FOLLICULAR CARCINOMA (FC) (Figs. 28-22 through 28-31)

Definition: Malignant follicular epithelial cell, not belonging to papillary carcinoma, characterized by

invasive growth (i.e., capsular and/or vascular invasion) and/or metastatic disease.

Clinical

- Represents approximately 10% to 20% of all malignant thyroid tumors

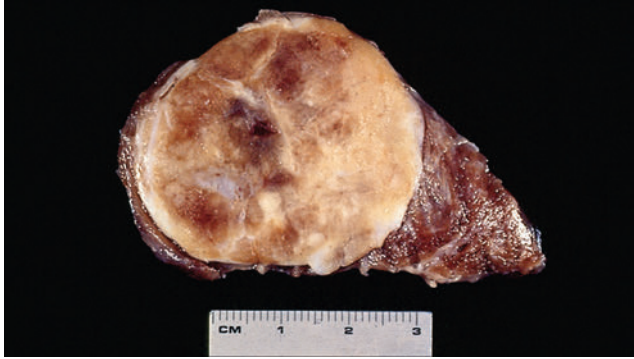


Fig. 28-23. Follicular carcinoma.

The gross appearance of this thyroid tumor is identical to that of follicular adenoma. Only following histologic evaluation with identification of invasion was a diagnosis of follicular carcinoma rendered.

- More common in women than in men; occurs over a wide age range but is most common in the fifth to sixth decades of life:
 - Approximately one decade older than patients with papillary thyroid carcinoma
 - Rare but does occur in children and adolescents
- Clinical presentation usually solitary, painless neck mass:
 - Pain may occur later in disease course.
 - Initial presentation may be as a pulmonary metastasis or pathologic fracture secondary to osseous metastasis.
- Patients are usually euthyroid:
 - Uncommonly, patients may present with clinical manifestations of hyperthyroidism.
- Radiology
 - On thyroid scan (^{123}I), most often solitary, “cold,” or hypofunctioning nodules
- Etiology:
 - Incidence greater in iodine-deficient regions of the world

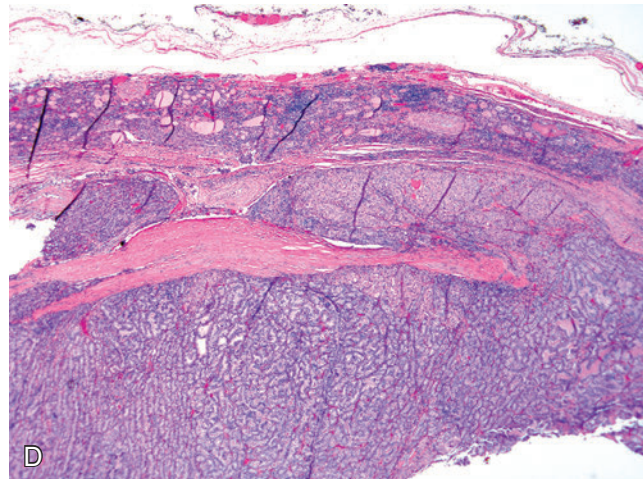
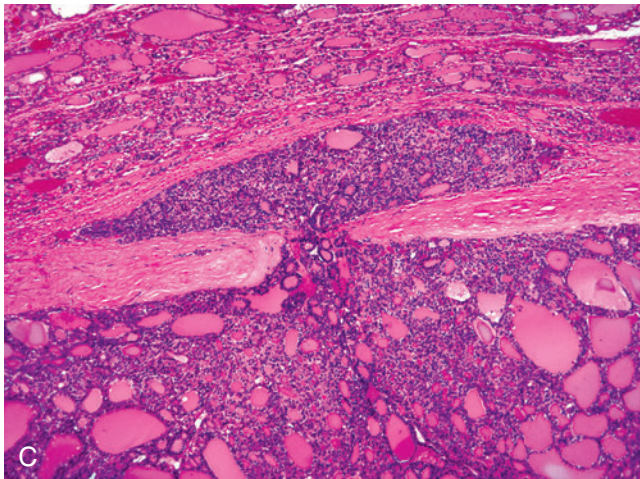
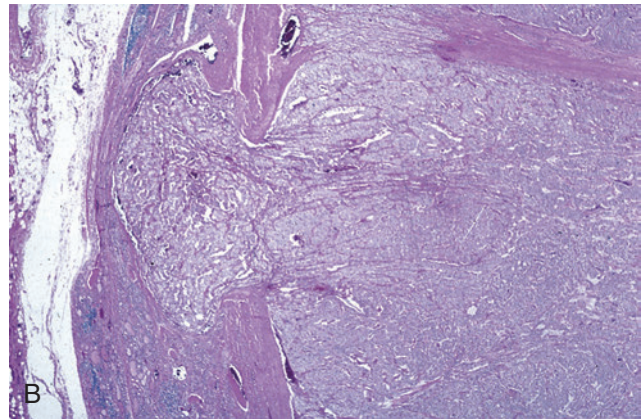
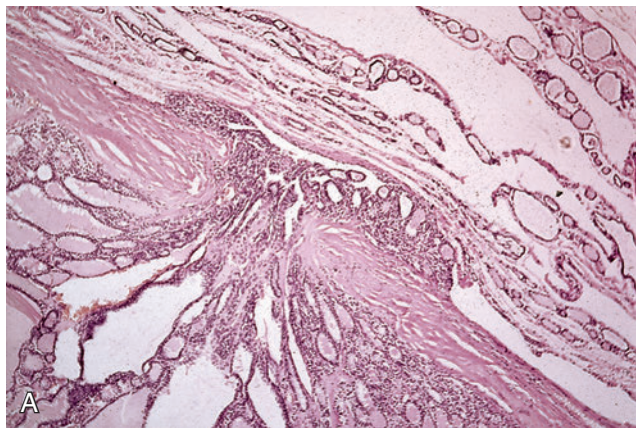


Fig. 28-24. Follicular carcinoma with capsular invasion.

Various degrees of capsular invasion but in all images the tumor transgresses the entire thickness of the capsule with varying extension beyond the capsular delimitation, including mushroom-like protrusion.

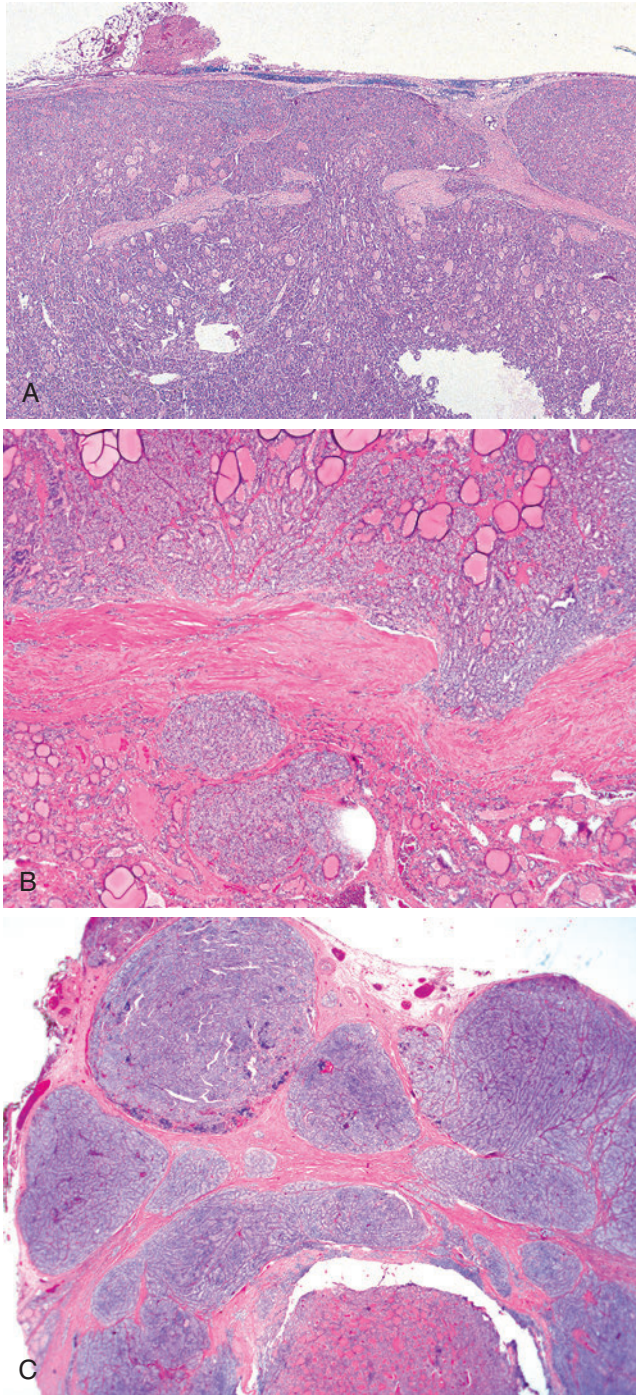


Fig. 28-25. Follicular carcinoma with capsular invasion.

A through **C**, More extensive invasion including one or more nodules separate from the main mass, some within adjacent thyroid parenchyma. **C**, Clear-cut invasion beyond capsular delimitation is present with extensive invasion such that a capsule not readily identifiable supporting a diagnosis of a widely invasive follicular carcinoma. In addition, extensive vascular invasion was present in this case (not shown).

- Partly for this reason occurs in glands that have been enlarged for long periods
- Addition of supplemental iodine to diet associated with decrease in incidence of follicular carcinoma
- Development linked to:
 - Exposure to ionizing radiation:
 - Risk not as high as compared to that associated with papillary thyroid carcinoma
 - Pre-existing thyroid disease including:
 - Follicular adenoma:
 - Direct precursor lesion to follicular carcinoma
 - Goiter (adenomatoid nodules):
 - Predisposition owing to prolonged TSH stimulation, which in turn increases rate of cell proliferation that may result in increase chance of mutations in dividing cells
 - Familial syndromes such as phosphatase and tensin homolog (PTEN) hamartoma syndrome, which includes Cowden disease and other rare syndromes:
 - Cowden disease characterized by multiple mucocutaneous hamartomas and predisposition to malignant neoplasms, mostly breast and thyroid:
 - 10% to 20% develop follicular carcinoma

Pathology

Fine-Needle Aspiration Biopsy

- Excellent screening tool in evaluation of a thyroid mass but utility limited in presence of differentiated (nonanaplastic) follicular epithelial cell lesion differentiating follicular adenoma from follicular carcinoma
 - Differentiation primarily predicated on presence or absence of invasive growth (capsular or vascular) and not cytomorphology, a feature not seen in needle aspiration
 - Often FNAB diagnosis is “follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV),” which informs treating physician that a neoplasm is present that requires surgical removal (e.g., lobectomy)
- Cellular with minimal to absent colloid
- Cells often arranged in microfollicular pattern but trabecular pattern can also be seen.
 - Small three-dimensional clusters with syncytial configuration can be seen.
 - Isolated cells are often found.
- In general, cells are monomorphic and enlarged as compared to non-neoplastic follicular epithelial cells characterized by uniform, round to oval nuclei with evenly distributed, finely granular (coarse) chromatin, small to inconspicuous nucleoli, and pale to clear cytoplasm with indistinct cell margins.

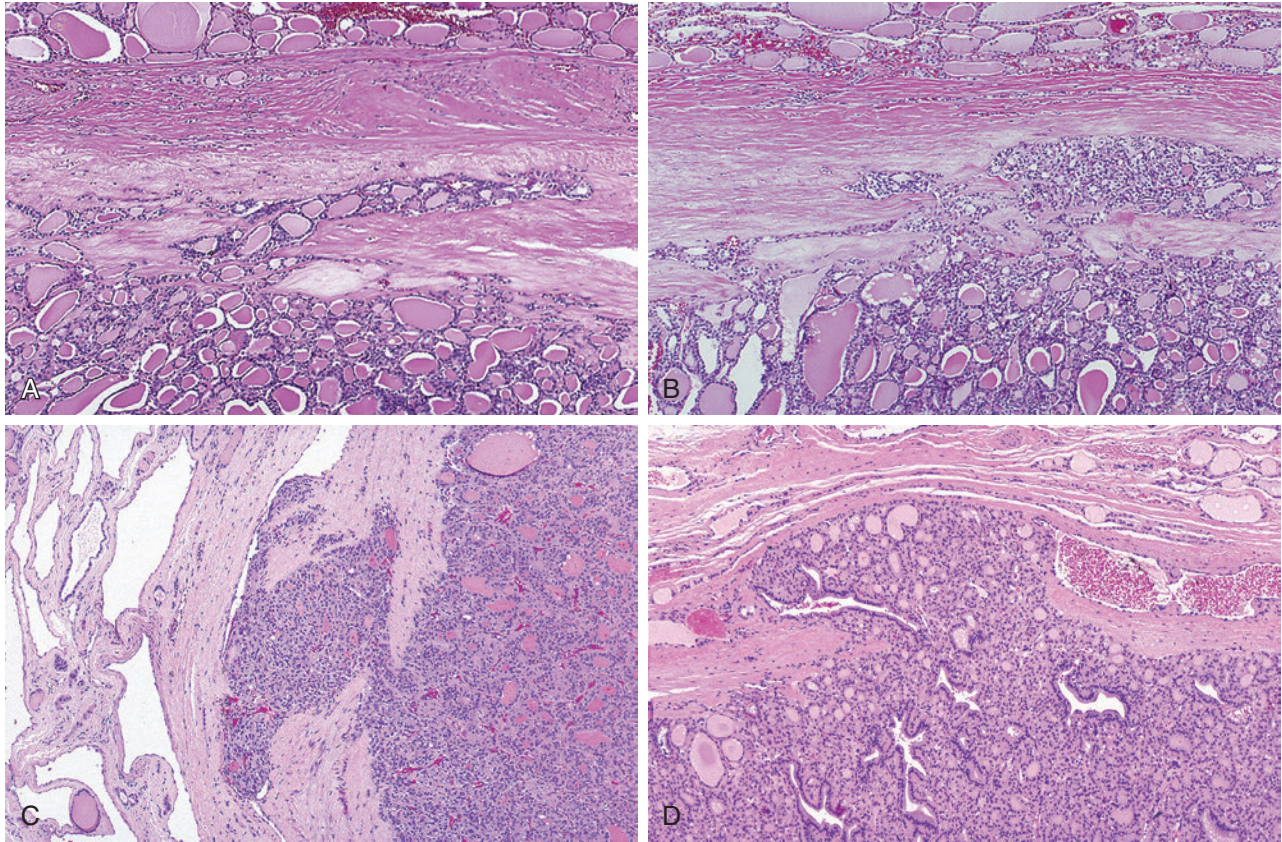


Fig. 28-26. Equivocal capsular invasion.

Follicular neoplasms with equivocal capsular invasion including **(A and B)** less than complete transgression of the entire thickness of the capsule; **(C)** tangential sectioning; **(D)** presence of intracapsular blood vessels creating distortional changes and the suggestion of capsular invasion; note the rounded or smooth contour of the external edge of the lesion lying in the same plane as the thin fibrous capsule. In these examples there was no evidence of vascular invasion and, given the less-than-diagnostic features for invasion, should be diagnosed as an adenoma (arguable with atypical features) and not carcinoma.

- Nuclei may vary in appearance:
 - Anisokaryosis and anisochromatosis can be seen.

Histology

- Similar to their benign counterparts follicular carcinomas are encapsulated tumors:
 - Typically (but not always), capsule tends to be thicker than capsule in follicular adenoma:
 - May vary in thickness from 0.1 to 0.3 cm to thicker
 - For widely invasive follicular carcinomas a distinct, readily identifiable capsule may be absent.
- In general, usually shows single architectural pattern but may show admixture of growth patterns, including:
 - Follicular and/or microfollicular:
 - Uniform-appearing colloid-filled follicles
 - Solid
 - Trabecular
 - Insular:
 - Presence of increased mitotic activity and necrosis (as well as so-called cleaved nuclei) required for diagnosis of poorly differentiated thyroid carcinoma (see later in chapter)
- Cellularity and cytologic appearance vary from tumor to tumor and even within the same tumor:
 - Tendency to demonstrate greater cellularity as compared to follicular adenoma
 - Lesional cells generally uniform with defined cell borders
 - Nuclei are:
 - Regularly shaped (round to oval), often aligned along basal aspect of cell
 - Small to medium in size, hyperchromatic with coarse nuclear chromatin
 - Absent to inconspicuous nucleoli
 - Variable amount of cytoplasm
 - Cytoplasm may be amphophilic, eosinophilic, oncocyctic, and/or clear

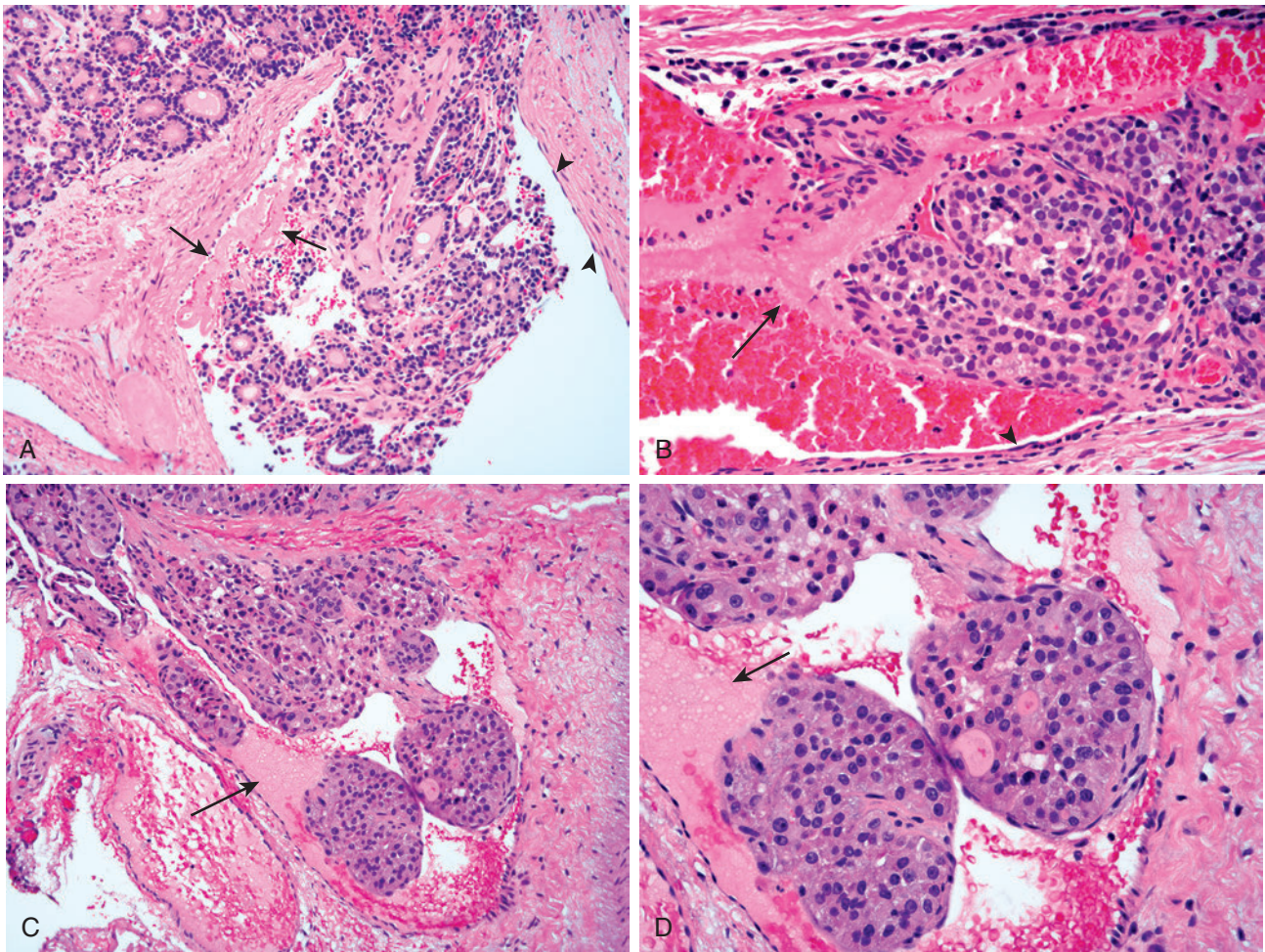


Fig. 28-27. Follicular carcinoma with vascular invasion.

In these examples the vascular spaces are either in the capsule or beyond the capsule. **A** and **B**, Tumor in endothelial lined vascular spaces (*arrowheads*) with thrombus formation (*arrows*). **C** and **D**, Tumor with direct extension/protrusion into endothelial lined blood vessel with thrombus formation (*arrows*).

- In presence of oncocytic cytoplasmic changes, nuclei may be enlarged with prominent nucleoli but retain uniformity in shape and coarse nuclear chromatin.
- Nuclear pleomorphism may be present:
 - Endocrine atypia characterized by markedly enlarged and hyperchromatic nuclei may be focally identified.
- Colloid filled follicles are generally readily apparent but in some instances may be difficult to identify:
 - Periodic acid Schiff (PAS) stains of assistance in delineating presence of colloid
- Mitotic figures can be seen but are usually uncommon:
 - Increased mitotic activity may be present in more widely invasive follicular carcinoma.
- Necrosis typically absent
- Intratumoral vascularity in form of delicate capillaries may be present but often inconspicuous by routine light microscopy.
- Retrogressive changes often seen in adenomatoid nodules not commonly present but may be seen in particular follicular carcinomas with predominance of cells with oncocytic cytoplasmic changes
- Immunohistochemistry:
 - In general, immunohistochemical staining unnecessary in diagnosis and differential diagnosis of follicular epithelial-derived tumor, including follicular carcinoma
 - Thyroglobulin most useful stain:
 - Reactivity in cytoplasm and luminal colloid
 - TTF-1 (nuclear), PAX8 (nuclear) positive
 - Cytokeratins, including AE1/AE3, CAM 5.2, CK7:
 - CK20 negative

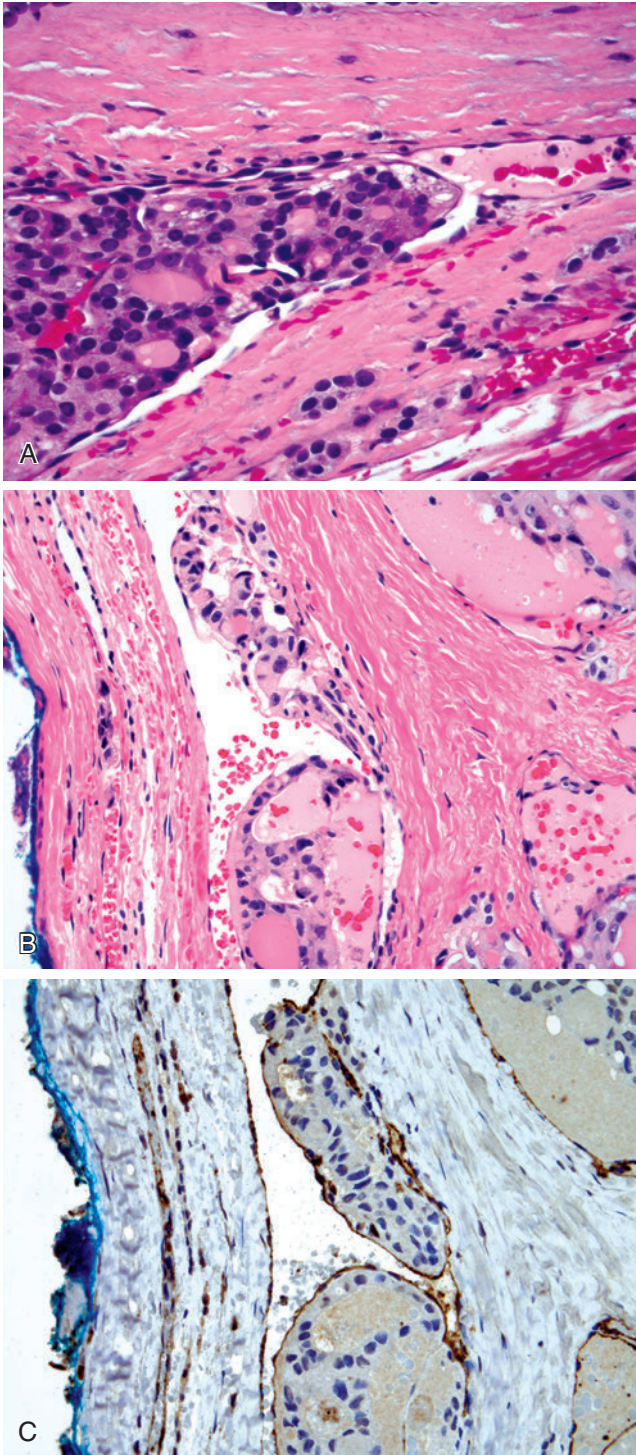


Fig. 28-28. Follicular carcinoma with vascular invasion.

A and **B**, Tumor cells invade vascular spaces covered by endothelial cell layer identified over bulging tumor nests (endothelialization). **C**, CD31 immunoreactivity assists in confirming the presence of the endothelial cells.

- Calcitonin, synaptophysin, chromogranin negative
- CD56 may be positive.
- Cytogenetics and molecular genetics:
 - *RAS* mutations
 - 30% to 50%
 - *PAX8/PPAR γ* rearrangement:
 - Occurs in approximately 20% to 50% of follicular carcinomas
 - Strong evidence of malignancy
 - Reported in approximately 8% of follicular adenomas

Invasion in Follicular Carcinoma

- Diagnosis of follicular carcinoma predicated on invasive growth, including:
 - Capsular invasion
 - Vascular invasion
 - Invasion into adjacent thyroid parenchyma and/or outside the thyroid gland (extrathyroidal extension)
- Tumors showing vascular invasion frequently also show capsule invasion.
- Although presence of invasive growth conceptually appears to be straightforward, there are discrepancies among pathologists, including experts in thyroid pathology, as to which microscopic findings constitute capsular invasion and/or angioinvasion.
- Owing to formation of fibrous tissue along advancing edge of tumor, rarely identify direct contact between lesional cells and adjacent normal thyroid parenchyma
- Certainly, diagnosis of follicular carcinoma includes presence of metastatic tumor but in general uncommon for encapsulated thyroid follicular neoplasm to metastasize in absence of invasive growth

Capsular Invasion

- Extent of capsular invasion source of contention:
 - Some authorities believe that any degree of extension of tumor into capsule qualifies as capsular invasion:
 - Too low a threshold
 - Not considered diagnostic as invasion
 - Partial invasion of capsule:
 - Owing to reported absence of recurrence or metastasis many authorities (although not all) do not accept partial capsular invasion as diagnostic for carcinoma.
 - Most authorities require penetration of entire thickness of capsule to be regarded as unequivocal evidence of capsular invasion.
- Elastic stains may be helpful in determining whether capsular invasion has occurred.
- Problematic features relative to diagnostic interpretation include:

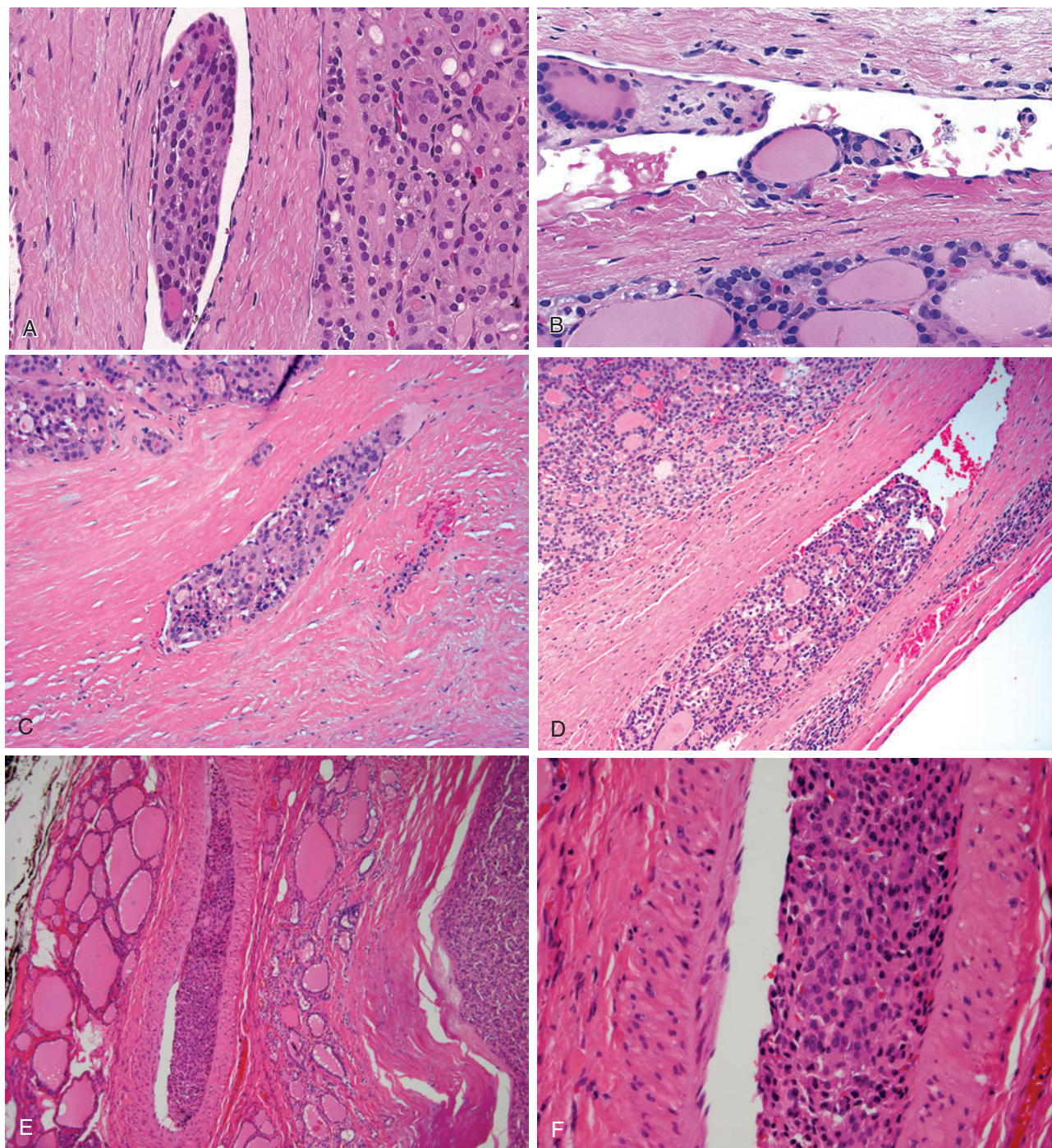


Fig. 28-29. Vascular invasion.

The strict criteria proposed for vascular invasion requiring tumor cells invading through vessel wall and endothelium with thrombus adherent to intravascular tumor may be too strict. **A** through **F**, Examples of tumor lacking the proposed strict criteria for vascular invasion but nonetheless show tumor within vascular spaces that should be considered as significant representing vascular invasion.

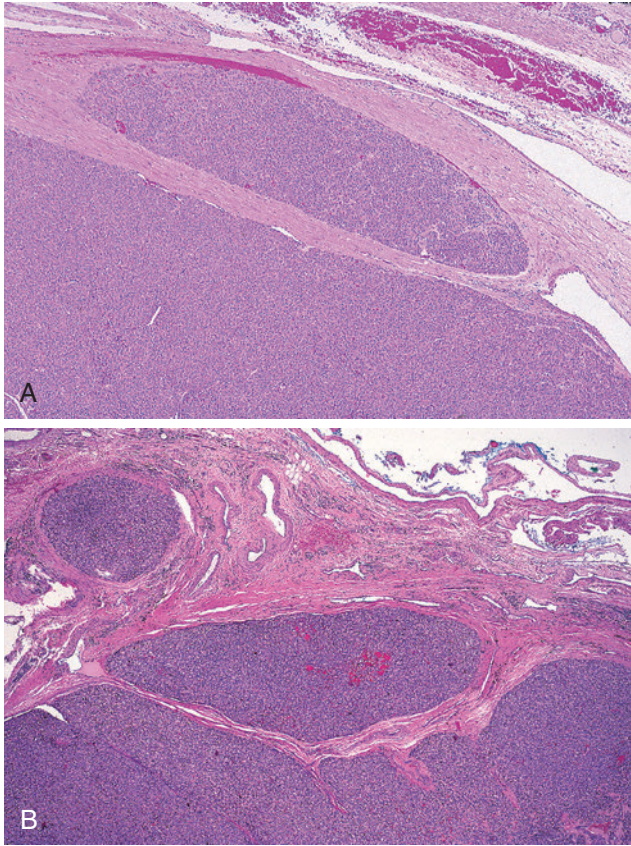


Fig. 28-30. Separate but histologically similar nodule(s).

The presence of tumor nodules separate from (but histologically similar to) the main mass within the fibrous capsule (or beyond) with rounded appearance/edges suggests vascular invasion. However, there is no clear-cut identification of endothelial cells by light microscopy and/or immunohistochemical staining for endothelial markers (e.g., CD31) and no associated thrombus formation. Multiple deeper sections fail to show continuity of the nodules to the main mass so that capsular invasion cannot be confirmed. Assuming there are no other findings that might be diagnostic for malignancy, in such cases a diagnosis of a follicular adenoma with atypical features can be considered with the caveat that a follicular carcinoma cannot be excluded.

- Irregular contour(s) of the tumor:
 - May be caused by presence of thick-walled vascular spaces in capsule
- Tangential sectioning or folding of capsule at edge of section
- Changes secondary to prior fine-needle aspiration biopsy, including capsular pseudoinvasion:
 - May take the form of a needle tract in which there is a linear-appearing “bud” into fibrous capsule

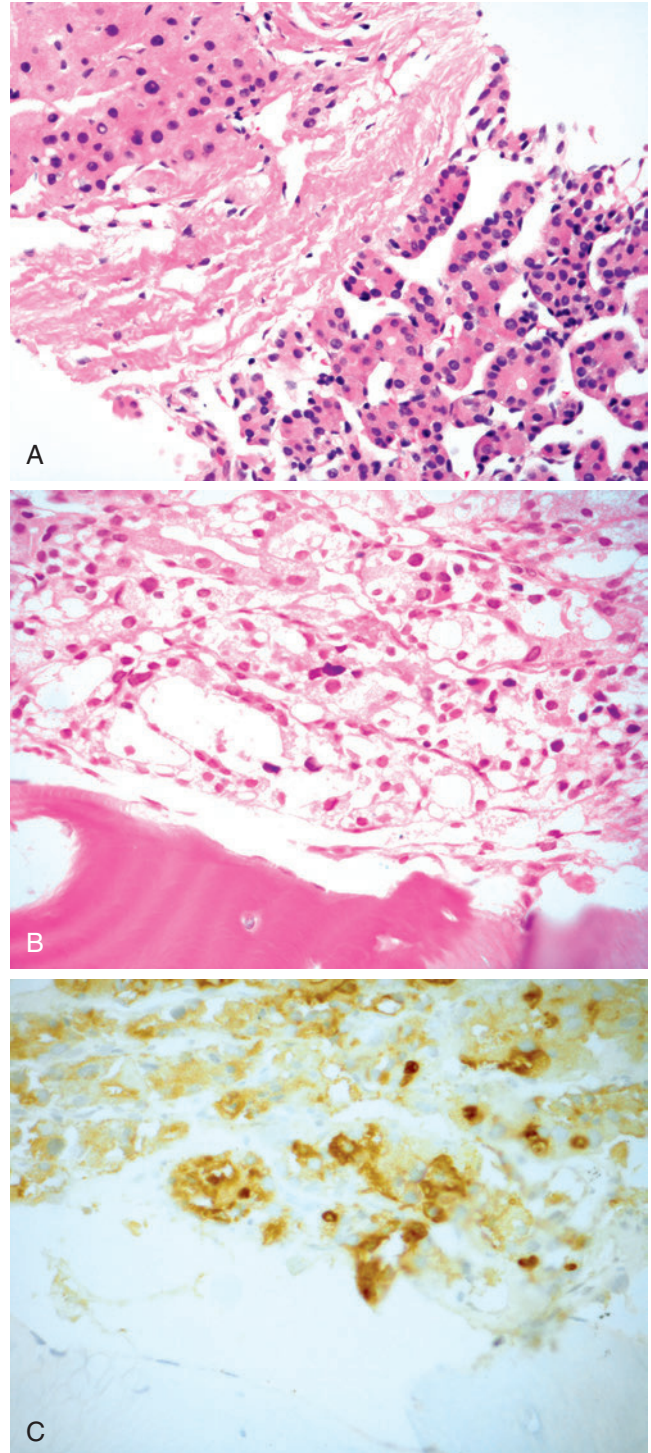


Fig. 28-31. Metastatic follicular carcinoma.

Follicular thyroid carcinoma typically metastasizes by hematogenous routes and may include metastatic tumor to (A) liver and (B) bone. C, Thyroglobulin immunoreactivity in the lesional cells confirms thyroid follicular cell origin.

- Low magnification appearance suggests capsular invasion, but at higher magnification follicular epithelium does not violate capsule.
- Needle tract composed of dense fibrosis as well as chronic inflammatory cells infiltrate, including macrophages and giant cells with or without hemorrhage (recent and remote, latter in form of hemosiderin deposition); cholesterol granuloma formation may be present
- Epithelial displacement or entrapment:
 - May take form of small clusters of follicular cells within capsule
- Separate nodule lying immediately outside the capsule of main tumor mass:
 - In this setting, serial sections to determine whether there is a connection present or not is indicated
 - Presence of continuity between main mass and nodule outside the capsule would be indicative of invasion and diagnostic for a carcinoma.
 - Absence of any connection does not exclude a diagnosis of carcinoma.
 - May be indicative of multiple adenomatoid nodules
 - Important to try to determine if separate nodule(s) is or is not histologically similar to main lesion:
 - Histologic similarity with or without direct continuity may be indicative of invasion.
 - Histologic dissimilarity may be indicative of separate adenomatoid nodule(s).
- As nodal metastasis is rare in follicular carcinoma, invaded vascular space are not lymphatics
- Vascular space must lie within capsule or beyond the capsule:
 - Involvement of vascular space within substance of tumor does not qualify as vascular invasion.
- Criteria for diagnosing vascular invasion:
 - Presence of tumor within endothelial-lined space:
 - Tumor adherent to wall lined by identifiable endothelial cells with or without associated thrombus formation
 - Tumor cells protruding into vascular space with endothelial layer identified over bulging tumor nests (endothelialization):
 - Includes vessels within capsule and/or outside capsule
 - Tumor cells within vessel lumen not adherent to wall and not endothelialized still qualifies as vascular invasion if there is thrombus formation
- Minimal requirements for clinically meaningful vascular invasion currently point of controversy:
 - Historically, presence of endothelialized tumor alone has been minimal criterion to identify vascular space invasion, a finding supported in literature.
 - More recently stricter criteria proposed for “significant” vascular invasion requiring both of the following findings:
 - Tumor cells invade through vessel wall and endothelium.
 - Thrombus adherent to intravascular tumor:
 - Application of rigid criteria felt to predict distant metastasis in thyroid carcinoma especially well-differentiated thyroid carcinoma
 - Risk of metastasis when strict criteria not fulfilled is not entirely absent:
 - Strict criteria requiring tumor cells invading through vessel wall and endothelium with thrombus adherent to intravascular tumor may be too strict.
 - Presence of tumor cells protruding into vascular space with endothelial layer identified over bulging tumor nests but without obvious thrombus represents “organization” of a tumor thrombus and is still considered significant.
- Problematic features relative to diagnostic interpretation of VI include:
 - Presence of tumor within fibrous capsule conforming to contour of a blood vessel (rounded edges) suggests but not definitively diagnostic for vascular invasion:
 - Special stains (e.g., CD31) of limited to no utility as tumor may obscure identification of endothelial cells

Tissue Sectioning

- In a follicular neoplasm with worrisome features (i.e., thickly encapsulated, high cellularity with increased mitotic figures and necrosis) but initial sections lack definitive evidence for a diagnosis of carcinoma, most critical issue is adequate and appropriate sectioning of tumor to evaluate the tumor-capsule-thyroid parenchymal interface for evidence of invasive growth.
- No set criteria for number of sections required for adequate histologic evaluation:
 - Guideline to number of sections considered adequate to exclude presence of invasion is:
 - For tumor measuring <6 cm = submit the entire tumor
 - For tumor measuring 6 cm = submit at least 10 blocks
 - For tumor measuring >6 cm = submit one additional block per centimeter of tumor

Vascular Invasion (VI)

- Represents more reliable feature of malignancy than capsular invasion

- Tumor cells “floating” within space not adherent to vessel, without endothelialization, and without thrombus formation do not represent vascular invasion:
 - Represent artifactual placement within vessel lumen
- Tumor cells in capsule associated with artifactual retraction in tissue suggesting vascular space but lacking identifiable endothelial cells is not diagnostic for vascular invasion.
- Tumor cells surrounding vessels or slightly pushing against wall without protrusion into lumen is not diagnostic for vascular invasion.
- Presence of papillary endothelial hyperplasia (Masson tumor-like reaction):
 - May suggest presence of vascular invasion
 - May be associated with dilated vascular spaces and intravascular organized thrombus
 - Reactive phenomenon secondary to prior fine-needle aspiration biopsy
 - Temporal sequence from FNAB to surgical removal important factor in interpretation

Special Stains in Evaluation for Vascular Invasion

- Histochemistry:
 - Elastic tissue stains or trichrome may be helpful but because a continuous smooth muscle layer may not be present they usually are of only limited assistance.
- Immunohistochemistry:
 - Stains for endothelial markers including Factor VIII-related antigen, CD31, CD34, Fli1 (nuclear), ERG (nuclear) may assist confirming presence or absence of tumor cells within endothelial cell-lined space.

Classification of Follicular Carcinoma

- Traditional classification of follicular carcinoma includes two categories:
 - Minimally invasive follicular carcinoma
 - Widely invasive follicular carcinoma
- Based on extent of invasion and biologic behavior an expanded classification can be used, including:
 - Follicular carcinoma with capsular invasion only
 - Follicular carcinoma with limited vascular invasion, including less than four vascular spaces
 - Follicular carcinoma with extensive vascular invasion, including four or more vascular spaces (also referred to as moderately invasive follicular carcinoma)
 - Widely invasive follicular carcinoma

Minimally Invasive Follicular Carcinoma

Definition: Encapsulated follicular epithelial neoplasm histologically showing limited evidence of invasion and lacking features of papillary thyroid carcinoma.

Synonyms: Encapsulated type of follicular carcinoma; low-grade follicular carcinoma

Pathology

Gross

- Essentially similar to that of follicular adenoma

Histology

- Within this category, tumors may be further subdivided on basis of whether there is:
 - Capsular invasion only
 - Limited vascular invasion (less than four vascular spaces)
 - Extensive vascular invasion (four or more vascular spaces)

Differential Diagnosis

- Primarily but not exclusively follicular adenoma
- Adenomatoid nodule(s)
- Papillary thyroid carcinoma
- Medullary thyroid carcinoma

Treatment and Prognosis

- Treatment options include conservative versus more aggressive radical approaches:
 - Conservative therapy includes limited resection (lobectomy or subtotal thyroidectomy) without radioactive iodine therapy:
 - Can be used in presence of low-risk patients, including:
 - Females ≤ 50 years; men ≤ 40 years
 - Tumors less than 5 cm in greatest dimension
 - No distant metastases
 - Radical therapeutic intervention includes total thyroidectomy followed by administration of radioactive iodine:
 - Used in presence of high-risk patients, including:
 - Females > 50 years; men > 40 years
 - Tumors greater than 5 cm in greatest dimension
 - Presence of distant metastases
 - Some authorities would argue that any evidence of VI even less than 4 vascular spaces potentially confers aggressive behavior requiring more aggressive (radical) management.
- Prognosis considered excellent but varies depending on invasive component:
 - Follicular carcinoma with capsular invasion only:

- Essentially no risk of distant metastasis
- Very low to no risk of mortality
- Follicular carcinoma with limited vascular invasion (less than four vascular spaces):
 - Low risk of distant metastasis (approximately 5%):
 - If occurs may do so years following diagnosis
 - Risk of death less than 5%
- Follicular carcinoma with extensive vascular invasion (four or more vascular spaces):
 - Distant metastasis may occur.
 - Higher risk of mortality

Widely Invasive Follicular Carcinoma

Definition: Follicular epithelial neoplasm with widespread invasion (grossly and/or histologically) of thyroid parenchyma, vascular invasion, and/or extrathyroidal invasion but lacking features of papillary thyroid carcinoma:

- Often tumor capsule not present
- Capsule may be identified with obvious complete transgression by tumor.

Clinical

- Much less common than minimally invasive counterpart
- Tend to occur in patients slightly older than those with minimally invasive follicular carcinoma

Pathology

Gross

- Fleshy, solid mass usually measuring greater than 4 cm and may be as large as 10 cm
- Extensive invasive growth can be seen.
- Yellow to red-pink, tan-brown or orange
- Central fibrosis may be seen but irregular fibrosis and cyst formation are uncommon.

Histology

- Less diagnostic dilemma with less subjectivity as compared to minimally invasive follicular carcinoma
- Clear-cut invasion beyond capsular delimitation of tumor with extension into adjacent thyroid parenchyma:
 - Owing to extensive invasion a capsule may not be readily identifiable.
- Vascular invasion readily identified often into medium and large caliber-sized vascular spaces
- Tend to:
 - Show solid or trabecular growth patterns
 - Be hypercellular with nuclear hyperchromasia

Differential Diagnosis

- Papillary thyroid carcinoma
- Poorly differentiated thyroid carcinoma
- Medullary thyroid carcinoma

Treatment and Prognosis

- Aggressive management indicated including total thyroidectomy and postoperative radioactive iodine therapy
- Prognosis varies but generally considered poor:
 - Commonly recur and metastasize:
 - Metastatic rates from 30% to 70%
 - Hematogenously metastasize to bones, lungs, and brain
 - Cutaneous metastasis also occurs.
 - Metastatic disease may be identified at initial presentation.
 - Metastatic tumor treated with radioactive iodine therapy, which may offer long-term palliation but not a cure.
 - Metastatic foci are histologically similar to primary tumor and may appear bland, lacking cytologic atypia.
 - Mortality rate of approximately 50%
 - Adverse prognostic factors include:
 - Presence of extrathyroidal extension into adjacent soft tissues
 - Presence of distant metastasis
 - Lymph node metastasis in follicular carcinoma:
 - Exceedingly rare
 - Many cases reported with nodal metastasis likely were variants of papillary thyroid carcinoma
 - In general nodal metastasis in association with thyroid carcinoma confers a diagnosis of papillary thyroid carcinoma:
 - Exception is in association with follicular carcinoma, oncocytic type, which may metastasize to lymph nodes in 5% to 10% of cases

Follicular Carcinoma, Oncocytic Type (Figs. 28-32 and 28-33)

Definition: Follicular epithelial cell-derived neoplasm exclusively or predominantly (at least 75%) composed of cells with prominent granular eosinophilic cytoplasm (rich in mitochondria) with evidence of invasion but without diagnostic features for papillary thyroid carcinoma:

- Similar to nononcocytic follicular carcinomas; classification includes low-grade (minimally invasive) and widely invasive depending on extent of invasion
- Simply because a tumor has oncocytic cells does not correlate to an aggressive neoplasm; however, higher proportion of solitary encapsulated oncocytic follicular tumors are invasive and therefore

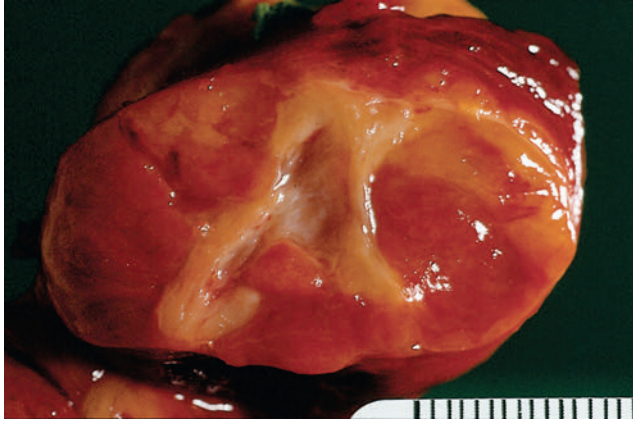


Fig. 28-32. Follicular carcinoma, oncocytic type.

Large circumscribed thyroid tumor characterized by orange color. Microscopically, invasive growth was present.

malignant as compared to solitary encapsulated nononcocytic follicular tumors.

- Whether follicular carcinoma, oncocytic type is a histologic variant of conventional follicular carcinoma or a distinct type of follicular carcinoma remains debatable:
 - Similar pathologic features, aside for presence of oncocytes, support inclusion as variant of conventional follicular carcinoma
 - Differences in biologic behavior and natural history support distinct tumor type

Synonyms: Hürthle cell carcinoma, oncocytic follicular carcinoma, oxyphilic cell carcinoma

Clinical

- More common in women than in men; tends to occur in patients approximately 10 years older than those with follicular adenoma, oncocytic type

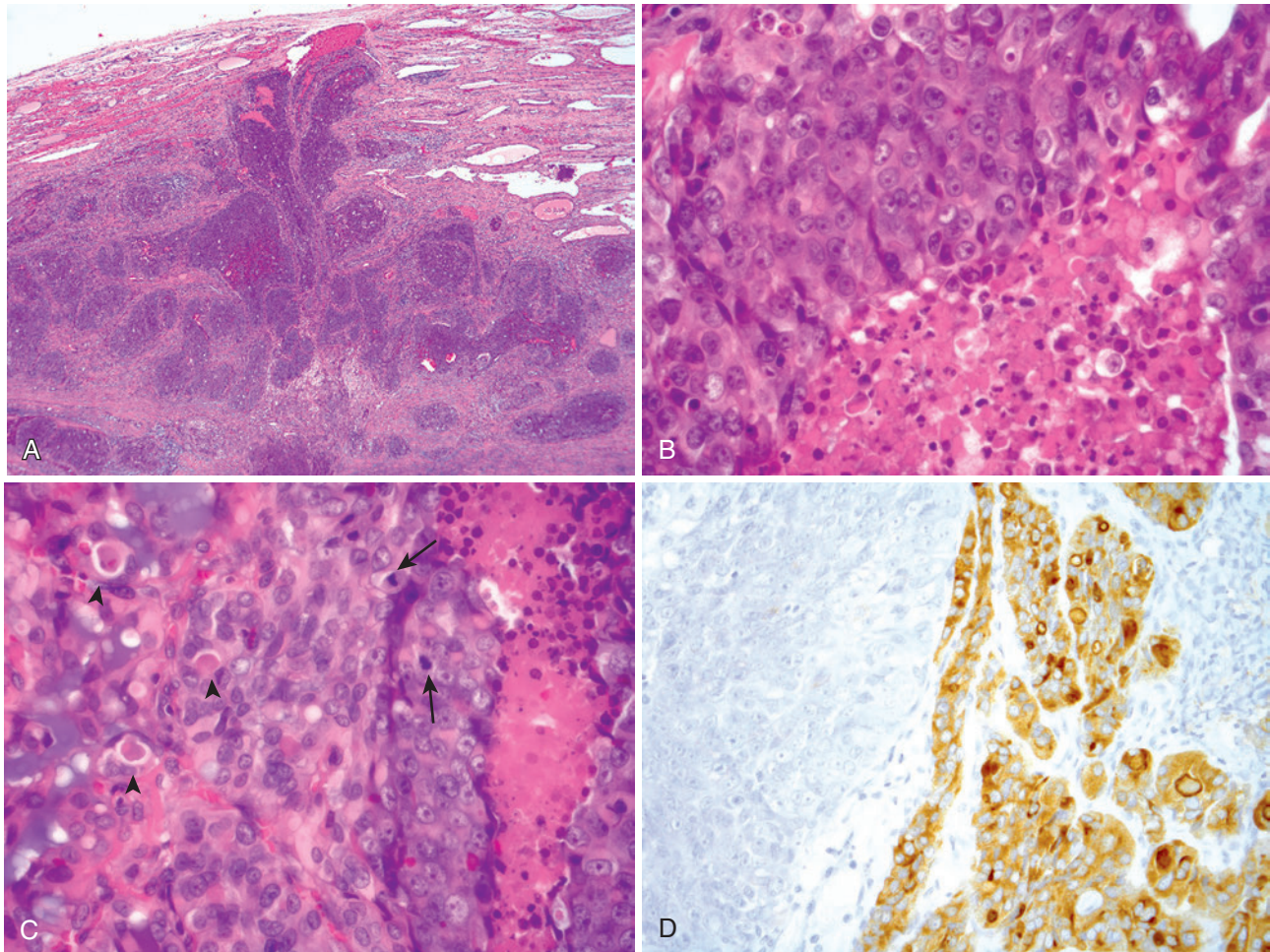


Fig. 28-33. Follicular carcinoma, oncocytic type.

A, Extensive capsular invasion by a tumor with solid growth. **B**, At higher magnification the cells show oncocytic cytoplasmic changes, enlarged nuclei with prominent nucleoli, and areas of necrosis (*bottom*). **C**, Focal follicular differentiation in the form of colloid-filled follicles are seen (*arrowheads*) as well as increased mitotic activity (*arrows*) and necrosis (*right*). **D**, Thyroglobulin reactivity.

- As a group follicular carcinomas with oncocytic cells tend to:
 - Occur in older patients than adenomas (approximately 1 decade older)
 - Be larger tumors (approximately 2.0 cm larger)
 - Such features often associated with higher frequency of malignancy as compared to nononcocytic follicular neoplasms.
- Clinical and radiographic features are similar to other follicular carcinomas:
 - Painless thyroid nodule
 - Most are solitary; rarely may be multifocal or bilateral

Pathology

Fine-Needle Aspiration Biopsy

- Cytology essentially similar to follicular adenoma with oncocytic cells
- Smears or aspirates are dominated by enlarged oval to polygonal cells, often in sheets, that have abundant, granular-appearing cytoplasm.
- Due to the oncocytic cytoplasm, there is nuclear enlargement:
 - Nuclei are round to oval and eccentrically located
 - Binucleated cells can be seen.
 - In contrast to its benign counterpart, in follicular carcinoma with oncocytic cells there may be greater nuclear enlargement and increased nuclear pleomorphism, but these findings are not diagnostic for a malignancy.
 - Prominent round, eosinophilic nucleoli are seen.
- Colloid is minimal to absent.

Gross

- Macroscopic appearance is similar to their benign counterparts, although carcinomas tend to be larger than adenomas.

Histology

- Findings similar to follicular adenoma, oncocytic type except that invasion is present:
 - Criteria identical to those described in conventional follicular carcinoma including capsular and/or vascular invasion (see previous)
 - Classification includes minimally and widely invasive categories.
- Histologic features that may be different from follicular adenomas with oncocytic cells include:
 - Thicker capsule
 - Greater degree of solid or trabecular growth
 - Increased nuclear-to-cytoplasmic ratio
 - Presence of increased mitotic activity
 - Presence of necrosis (individual cell or confluent areas)
- Colloid:
 - May be readily apparent or limited in extent

- May calcify including concentric laminations, suggesting presence of psammoma bodies and a possible diagnosis of papillary thyroid carcinoma:
 - Typically located within lumens, not usual location in papillary thyroid carcinomas
 - Cytomorphologic (i.e., nuclear) features not those of papillary thyroid carcinoma
- Oncocytic cells owing to oxygen-sensitive nature of mitochondria more readily undergo retrogressive changes either spontaneously or following traumatic event such as post-fine-needle aspiration biopsy; such alterations may include:
 - Infarction
 - Necrosis
 - Hemorrhage (recent and remote in form of hemosiderin-laden macrophages)
 - Papillary architecture
 - Cyst formation
 - Fibrosis
 - Calcifications
- Histochemistry:
 - Stains for mitochondria may be positive and include:
 - Phosphotungstic acid hematoxylin (PTAH): red staining
 - Novelli stain: dark purple staining
- Immunohistochemistry:
 - Cytokeratin, thyroglobulin, and TTF-1 positive:
 - Thyroglobulin reactivity less intense than in nononcocytic follicular cells
 - CK14 reported as selective marker for thyroid oncocytic cells
 - Chromogranin, synaptophysin, and calcitonin negative
- Electron microscopy:
 - Oncocytic cells are packed with mitochondria.
 - Mitochondrial abnormalities can be seen including quantitative and qualitative (size, shape, content) changes.
- Cytogenetics and molecular genetics:
 - *RAS* mutation in 12% to 25%
 - *PAX8/PPAR γ* rearrangement in 27%:
 - Most with follicular architecture
 - *RET/PTC* rearrangement in 38%:
 - All with solid pattern of growth
 - Identification of *RET/PTC* using highly sensitive methods possibly reflecting very low rearrangement level disputes this finding
 - Other studies failed to identify *RET/PTC* in oncocytic follicular tumors.
 - *GRIM-19* mutation
 - *TERT* C228T promoter mutation detected (in widely and minimally invasive tumors)
 - Identification of aneuploidy in an oncocytic follicular neoplasm does not differentiate an oncocytic follicular adenoma from an oncocytic

follicular carcinoma because both tumor types may show aneuploid cell populations.

- PIK3CA-Akt-mTOR and Wnt/ β -catenin pathways reported to differentiate follicular carcinoma, oncocyctic type from follicular adenoma, oncocyctic type

Differential Diagnosis

- Follicular adenoma, oncocyctic type:
 - Term Hürthle cell neoplasm of uncertain malignant potential ascribed to those tumors showing worrisome but inconclusive features of malignancy, including:
 - Smaller cells with high nuclear-to-cytoplasmic ratio
 - Increased mitotic activity
 - Because these tumors have uniformly followed a benign clinical course this terminology is not advocated, and designation of follicular adenoma, oncocyctic type is preferred.
- Papillary thyroid carcinoma, oncocyctic type
- Medullary thyroid carcinoma, oncocyctic type
- Oncocyctic tumor of parathyroid gland origin

Treatment and Prognosis

- Treatment often includes total thyroidectomy and postoperative radioactive iodine therapy
 - Generally less avidity for uptake of radioactive iodine as compared to nononcocyctic follicular carcinomas
- 5-year mortality rates of 20% to 40%
- Metastases occur to:
 - Lungs and bone
 - Less commonly to regional lymph nodes:
 - Reported 5% to 10% of cases
 - Tends to occur in association with locally advanced disease or distant metastases
 - In presence of nodal metastasis strict criteria must be applied as to exclude diagnosis of papillary thyroid carcinoma, oncocyctic type
 - When spreads to neck occurs usually does so as soft tissue implants rather than to lymph nodes:
 - Likely resulting from spread within venous channels
- Overall mortality rate of 30% to 70%:
 - Worse prognosis as compared to nononcocyctic follicular carcinomas may correlate to:
 - Tend to occur in an older population, which carries a greater risk of aggressive behavior
 - Higher percentage show presence of extrathyroidal extension
 - Higher percentage of tumors recur more often and metastasize more frequently.

- Less avidity to take up radioactive iodine
- Unfavorable prognosis factors may include:
 - Occurrence in men
 - Older age
 - Larger tumor size (≥ 4 cm in greatest dimension)
 - Aneuploidy tumors behave more aggressively than diploid tumors.
- Recent literature reports improvement in survival for follicular carcinoma, oncocyctic type such that survival rates now similar to those of conventional follicular carcinoma
 - Improvement in survival reported for both genders, in patients ≥ 45 years of age, in local and regional disease, and for tumors > 4 cm

Rare Variants of Follicular Carcinoma

- These variants of follicular carcinoma share similar diagnostic criteria, therapeutic interventions, and prognostic indicators as conventional type of follicular carcinoma.
- Follicular carcinoma with clear cells:
 - Defined as follicular epithelial cell-derived neoplasm predominantly composed ($> 75\%$) of cells with clear cytoplasm, evidence of invasion, and absence of nuclear features diagnostic for papillary thyroid carcinoma
 - Presence of cells with clear cytoplasm result of accumulation of glycogen, lipid, and thyroglobulin or ballooning of mitochondria
 - Intracytoplasmic diastase-sensitive, PAS-positive material present indicative of glycogen
 - Clear cells are thyroglobulin and TTF-1 (nuclear) positive.
 - Must be differentiated from metastatic renal cell carcinoma ([Table 28-8](#))
- Follicular carcinoma with signet ring cells:
 - Defined as follicular epithelial cell-derived neoplasm characterized by cells with cytoplasmic vacuoles displacing the nuclei to one side and creating a signet ring appearance, evidence of invasion, and absence of nuclear features diagnostic for papillary thyroid carcinoma
 - Signet ring cells may be focal or diffuse
 - Intracytoplasmic diastase-resistant, PAS-positive but negative mucicarmine and alcian blue staining
 - Cytoplasmic vacuoles are immunoreactive for:
 - Thyroglobulin
 - TTF-1, CK7
 - Lesional cells immunoreactive for:
 - Thyroglobulin, TTF-1 (nuclear), CK7
 - Ultrastructural analysis:

- Cytoplasmic vacuoles shown to be intracellular lumina or dilated vesicles lined by microvilli
- Follicular carcinoma, mucinous variant:
 - Follicular epithelial cell-derived neoplasm with evidence of invasion characterized by presence of abundant extracellular basophilic mucinous material with evidence of invasion
 - Growth patterns of the follicular epithelial proliferation may include microcystic, multicystic, and reticular.
 - Presence of abundant extracellular basophilic mucinous material, which may also be identified within follicular lumens
 - Mucinous material stains for mucicarmine and alcian blue and is diastase-resistant, PAS-positive.
 - In presence of such histologic findings it is imperative to exclude a metastatic mucinous carcinoma from another site, including the gastrointestinal tract, breast, and others.
- Hyalinizing trabecular carcinoma:
 - Considered to be malignant counterpart of hyalinizing trabecular adenoma
 - Some cases reported may in fact represent cribriform-morular variant of papillary thyroid carcinoma that may be associated with familial-adenomatous polyposis (FAP).
 - Measure from 2.5 to 4 cm
 - Histology is identical to that hyalinizing trabecular adenoma except there is capsular and/or vascular invasion.
 - These minimally invasive tumors are biologically low grade.
 - Conservative surgical removal is indicated with close follow-up.
- Tends to occur more frequently in women than in men; occurs in all age groups including pediatric and adolescent but is most common in third through fifth decades of life:
 - Most common thyroid malignant tumor in pre-pubertal age group
- Presentation:
 - Usually asymptomatic (painless) thyroid or neck mass:
 - May or may not be palpable
 - With or without enlargement of regional (cervical) lymph nodes
 - May initially present as lateral neck mass representing nodal metastasis from primary thyroid cancer:
 - Reported in 27% of patients at presentation
 - Primary cancer most often in ipsilateral thyroid lobe
 - Primary cancer may be very small and difficult to detect by clinical and/or radiologic imaging.
 - Metastasis may be predominantly/exclusively cystic and clinically considered to be branchial cleft cyst especially in absence of thyroid mass.
 - Hoarseness and dysphagia may occur:
 - Seen in approximately 20% of patients
 - Indicative of recurrent laryngeal nerve involvement with vocal cord paralysis or tracheal compression
- Any part of the thyroid gland can be affected.
- Radiology
 - Thyroid scan (^{123}I), most often “cold” or hypo-functioning nodules
- Etiology:
 - Radiation exposure:
 - Radiation exposure to neck region is known etiologic factor associated with the development of thyroid cancer in general and PTC in specific
 - Types of radiation exposures include:
 - External beam radiation therapy for treatment of malignant neoplasms and benign conditions:
 - Use of radiation in treatment of benign conditions such as acne relatively common in the earlier part of the twentieth century but essentially abandoned starting the mid-to latter part of twentieth century
 - γ radiation from nuclear reactor accident or nuclear weapon explosion
 - Development of carcinoma is dose dependent (linear correlation) and may arise in a relatively short time period if exposure is large (e.g., following Chernobyl exposure or atomic bomb) or decades later if radiation exposure is less intense (e.g., treatment of acne).

PAPILLARY THYROID CARCINOMA (PTC), USUAL OR CONVENTIONAL TYPE (Figs. 28-34 through 28-44)

Definition: Malignant epithelial cell-derived neoplasm with evidence of follicular cell differentiation defined or diagnosed on basis of characteristic nuclear features:

- Papillary architecture is not a requisite feature for diagnosis.
- Invasive growth is not a requisite feature for diagnosis.

Clinical

- Most common malignant thyroid neoplasm
 - In countries with iodine-sufficient or iodine-excess diets (i.e., nonendemic) makes up to 80% of all thyroid malignant tumors

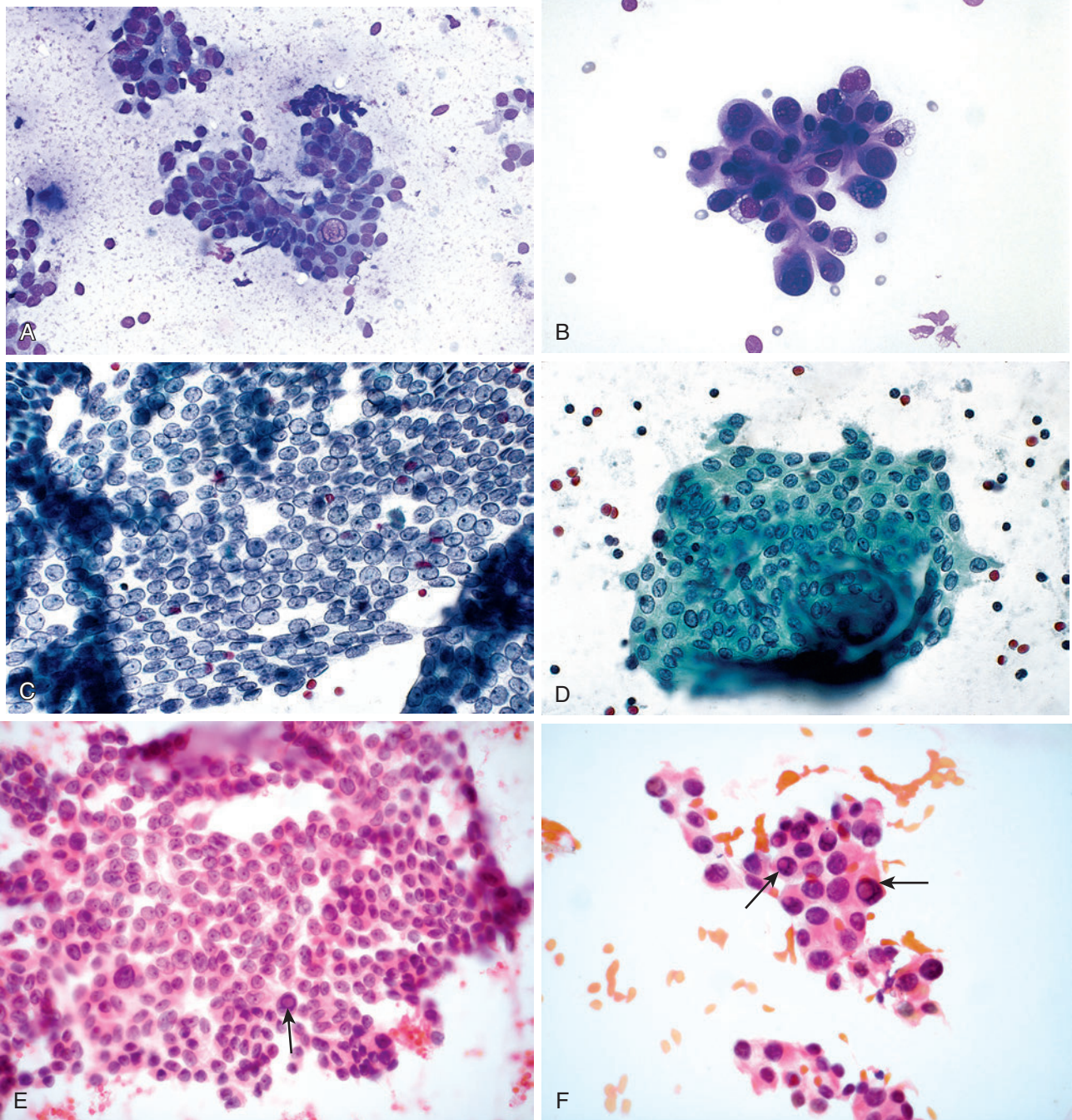


Fig. 28-34. Papillary thyroid carcinoma, fine-needle aspiration biopsy (FNAB).

A, An epithelial fragment exhibits nuclear crowding and loss of polarity, as well as an intranuclear cytoplasmic inclusion (Diff-Quik). **B**, Nuclear enlargement and tiny vascular core is identified (Diff-Quik). **C**, Nuclei with fine, evenly distributed chromatin with margination of chromatin along the nuclear membrane gives the nuclei in this aspirate the clear, watery appearance that is the cytologic hallmark of papillary carcinoma; irregularities of nuclear contour ("grooves") are apparent (Papanicolaou). **D**, Fragment of epithelium surrounds a refractile psammoma body (Papanicolaou). **E**, Nuclei with fine, evenly distributed chromatin, irregularities in size and shape, and the presence of an intranuclear pseudoinclusion (*arrow*) (H&E). **F**, Many nuclear pseudoinclusions (*arrows*) (H&E). The FNAB diagnosis in all these images was "malignant; papillary thyroid carcinoma (Bethesda VI)." A total thyroidectomy was performed.

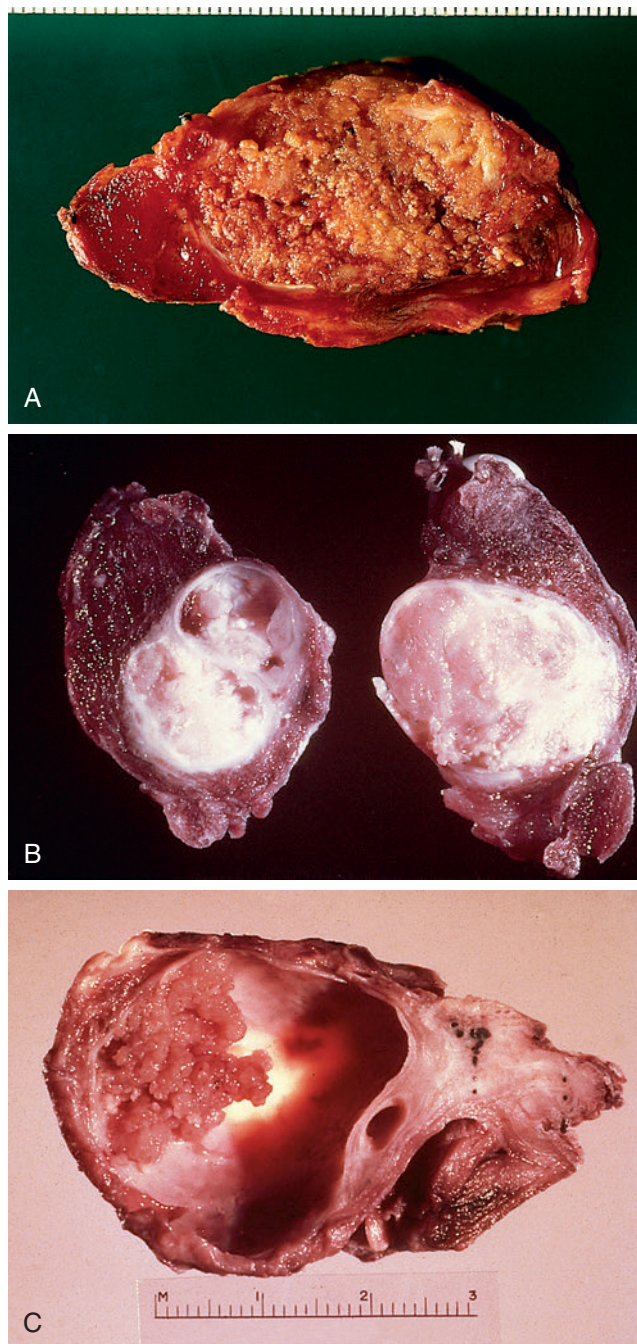


Fig. 28-35. Papillary thyroid carcinoma.

The gross appearance of papillary thyroid carcinoma may include **(A)** a predominantly solid tumor with papillary growth; the tumor is only partially encapsulated and toward its left upper outer area loses its circumscription and appears to be invasive (which it was on histologic evaluation); **(B)** encapsulated, predominantly solid but focally cystic tumor; intratumoral fibrosis is grossly apparent; **(C)** predominantly cystic and partly solid with papillary appearance; if metastasis develops from such a tumor, the metastatic foci may also be predominantly or exclusively cystic.

- Thyroid cancer risk following radiation exposure:
 - Highest following radiation at a young age:
 - Highest in children exposed during infancy
 - Decreases with increasing age at treatment
 - Increases with follow-up duration
- Radiation-induced thyroid cancers:
 - Most commonly are PTCs
 - Show solid or mixed solid and follicular growth patterns
 - Primarily have chromosomal rearrangements (e.g., *RET/PTC*) rather than point mutations (e.g., *BRAF*, *RAS*)
- Excess dietary iodine:
 - In areas of endemic goiter, addition of iodine to diet associated with an increase in incidence of PTC and decrease in incidence of follicular carcinoma
- Genetic predisposition:
 - Approximately 5% of PTCs are familial:
 - As component of known hereditary cancer syndrome, including:
 - Familial adenomatous polyposis (FAP): autosomal dominant disease caused by germline mutation of *APC* gene located on 5q21; approximately 1% to 2% of patients develop thyroid carcinoma, primarily PTC and, in particular, cribriform-morular variant (see later in this chapter)
 - Other hereditary cancer syndromes that may develop PTC include: Carney complex, Werner syndrome.
 - Familial PTC development in individuals in families with thyroid cancer but no known hereditary cancer syndrome:
 - PTC occurs within families
 - Reported inheritance as autosomal dominant disorder with incomplete penetrance
 - Tend to be multifocal and arise in association with benign lesions (nodules)
- Pre-existing thyroid disease including:
 - Increase risk of PTC in association with:
 - Adenomatoid nodules and adenoma:
 - Mechanisms not fully understood
 - Chronic lymphocytic (Hashimoto) thyroiditis:
 - More controversial association with mixed evidence weighing for but also against risk for PTC in setting of chronic lymphocytic (Hashimoto) thyroiditis
 - Graves disease:
 - No clear-cut evidence to support Graves disease as risk factor for developing PTC

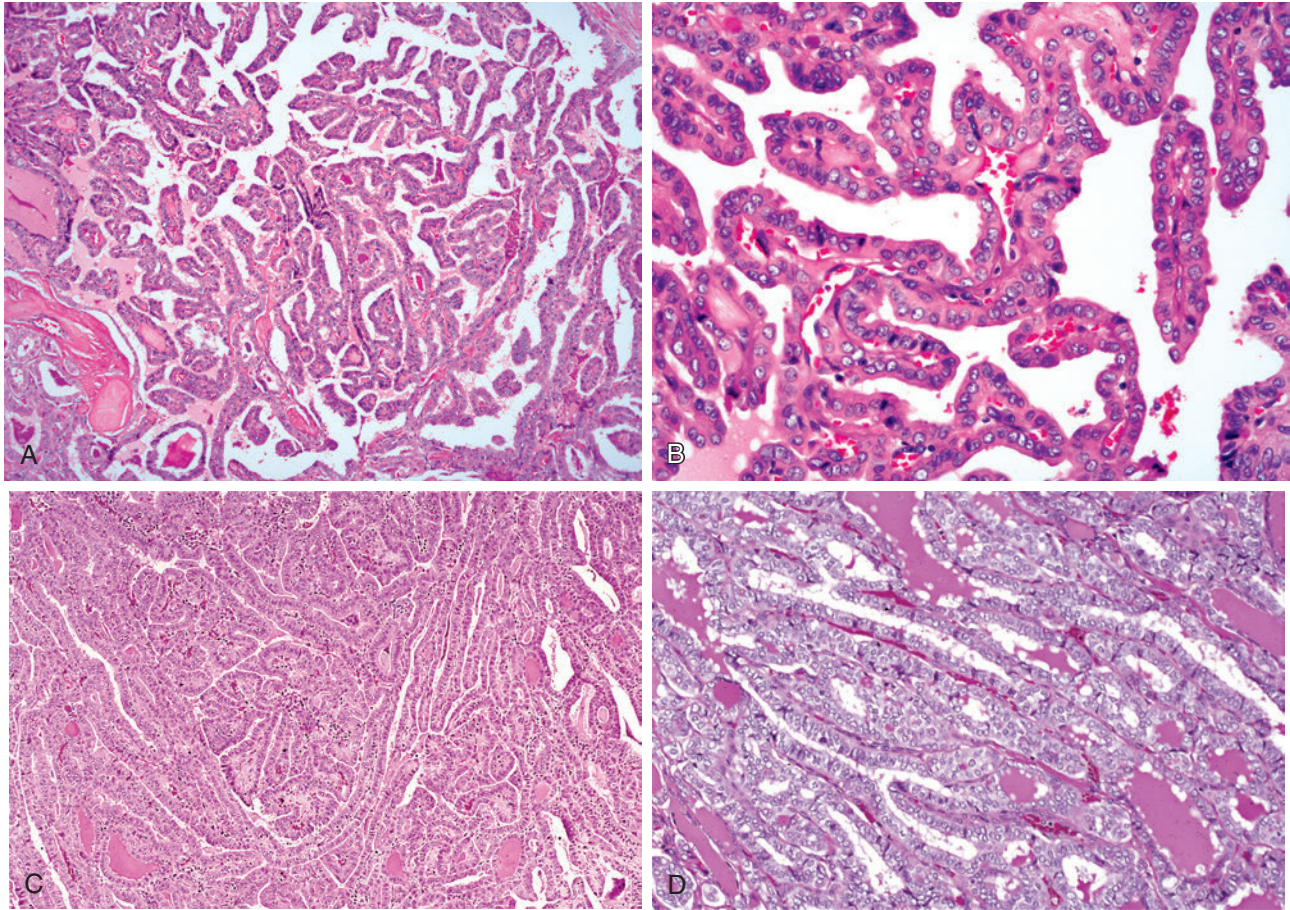


Fig. 28-36. Papillary thyroid carcinoma, usual type.

A and B, Classic papillary growth pattern including complex arborizing growth and narrow papillae with thin fibrovascular cores. **C and D,** Another example showing complex papillary pattern including narrow and elongated papillae running in parallel (railroad track-like) and fibrovascular stroma.

Pathology

Fine-Needle Aspiration Biopsy

- In contrast to follicular adenoma and follicular carcinoma, cytologic features of PTC are diagnostic by FNAB, making needle aspiration an excellent diagnostic tool.
- Findings include:
 - Cellular aspirates and smears
 - Colloid is scant and may be absent.
 - Cells may be arranged in papillary formations, monolayers, follicles, small or large cell clusters (syncytium-like formations), or individually dispersed.
 - Papillary formations may be sharply outlined with complex branching and central vascular core.
 - Key diagnostic components are nuclear features, which include:
 - Enlargement with irregularities in size and shape
 - Powdery or dusty chromatin pattern:
 - Nuclear clearing “orphan Annie” seen in histologic preparations not found in cytologic preparations
 - Intracellular (pseudo)inclusions
 - Nuclear grooves
 - Nuclear crowding or overlapping
 - Cytoplasm usually abundant and includes pale, vacuolated, or foamy appearance
 - Cytoplasmic features are not of much assistance in diagnosis.
 - Psammoma bodies can be seen and are helpful in the diagnosis.
 - Multinucleated cells can be seen and sometimes are abundant.

Gross

- Most are solid with poor circumscription:
 - May be circumscribed with or without identifiable capsule:

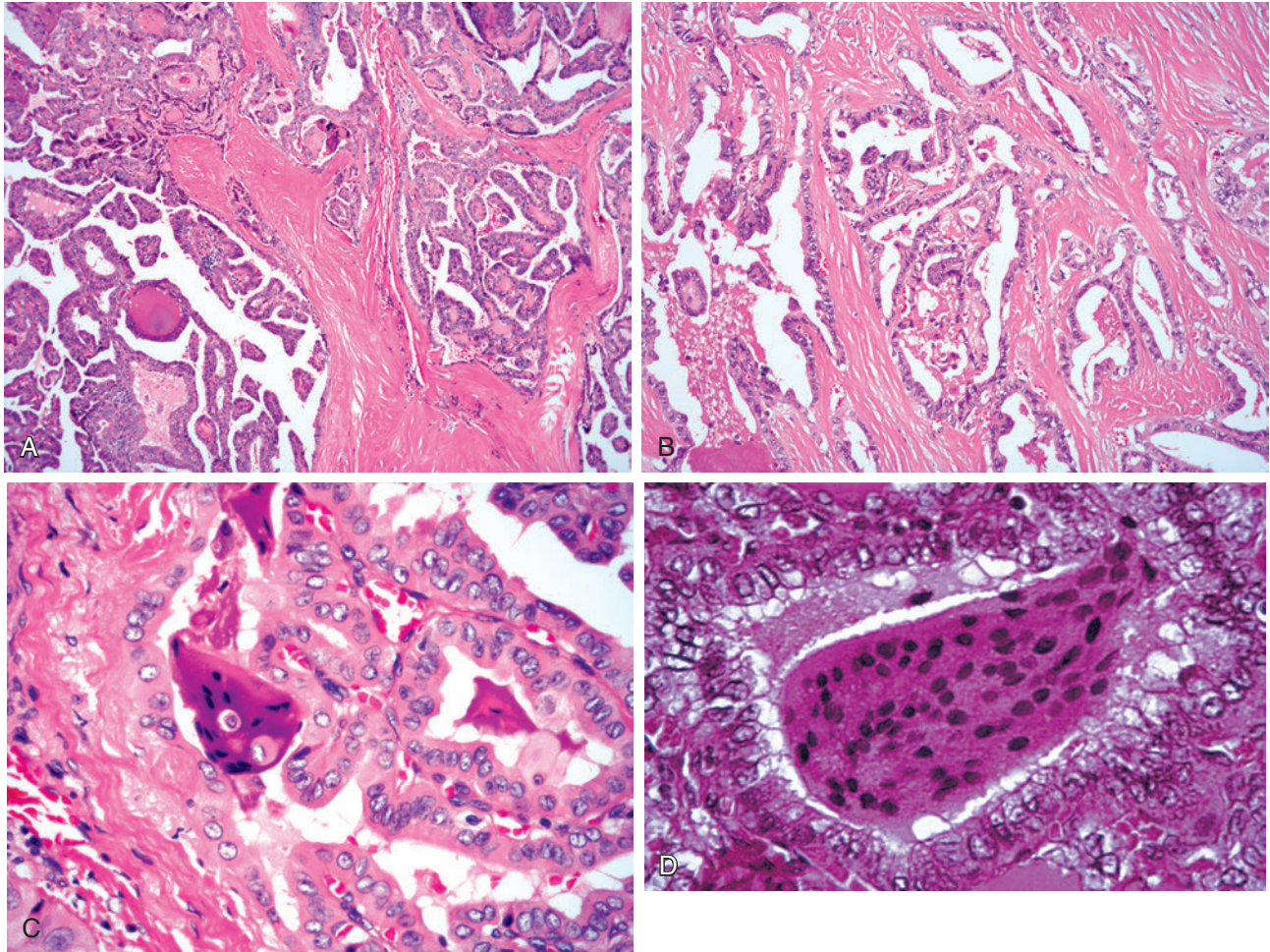


Fig. 28-37. Papillary thyroid carcinoma.

Additional features that can be seen in papillary thyroid carcinoma include **(A and B)** intralesional fibrosis and **(C and D)** multinucleated giant cells identified in the lumens of the lesional follicles.

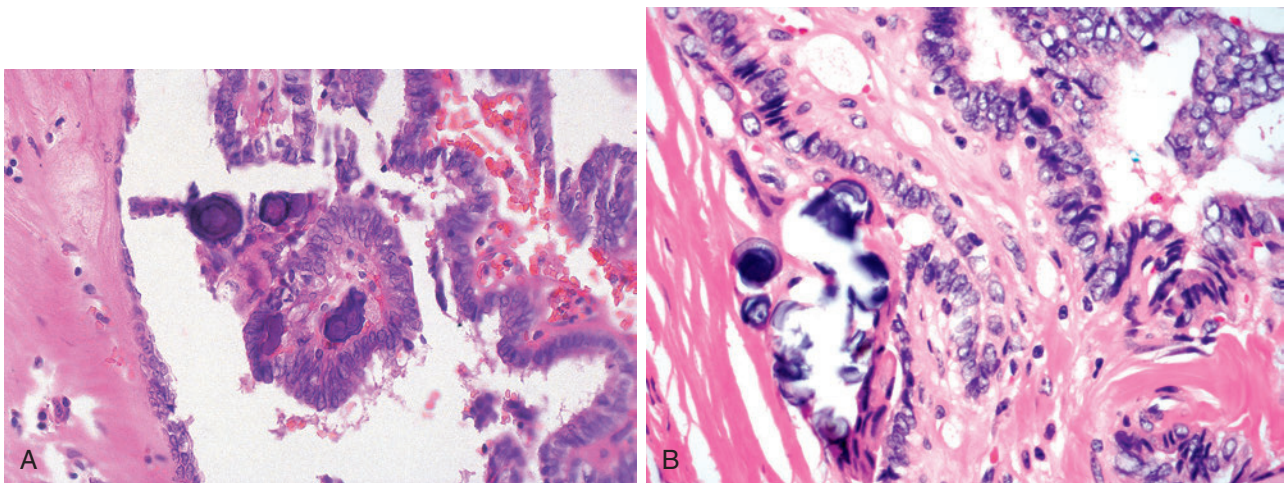


Fig. 28-38. Papillary thyroid carcinoma.

A and B, Psammoma bodies represent a characteristic feature seen in association with papillary thyroid carcinomas appearing as round, calcified concretions with concentric laminations. Psammoma bodies are felt to represent necrotic tumor cell(s) that form the nidus for deposition of calcium salts.

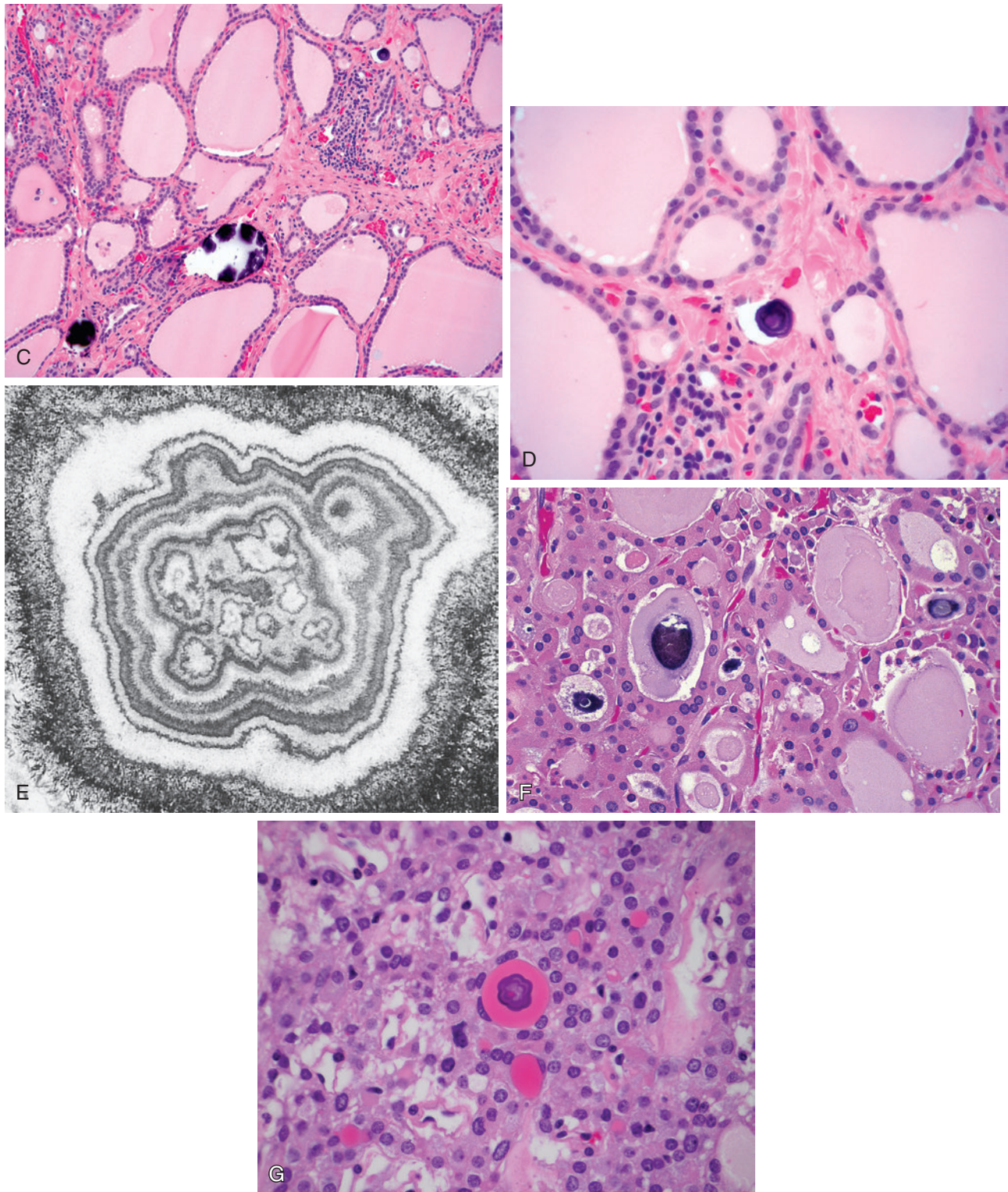


Fig. 28-38, cont'd

C and **D**, Isolated or “naked” psammoma bodies represent strong evidence for presence of PTC and can be seen in normal thyroid parenchyma felt to represent intrathyroidal spread of PTC. **E**, Electron microscopic depiction of a psammoma body shows the concentric layering of this calcified nidus of tumor. **F**, Mineralization of colloid may simulate the appearance of psammoma bodies; however, in contrast to psammoma bodies there is an absence of concentric laminations and appear in the center of follicles composed of cells lacking diagnostic features for thyroid papillary carcinoma. **G**, Psammoma bodies are not specific for papillary thyroid carcinoma as seen in this example of a psammoma body with concentric laminations located within a follicle composed of cells lacking diagnostic features for thyroid papillary carcinoma.

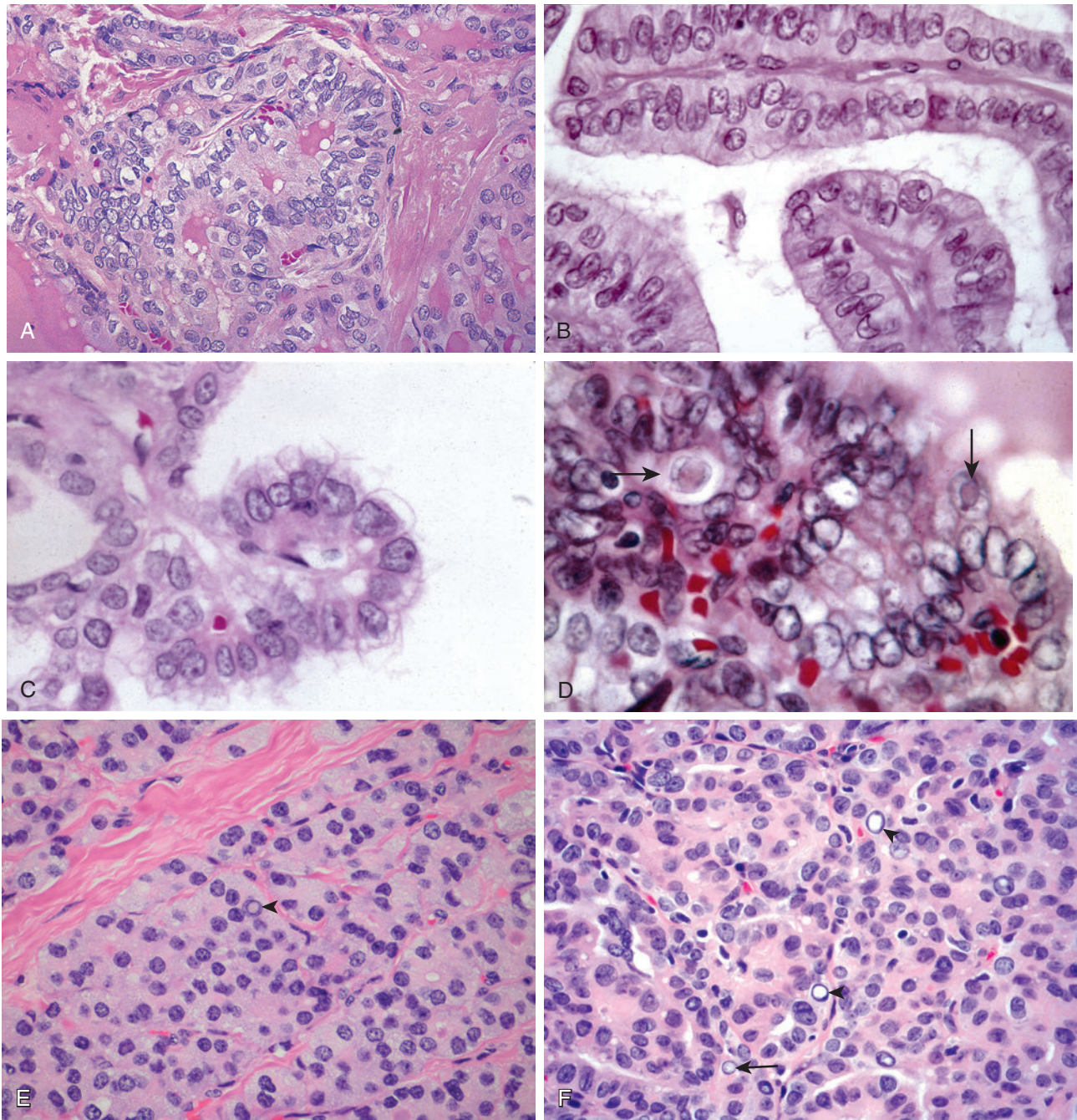


Fig. 28-39. Papillary thyroid carcinoma.

The diagnosis of papillary thyroid carcinoma (PTC) ultimately hinges on the nuclear features that include **(A and B)** enlarged nuclei with irregularities in size and shape, dispersed to clear-appearing nuclear chromatin, nuclear crowding and overlapping with loss of the basal polarity of the nuclei that randomly are arrayed in all portions of the cell, and nuclear grooves; **(C)** nuclear features diagnostic for PTC but, rather than appearing clear, the nuclear chromatin may be fine and evenly (finely) dispersed; **(D)** in addition to the optically clear-appearing nuclei, the presence of nuclear pseudoinclusions with eosinophilic appearance and distinct outlines or margins (*arrows*) is a very helpful diagnostic but not pathognomonic finding for PTC as they may be seen in lesions other than PTC including but not limited to a **(E)** follicular adenoma (*arrowhead*). In comparison to the nuclear inclusions associated with PTC, there may be artifactual “inclusions” or holes with clear appearance and absence of distinct margination. Such holes (*arrowheads*) may be seen **(F)** in association with nuclei showing diagnostic features for PTC or **(G)** in follicular lesions (e.g., adenomas, nodules) lacking such diagnostic nuclear features in which **(H)** they may be numerous. A diagnosis of PTC should not be predicated solely on pseudoinclusions but on a constellation of nuclear features; arguably the most helpful include the nuclear chromatin features and marked variation in the nuclear contours. Further, holes lacking an eosinophilic appearance and distinct outlines should not be mistaken for the pseudoinclusions associated with PTC.

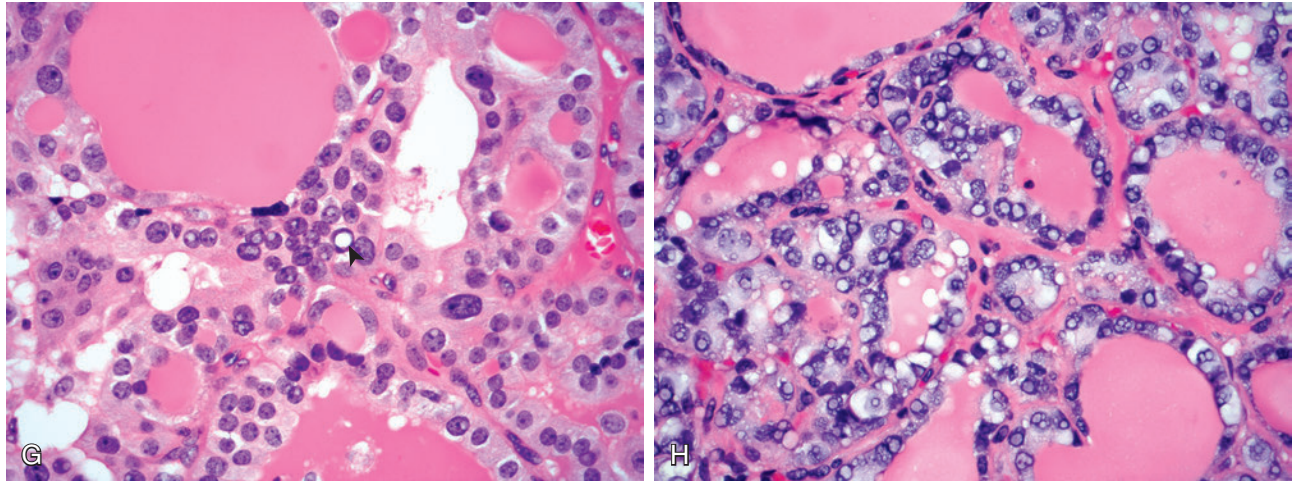


Fig. 28-39, cont'd

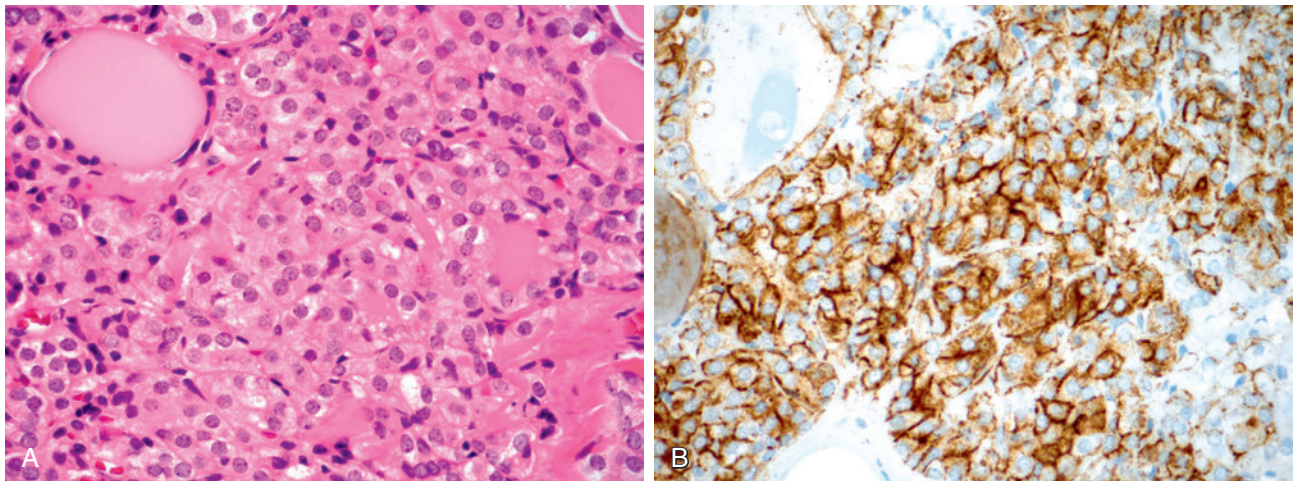


Fig. 28-40. HBME1 reactivity in follicular adenoma.

Immunohistochemical staining—in particular, strong membranous staining for HBME—1 has been reported to support a diagnosis of PTC and differentiate it from other follicular (non-PTC lesions). However, immunohistochemical staining is not sensitive or specific for PTC and can be seen in other lesions including (A) follicular adenoma showing (B) strong membranous HBME1 reactivity.

- Capsule typically absent
- Capsule may be seen in certain variants such as follicular variant.
- May or may not show infiltration into adjacent thyroid parenchyma
- Most confined to thyroid without grossly identifiable extrathyroidal extension, but some may show gross evidence of extension into perithyroidal soft tissues
- Variations in size but most measure from 1 to 3 cm in greatest dimension
- Cut section varies and may include:
 - Tan-white, solid tumors with rubbery to firm consistency
 - Partly or wholly cystic tumors filled with clear to yellow/brown fluid
 - Papillary appearance may be apparent by macroscopic examination.
 - May have gritty consistency owing to presence of psammoma bodies:
 - Extensive foci of calcification or ossification may be present.
- Fibrosis is common finding in and around tumor appearing as white area with firm consistency.

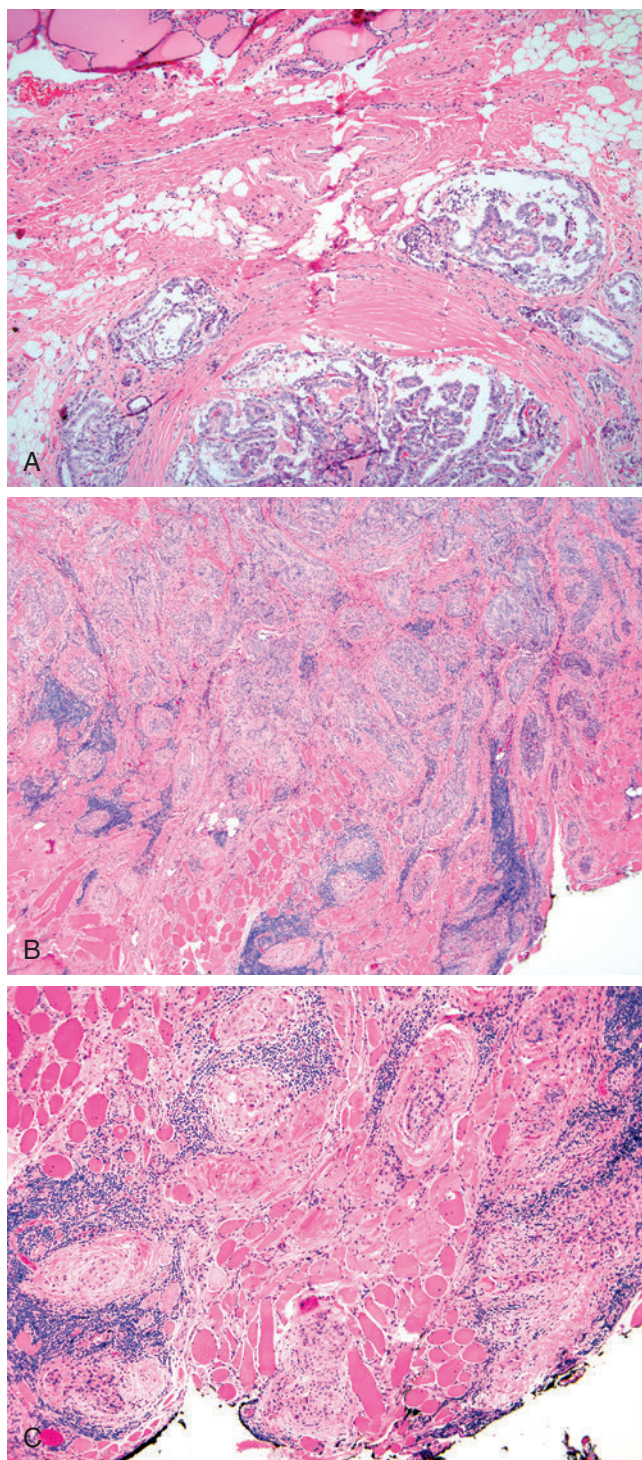


Fig. 28-41. Minimal extrathyroidal extension.

PTC with minimal extrathyroidal extension including invasion into **(A)** perithyroidal adipose tissue and **(B and C)** skeletal muscle.

BOX 28-4 Histomorphologic Features of Papillary Thyroid Carcinoma

Architectural Features

- Growth patterns:
 - Papillary, follicular, solid, trabecular, organoid; multiple growth patterns in a single lesion can occur
 - Elongated or twisted follicles with little colloid
- Other findings:
 - Psammoma bodies (concentric laminations)
 - Intratumoral irregular fibrosis
 - Inspissated colloid (darker-appearing colloid as compared to the surrounding thyroid)

Cytomorphologic Features

- Nuclear alterations:
 - Nuclear enlargement
 - Nuclear irregularities in size and shape of nuclear contour
 - Dispersed (very fine) to optically clear-appearing (“Orphan Annie”) nuclear chromatin
 - Margination of chromatin along the nuclear membrane
 - Loss of nuclear basal polarity with haphazardly arrayed nuclei within the cell
 - Nuclear crowding and overlapping
 - Nuclear grooves
 - Nuclear (pseudo)inclusions

- Multifocal disease is common.
- Can be divided by size and extent of invasion into:
 - Microcarcinoma (occult, minute, or microscopic): <1.0 cm
 - Intrathyroidal: encapsulated; invasive; diffuse; cystic
 - Extrathyroidal (massive)

Histology (Boxes 28-4 and 28-5)

- Includes architectural and cytomorphologic features

Architecture

- Classic example includes presence of papillary growth:
 - Papillae tend to be narrow with thin fibrovascular cores and show complexity in growth with arborization.
 - Papillary growth not required for diagnosis and some variants devoid of papillary architecture entirely composed of a tumor with a follicular growth (see **Follicular Variant** later in this chapter)
 - Parenthetically, papillary growth can be seen in other thyroid lesions, including:
 - Diffuse hyperplasia (Graves disease; dyshormonogenetic goiter)
 - Adenomatoid nodules: as retrogressive change occurring spontaneously or following a traumatic event such as prior fine-needle aspiration biopsy

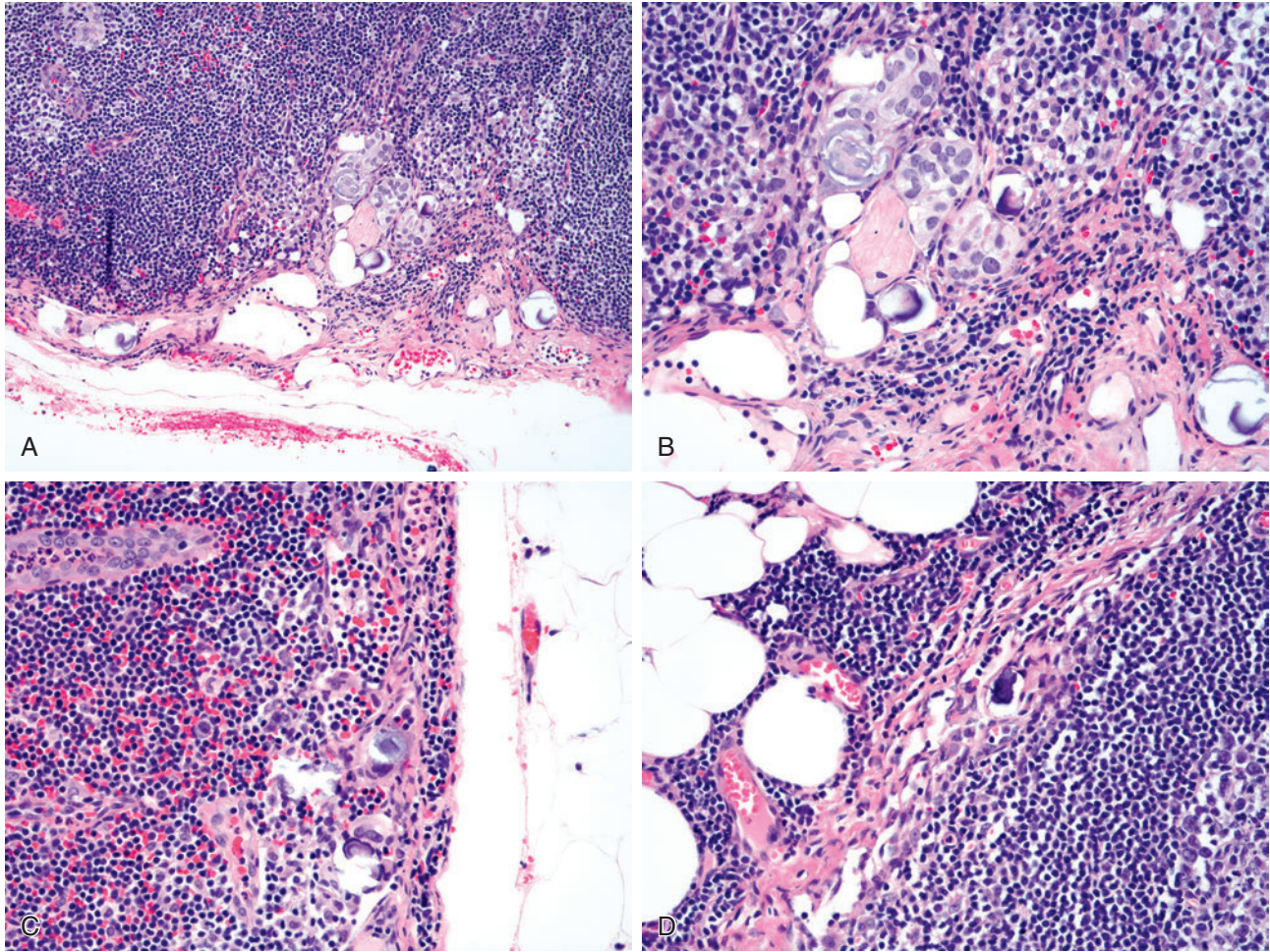


Fig. 28-42. Metastatic PTC to cervical neck lymph nodes without extranodal extension.

A and B, Nests of tumor without lymph node parenchyma with associated psammoma bodies. **C and D,** Isolated or “naked” psammoma bodies in nodal subcapsular sinuses support a diagnosis of metastatic PTC.

BOX 28-5 Papillary Thyroid Carcinoma: Diagnostic Major and Minor Criteria*

Most Important Criteria (in Order of Importance)

[Brackets contain percentage of cases showing these features.]

1. Cytoplasmic invaginations (pseudoinclusions) into nucleus [25%]
2. Abundant nuclear grooves [100%]
3. Ground glass nuclei [98%]
4. Psammoma bodies [16%]
5. Enlarged overlapping nuclei [99%]
6. Irregularly shaped nuclei [100%]

Less Important Criteria

- Dark staining colloid [86%]
- Irregular contours of follicles [64%]
- Scalloping of colloid [59%]
- Elongated follicles [80%]
- Multinucleated macrophages in lumen of follicles [14%]

*From Lloyd RV, Erickson LA, Casey MB, et al: Observer variation in the diagnosis of follicular variant of papillary thyroid carcinoma, *Am J Surg Pathol* 28:1336-1340, 2004.

- Follicular adenoma: as retrogressive change occurring spontaneously or following a traumatic event such as prior fine-needle aspiration biopsy
- Other growth patterns include:
 - Solid, trabecular, microfollicular, macrofollicular, insular, and cystic:
 - Any of these patterns may be sole pattern seen or multiple admixed patterns can be seen in any one tumor
 - Predominantly solid tumors are those in which solid elements make up nearly all of the neoplasm.
- Follicles often are elongated or twisted in appearance:
 - Extremely variable (but not pathognomonic) feature especially in papillary cancers without a papillary architecture and may be useful in diagnosis at time of frozen section

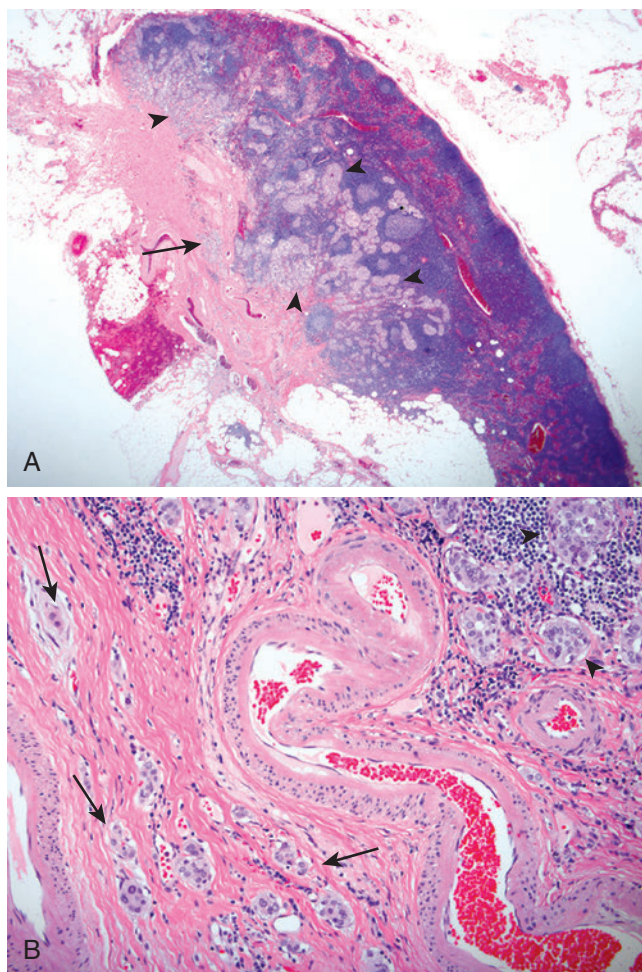


Fig. 28-43.

A, B, Metastatic PTC to cervical neck lymph nodes with (minimal) extranodal extension. The metastatic foci are present within the node parenchyma (*arrowheads*) with extension of tumor into perinodal soft tissue (*arrows*).

- Tend not to be features seen in follicular adenoma/carcinoma or medullary thyroid carcinoma

Cytomorphology

- Nuclear features are paramount in diagnosis:
 - In presence of diagnostic nuclear features, a diagnosis of PTC can be rendered in absence of invasion (i.e., invasion is not a requisite finding for diagnosis)
 - Nuclear alterations remain constant finding irrespective (with some exceptions) of type of PTC under consideration.
- Diagnosis is predicated on constellation of nuclear alterations and should not be decided on basis of a single alteration as many individual nuclear alterations may be present in lesions that are not PTC.

NOTE: To properly evaluate nuclear features in thyroid lesions well-fixed and thin sections (4 microns) are recommended.

Components of Nuclear Alterations

- Nuclear enlargement:
 - As a general rule, nuclei in papillary carcinoma are always larger (two to three times) than those of normal thyroid follicles, adenomatoid nodules, and follicular tumors (adenomas, carcinomas).
 - Presence of oncocytic cytoplasm may induce nuclear enlargement, suggesting a diagnosis of PTC.
- Irregularities in nuclear contour: Irregularities in size and shape of nuclei are a hallmark finding:
 - Nuclear membrane contour is irregular and may take on many appearances including semi-lunar, crenated, or convoluted.
- Nuclear chromatin, including:
 - Nuclear clearing or dispersion with margination of chromatin along nuclear membrane creating optically clear-appearing nuclei (so-called Orphan Annie eyes nuclei):
 - Represent an artifact of fixation
 - Not identified in frozen sections or fine-needle aspiration
 - Often includes very fine (evenly dispersed) to ground glass appearance
- Nuclear grooves:
 - Discrete longitudinal fold appearing as linear line usually along long axis of nucleus
 - Result from irregularity of nuclear contours
 - By electron microscopy represents deep invagination of nuclear membrane
 - Often used as an essential and diagnostic feature of PTC but not specific or unique to PTC and can be seen in non-neoplastic and other thyroid neoplasms (benign and malignant)
- Nuclear orientation:
 - Loss of basal polarity of nuclei with random dispersion in all portions of cell resulting in crowded and overlapping of nuclei
- Nuclear pseudoinclusions:
 - Formed by cytoplasmic invaginations into nucleus
 - Appear as large, round eosinophilic inclusions with sharp borders
 - If identified, represent reliable but not pathognomonic feature in diagnosis
 - Least common feature:
 - Identified in a minority of cases
 - Absence does not exclude diagnosis.
 - Presence does not ensure diagnosis.
 - Distortional changes in processing may result in intranuclear “bubbles” that simulate appearance of “true” intranuclear pseudoinclusions.

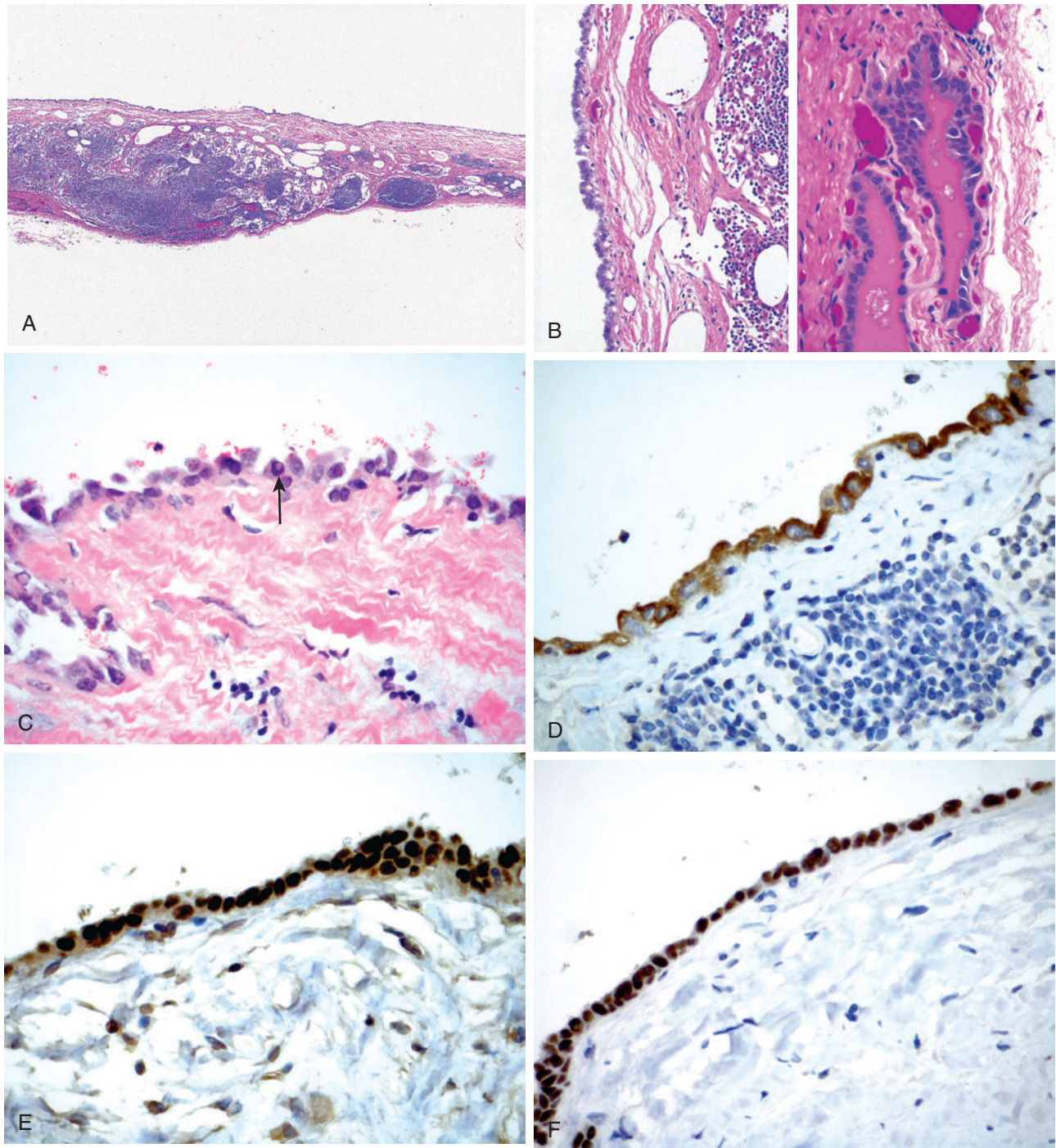


Fig. 28-44. Cystic metastatic papillary thyroid carcinoma.

Cystic metastatic PTC to the lateral cervical neck that clinically suggested a diagnosis of branchial cleft cyst. **A**, At low magnification the cystic neck lesion showed a thin epithelial-lined structure (*top*) with a fibrotic wall including lymphoid cells and lymphoid aggregates. **B**, *Left*, the cyst wall included a single layer of nondescript-appearing epithelium, but (*right*) isolated colloid-filled follicles were focally identified in the cyst wall. **C**, In areas the single cell layer showed nuclei with irregularities in size and shape with an identifiable inclusion (*arrow*). Immunohistochemical staining showed the cells to be reactive for **(D)** thyroglobulin, **(E)** TTF-1 (nuclear), and **(F)** PAX8 (nuclear). Based on the diagnosis of metastatic PTC a thyroidectomy was performed in which an occult focus of PTC was found in the ipsilateral thyroid lobe (not shown).

- To prevent this artifact, proper fixation and thin sections are recommended.
- Nucleoli:
 - When present, nucleoli are located along nuclear membrane but do not play a significant component in diagnosis.
- Cytoplasmic appearance:
 - No specific cytoplasmic changes that assist in diagnosis
 - Certain variants of PTC named according to cytoplasmic appearance, including:
 - Oncocytic PTC, clear cell PTC

Other Histologic Findings in PTC

- Psammoma bodies
 - Round, calcified concretions with concentric lamination
 - Felt to represent necrotic tumor cell(s) that form nidus for deposition of calcium salts
 - Name derived from Greek and means “salt-like”
 - Identified in up to 50% of PTCs
 - Located in tip of papillary stalk but can be found in solid neoplastic component or in the stroma between neoplastic follicles
 - Isolated or “naked” psammoma bodies represent strong evidence for presence of PTC
 - True whether found in normal thyroid (intra-thyroidal spread) from adjacent focus or from other lobe
 - In cervical lymph nodes (metastatic tumor)
 - Not specific for PTC but considered rare in benign thyroid diseases
 - Microcalcifications with an appearance similar to psammoma bodies may be found within follicle lumens but are not diagnostic and should be disregarded:
 - These microcalcifications usually lack concentric laminations seen in psammoma bodies.
- Intratumoral fibrosis
 - Dense fibrosis in and around lesional cells with irregular pattern (variable thickness) common feature of PTC
- Colloid:
 - Colloid in PTC tends to be thicker with more intense eosinophilia on H&E section than colloid of adjacent non-neoplastic thyroid follicles:
 - Weak criteria in diagnosis but in conjunction with other features may be helpful in overall histologic picture and diagnosis of PTC.
 - Additional features that can be seen in association with PTC include presence of:
 - Lymphocytic infiltration
 - Squamous metaplasia
 - Multinucleated giant cells and/or foamy histiocytes present in lumen of lesional follicles or between papillae
 - Can rarely be seen in benign thyroid lesions

- Mitotic figures but are uncommon
- Lymph-vascular invasion
- Multifocality or multicentricity:
 - May represent intraglandular spread/metastasis
 - Based on ancillary testing many of these foci have been shown to demonstrate monoclonality and different RET/PTC profiles supporting concept that they are independent primary tumors.
- Extrathyroidal extension (ETE):
 - When present most often manifests as minimal ETE
 - May occur in association with larger tumors or microcarcinomas (less than 1.0 cm in greatest dimension)

Immunohistochemistry

- Lesional cells are immunoreactive for
 - Thyroglobulin (cytoplasmic and luminal colloid), TTF-1 (nuclear), PAX8 (nuclear):
 - Thyroglobulin staining is diminished to absent in foci of squamous metaplasia.
 - Cytokeratins including AE1/AE3, CAM 5.2, CK7
 - CK20 negative
- Expression of Hectortin 1 (HBME1) (strong membranous staining with apical accentuation), galectin 3, cytokeratin 19, and CITED-1 suggested as differentiating PTC (positive reactivity) from lesions other than PTC:
 - Such stains are not sensitive or specific.
 - Similar staining may be present in normal thyroid follicles, follicular cells in non-neoplastic lesions (e.g., chronic lymphocytic thyroiditis), and benign follicular neoplasms.
- Loss of CD56 reactivity in PTC reported as potential useful marker as retention of CD56 staining is identified in benign thyroid lesions and non-PTC thyroid carcinomas
- Calcitonin, chromogranin, and synaptophysin negative

NOTE: To date, there is no single immunohistochemical marker or panel of immunohistochemical markers that are specific (or diagnostic) for PTC.

Cytogenetics and Molecular Genetics

- RET/PTC rearrangement:
 - Reported in 10% to 30% of PTCs
 - RET/PTC-1 most common followed by RET/PTC-3
 - Frequency higher among:
 - Children and young patients
 - Radiation induced PTCs especially:
 - ◻ Following exposure to radiation fallout from Chernobyl accident

- External radiation received during childhood
- Reported prevalence in PTC highly variable owing to geographic variation and detection methods used
- Not found in follicular neoplasms
- **BRAF** mutations:
 - Reliable marker of PTC
 - V600 *BRAF* mutation
 - Constitutes majority of *BRAF* mutations
 - Found in approximately 45% of PTC
 - Not found in follicular tumors and medullary thyroid carcinoma
 - Virtually diagnostic for PTC
 - Found in classic PTCs, tall cell variant, Warthin tumor-like variant, and oncocytic variant
 - Found in 10% to 15% of follicular variant of PTC
 - Much less frequent in PTCs in children and young patients
 - Prognostic significance
- **RAS** mutation
 - Found in 10% to 15% of PTCs essentially limited to follicular variant
 - *NRAS* codon 61 and *HRAS* codon 61 mutations most common
 - Not unique to PTC found in benign thyroid lesions and other malignant neoplasms

Differential Diagnosis

- Lesions that may have a papillary architecture:
 - Adenomatoid nodules, Graves disease, dyschormonogenetic goiter, others

NOTE: Not all lesions with a papillary architecture are papillary carcinomas, and the absence of a papillary architecture does not exclude a diagnosis of thyroid papillary carcinoma.

- Lymphocytic thyroiditis:
 - Lymphocytic infiltrate may be associated with oncocytic cytoplasmic change, which in turn may be associated with nuclear enlargement and vesicular nuclear chromatin raising concern for a diagnosis of PTC.
 - Despite nuclear enlargement and cleared chromatin, nuclei in lymphocytic thyroiditis remain round with regular contours and coarse nuclear chromatin lacking constellation of nuclear alterations seen in PTC.
- Follicular adenoma, including hyalinizing trabecular adenoma
- Follicular carcinoma
- Medullary thyroid carcinoma

Treatment and Prognosis

- Standard treatment is surgery as well as radioiodine therapy and thyroid hormone therapy for nearly all patients:

- Surgery
 - Extent of surgery may vary from lobectomy to subtotal thyroidectomy to total thyroidectomy.
 - Standard approach for tumors measuring ≥ 1.0 cm is total thyroidectomy, nodal sampling of palpable lymph nodes, and subsequent radioactive iodine ablation (^{131}I).
 - Total thyroidectomy traditionally advocated due to high frequency of tumor multifocality
 - For tumors measuring < 1.0 cm more conservative approach can be taken to include lobectomy and subtotal thyroidectomy; however, recommendations for more aggressive surgical approach have been advocated in presence of smaller foci of PTC, including total thyroidectomy and radioiodine ablation (see Micropapillary Carcinoma).
 - Conservative approach including lobectomy with or without isthmusectomy or subtotal thyroidectomy followed by suppression of thyroid-stimulating hormone secretion seems most reasonable in low-risk patient population (see below):
 - In patients falling into low-risk group, conservative therapeutic approach shown to be as effective with similar outcomes as more aggressive approaches to management
 - Complications of total thyroidectomy may include hypoparathyroidism and vocal cord paralysis.
- Surgical treatment of cervical lymph nodes is subject of debate:
 - In absence of cervical lymph node enlargement, a (modified) neck dissection need not be performed.
 - In face of clinically involved lymph nodes, neck dissection is performed:
 - Central compartment neck dissection:
 - Central compartment nodal metastasis is common with reported incidence of up to 50% in patients with PTC
 - Therapeutic central neck dissection prevents:
 - Sequelae of compression and invasion of critical aerodigestive and neural structures
 - Decreases incidence of lymphatic recurrence
 - May improve survival
 - Benefits of therapeutic central neck dissection widely accepted
 - Role of prophylactic neck dissection in patients with clinically negative node status remains controversial.
 - Lateral neck dissection:
 - Indicated in presence of clinically positive lymph nodes
 - For patients with macroscopically positive lymph nodes, neck dissection is associated

- with statistically significant improvement in disease-specific survival as compared to thyroidectomy alone.
- Modified radical neck dissection with preservation of sternocleidomastoid muscle is performed.
 - Utility in patients with clinically negative node status advocated for patients with significant risk factors for lateral metastasis, including:
 - Presence of extrathyroidal extension
 - Older age
 - Male gender
 - Larger primary tumor size
 - Large metastatic burden in central compartment
- Goals of surgical excision in PTC include:
 - Complete excision of cancer, including involved cervical lymph nodes:
 - Important determinant of outcome
 - Residual metastatic lymph nodes represent most common site of disease persistence/recurrence
 - Permit accurate staging
 - Facilitate postoperative treatment with radioactive iodine
 - Permit accurate long-term surveillance, including:
 - Measurement of serum thyroglobulin:
 - Represents highest sensitivity (95% to 100%) of detection of persistent or recurrent disease
 - Radioiodine whole body scanning
 - Minimize risk of recurrent and metastatic spread
 - Rationale for radioactive iodine (^{131}I) ablation includes:
 - Destruction of all thyroid tissue to include occult foci of carcinoma
 - Facilitation of postablative thyroid scanning to exclude persistent disease
 - Administration of ^{131}I cannot be performed in presence of residual normal thyroid gland; hence desire to perform total thyroidectomy
 - Because normal thyroid would concentrate majority of radioactive iodine, goal of destroying occult foci of carcinoma may not be achieved.
 - Radioactive iodine ablation is generally not administered in low-risk groups (see below) because surgery is considered sufficient.
 - Relapse after initial therapy is highest in first decade and may be associated with increased mortality:
 - Relapses may be delayed for decades (20 to 30 years) after initial diagnosis.
 - Overall recurrence reported in 15% to 35% of patients occurring in:
 - Tumor bed
 - Cervical neck lymph nodes
 - At distant sites
 - Incomplete surgical resection associated with increased risk of recurrence
 - Metastatic spread:
 - Preferentially via lymphatic drainage manifesting as intrathyroidal and/or regional lymph node metastasis
 - Distant (visceral) metastatic disease unusual occurring in 5% to 7% of cases
 - Lung is most common visceral metastatic site.
 - Bone, liver, and brain metastasis may also occur.
 - Prognosis:
 - PTC tends to be biologically indolent with an excellent prognosis:
 - 5-year survival of 96%
 - 10-year survival 93%
 - 20-year survival >90%
 - Prognosis influenced by clinical extent of disease (clinical stage):
 - Stage I: 99.8% 10-year survival
 - Stage IV: approximately 41% 10-year survival
 - Overall mortality rates for thyroid carcinoma is 0.2%:
 - Survival rates measured over 20 years vary per risk group:
 - Low risk: 99% 20-year survival
 - Intermediate risk: 88% 20-year survival
 - High risk: 43% 20-year survival
 - Prognosis in PTC can be categorized as to risk based on established criteria, including:
 - AMES: Age, Metastasis, Extent of primary cancer, and Size (Table 28-9)
 - DAMES: DNA, Age, Metastasis, Extent of primary cancer, and Size
 - GAMES: Grade, Age, Metastasis, Extent of primary cancer, and Size
 - AGES: Age, Grade, Extent of primary cancer, and Size
 - MACIS: Metastases, Age, Completeness of resection, Invasion, Size
 - Prognostic factors associated with PTC include:
 - Age and gender:
 - Mortality increases with age:
 - Patients <40 years generally not associated with death as compared to patients >40 years
 - Women fare better than men:
 - Low-risk group: men ≤40 years of age; women ≤50 years of age
 - High-risk group: men >40 years of age; women >50 years of age
 - Tumor size:
 - Risk of death increases with increasing tumor size.

TABLE 28-9 AMES Risk Assessment Parameters in Well-Differentiated Thyroid Cancer

Parameter	Low Risk	High Risk
Age (A)	Men ≤ 40 years of age; women ≤ 50 years of age	Men > 40 years of age; women > 50 years of age
Metastases (M)	Absent	Present
Extent (E) of primary cancer	Intrathyroidal without ETE Follicular carcinoma, minimally invasive	Presence of ETE Follicular carcinoma, widely invasive
Size (S)	< 5 cm	> 5 cm

ETE, Extrathyroidal extension.

- Tumor recurrence and spread increases when the tumors are large (measuring > 4 to 5 cm).
- Best prognosis seen with tumors ≤ 1.0 to 1.5 cm in diameter
- Staging
 - Extrathyroidal extension (ETE):
 - Represents presence of tumor beyond confines of thyroid gland into adjacent soft tissues
 - One of worst prognostic indicators in thyroid cancer
 - Extrathyroidal extension includes minimal extension and extensive extension.
 - Diagnostic findings for minimal extrathyroid extension include the presence of cancer extending into perithyroidal soft tissues, including infiltration of adipose tissue and skeletal muscle, as well as neurotropism.
 - Diagnostic findings for extensive extrathyroid extension would include the presence of carcinoma well beyond the thyroid gland proper with direct invasion (i.e., not metastasis) into one or more of the following structures: subcutaneous soft tissues; adjacent viscera, including the larynx, trachea, and/or esophagus; the recurrent laryngeal nerve, carotid artery, or mediastinal blood vessels.
 - Microscopic foci of PTC with extrathyroidal extension have outcomes that are better than those tumors with extensive invasion outside the gland.
 - Invasion into adjacent anatomic structures (e.g., trachea, esophagus, other) is an unfavorable prognostic finding associated with decreased survival.
 - Distant metastasis
 - Presence of distant metastasis associated with worse prognosis
 - Site of distant metastasis affects prognosis:
 - Osseous and visceral (other than pulmonary) metastasis represents an ominous prognostic finding.
 - Pulmonary metastasis is not associated with as dire a prognosis as with osseous (or other distant) metastatic disease but is associated with a moderate adverse outcome.
 - Nodal metastasis:
 - In general presence of nodal metastasis has limited impact on survival; however, the presence of extranodal extension (ENE) of tumor into soft tissues adversely affects survival with increased risk of distant metastasis and worse prognosis.
 - Histologically proven angioinvasion may be considered as a sign of an increased tendency toward hematogenous spread and consequent increase in the relative percentage of metastases affecting prognosis negatively.
 - Completeness of surgical excision:
 - Complete excision decreases risk of recurrence.
 - Incomplete excision increases risk of recurrence.
 - Tumor encapsulation:
 - Encapsulated tumors and/or tumors showing limited invasion without ETE are associated with a favorable prognosis.
 - Histology (type and differentiation):
 - Adverse prognosis has been related to cell type and/or growth pattern (e.g., columnar cell, tall cell, solid, hobnail, and diffuse sclerosing variants)
 - Molecular prognostic factors:
 - *BRAF* V600E mutation: conflicting information relative to prognostic import associated with presence of *BRAF* V600E mutation, including:
 - Association with more aggressive disease characteristics including:
 - Extrathyroidal extension, advanced stage at presentation, metastatic disease (locoregional, distant), increased patient-related mortality
 - More aggressive disease characteristics also associated with small size, low-stage tumors, and microcarcinomas

BOX 28-6 Histologic Types of Papillary Thyroid Carcinomas

Variants

- Papillary microcarcinoma
- Encapsulated variant
- Follicular variant
- Macrofollicular variant
- Oncocytic variant
- Clear cell variant
- Solid variant or radiation-induced pediatric variant
- Cribriform-morular variant
- Warthin-like variant
- Diffuse follicular variant

Biologically Aggressive Variants

- Diffuse sclerosing variant
- Tall cell variant
- Columnar cell variant
- Hobnail variant
- Poorly differentiated thyroid carcinoma
- Undifferentiated (anaplastic) thyroid carcinoma

- Alternatively, other publications found no significant or more limited association between presence of *BRAF* V600E with aggressive disease characteristics
- Telomerase reverse transcriptase (TERT) promoter mutations reported to be:
 - An independent prognostic indicator of clinically aggressive tumors correlated with worse outcome and disease-specific mortality in differentiated thyroid cancers, in particular PTC
 - Highly prevalent in advanced thyroid cancers, particularly those harboring *BRAF* or *RAS* mutations
- Other molecular findings that may be predictors of aggressiveness in PTC include *STRN/ALK* fusion and *PIK3CA* gene mutations.

VARIANTS OF PAPILLARY THYROID CARCINOMA

Papillary Microcarcinoma (Figs. 28-45 through 28-48)

Definition: Represents an incidentally identified focus of papillary carcinoma that measures 1.0 cm or less in greatest dimension (Box 28-6).

Synonyms: Papillary microtumor; occult thyroid papillary carcinoma; occult sclerosing thyroid papillary carcinoma; microscopic papillary thyroid carcinoma; latent thyroid papillary carcinoma

Clinical

- Common variant and considered most common variant in United States
- Presentation:



Fig. 28-45. Papillary microcarcinoma.

Gross appearance of an occult sclerotic papillary microcarcinoma measuring less than 1.0 cm discovered incidentally in thyroid gland removed for other reasons. Note its peripheral localization, a common location to find papillary microcarcinomas; in this location minimal extrathyroidal extension may occur.

- Usually an incidental finding in thyroid removed for other reasons or found at autopsy
- May be an occult primary tumor identified following diagnosis of cervical lymph node metastasis
 - Occult carcinomas may be microcarcinomas (measuring <1.0 cm) but may be larger tumors.
- May be identified by ultrasonography:
 - With greater use and more sophisticated techniques, microcarcinomas may be detected.

Pathology

Gross

- When visible, may appear as white to brown, firm nodule with stellate appearance and ill-defined contours to circumscribed and/or encapsulated (partial, complete) with more distinct margins
- May be identified in any portion of thyroid but often located along periphery of involved lobe
- May be multifocal in same lobe and/or in opposite lobe

Histology

- May be nonencapsulated or encapsulated:
 - Nonencapsulated microcarcinomas often sclerotic and invasive
 - In presence of prominent sclerosis a stellate appearance may be identified.
- Nuclear features diagnostic for PTC are present.
- Most show predominant follicular growth pattern, although papillary architecture may be present.
- May be multifocal in same lobe or in opposite lobe:
 - Reported in 30% to 40% of cases

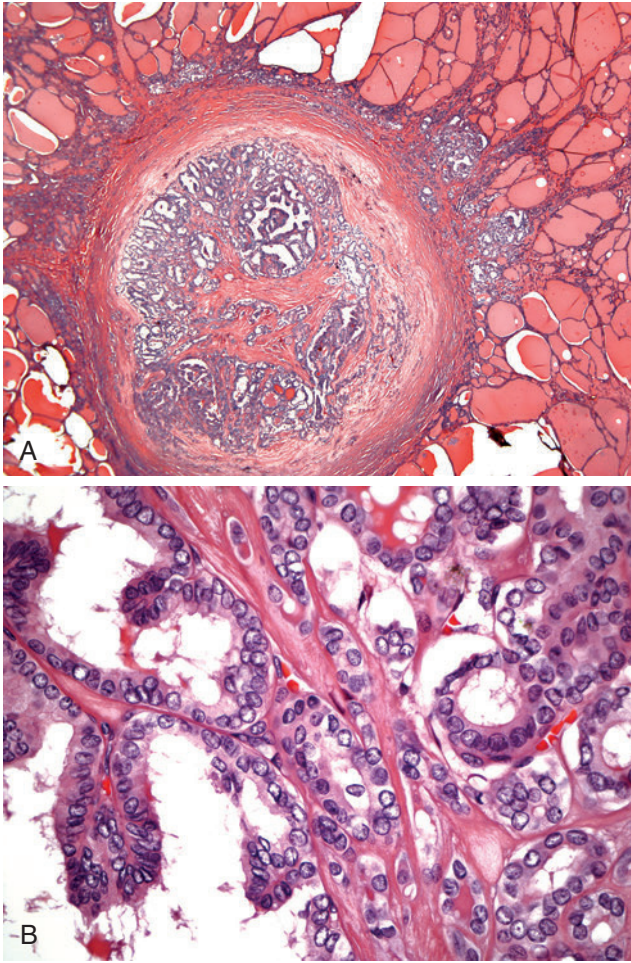


Fig. 28-46. Papillary microcarcinoma.

A, Incidentally identified encapsulated focus with invasion through the capsule into adjacent thyroid parenchyma. **B**, At higher magnification diagnostic nuclear features are present.

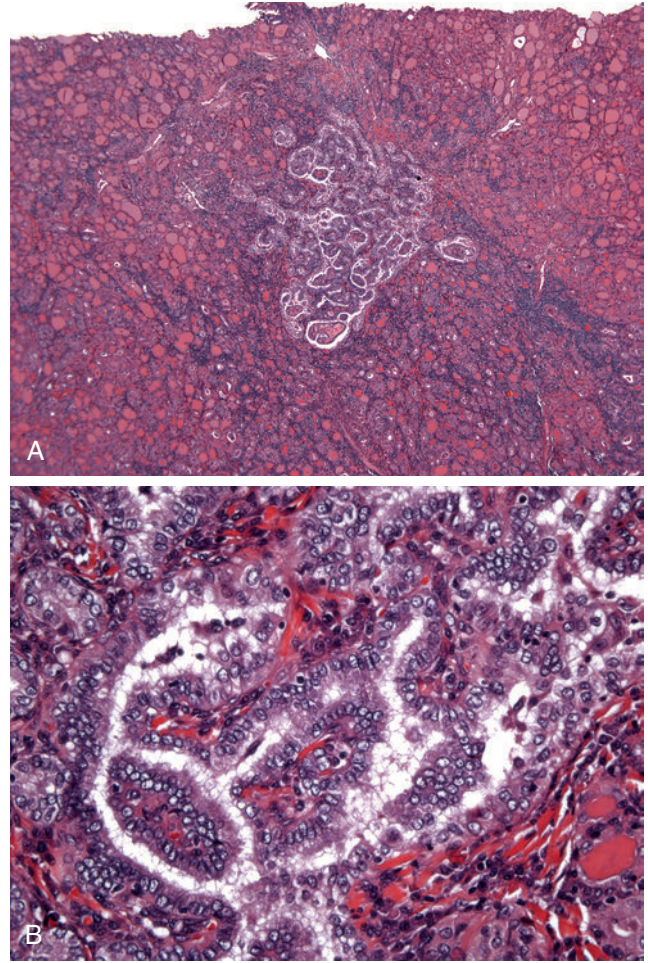


Fig. 28-47. Papillary microcarcinoma.

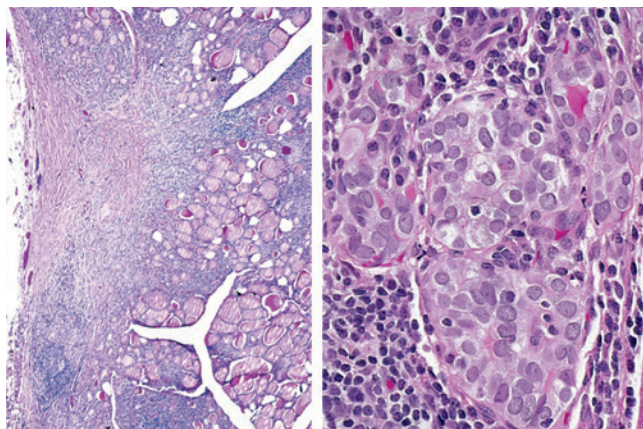
A, Incidentally identified focus of papillary microcarcinoma without associated sclerosis. **B**, At higher magnification diagnostic nuclear features are present.

- Those located at periphery of lobe may or may not have extrathyroidal extension.
- Cytogenetics and molecular genetics:
 - Loss of heterozygosity mutational profiles not different from larger papillary thyroid carcinomas
 - RET/PTC mutation is common.
 - *BRAF* mutations may be identified but not as frequent as in larger tumors.

Treatment and Prognosis

- Diagnosis of papillary microcarcinoma is not, by itself, an indication for additional treatment (i.e., surgery, radioactive iodine).
- May metastasize to regional lymph nodes in approximately 16% of cases
 - Metastatic foci are often microscopic.
 - Distant metastasis may occur but is rare occurrence

- Prognosis:
 - Excellent prognosis in majority of cases
 - Aggressive behavior may be seen in association with some cases, including those with:
 - Extrathyroidal extension (ETE)
 - Multifocality
 - Nodal metastasis with extranodal extension
 - *BRAF* V600E mutation:
 - Conflicting information in literature relative to correlation in *BRAF* mutational status and aggressiveness in papillary microcarcinomas
 - Variably reported from 24% to 63% of cases
 - Molecular-pathologic (MP) scoring system for risk assessment in papillary microcarcinomas (Table 28-10) includes combination of:
 - Histologic findings including:
 - ◻ Superficial tumor location: defined as location immediately adjacent to perithyroid

**Fig. 28-48.**

Left, Papillary microcarcinoma with superficial tumor location lying along the periphery of the thyroid with associated sclerosing tissue but no benign thyroid tissue between tumor and extrathyroid soft tissues. *Right*, Nuclear features diagnostic for PTC.

TABLE 28-10 Molecular-Pathologic Scores in the Validation Cohort of Thyroid Papillary Microcarcinomas and the Risk of More

Variable	Low Risk	Intermediate Risk	High Risk
MP _u score	0 to 2	3	4
MP _w score	7	8 to 10	12
Probability (%) of extrathyroid spread, recurrence or metastasis	0	20	60

From Niemeier LA, et al: *Cancer* 118:2069-2077, 2012.

MP_u, Unweighted molecular-pathologic score; MP_w, weighted molecular-pathologic score; MP score includes *BRAF* status and 3 histopathologic features including superficial tumor location, intraglandular tumor spread/multifocality, and tumor fibrosis.

adipose tissue with no benign thyroid tissue between tumor and extrathyroid soft tissues

- Intraglandular spread or multifocality defined as presence of either ≥ 2 separate tumors or (1) smaller tumor aggregates located close to main tumor separated by layer of normal thyroid parenchyma or tumor cells within lymphatic channels or (2) isolated psammoma bodies located in thyroid stroma outside tumor
- Tumor fibrosis scored as none; 1+ mild fibrosis with presence of few inconspicuous, delicate fibrous areas within or at the periphery of tumor nodule; 2+ moderate/

extensive fibrosis clearly recognizable with multiple fibrotic bands within and at periphery of tumor; fibrotic tumor capsule alone without significant fibrosis within tumor not sufficient to score tumor fibrosis as 2+

- Molecular profile:
 - *BRAF* mutation status
- Unweighted MP scores using sum of above features stratify papillary microcarcinomas as:
 - Low risk = score of 0 to 2 = 0 probability of nodal metastasis
 - Moderate = score of 3 = 20% probability of nodal metastasis
 - High = score of 4 = 60% probability of nodal metastasis
- Additional findings reported relative to papillary microcarcinomas:
 - Tall cell variant of papillary microcarcinoma (see Fig. 28-61 under Tall Cell Variant of PTC) associated with aggressive behavior:
 - 27 cases reported associated with extrathyroidal extension (33%), lymphovascular invasion (15%), multifocality (48%), metastasis to central compartment lymph nodes (30%) or lateral cervical nodes (11%), advanced stage (stage III/IVA) at presentation (36%), and *BRAF* V600E mutation (93%)
 - In contrast, 26 cases of age- and size-matched classic papillary microcarcinomas showed no to low extrathyroidal extension (0%), lymphovascular invasion (4%), central compartment lymph node metastasis (8%), lateral cervical node metastasis (4%), multifocal tumors (39%), *BRAF* V600E mutation (77%), and advanced stage (III/IVA) at presentation (8%).
 - Based on above findings recommendation made to differentiate tall cell variant of papillary microcarcinoma from other types of papillary microcarcinomas
 - Prophylactic central compartment neck dissection in papillary microcarcinomas recommended in men, tumors measuring >5 mm, presence of extrathyroidal extension, presence of lateral lymph node metastasis, and positive *BRAF* V600E mutation
 - Risk of lymph node metastases significantly higher in partially or nonencapsulated papillary microcarcinomas than in encapsulated tumors

Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)

Definition: Characterized by follicular pattern growth with absence of well-formed papillae and diagnosis

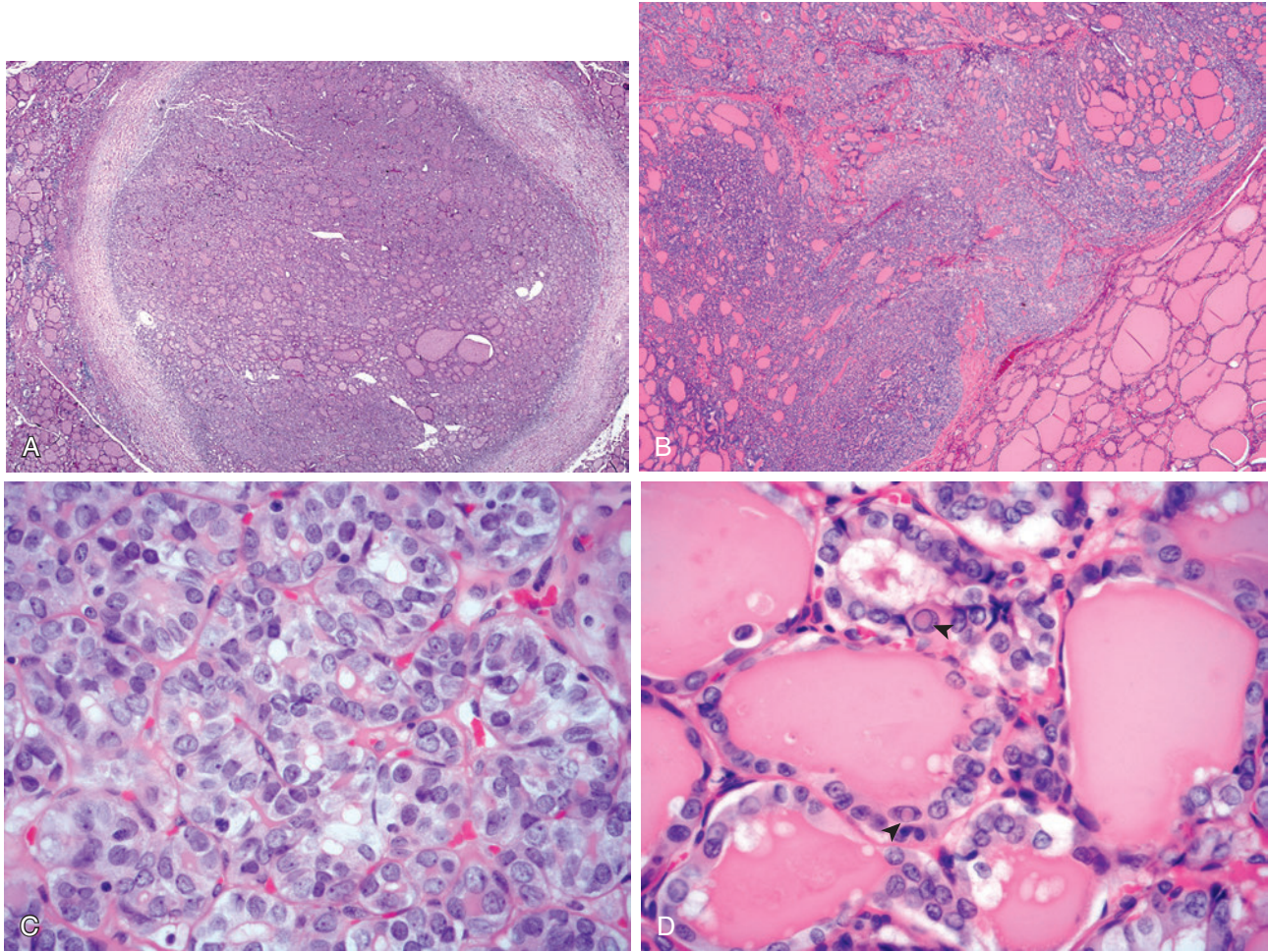


Fig. 28-49. Follicular variant of papillary thyroid carcinoma, noninvasive.

A, Encapsulated tumor. **B**, Circumscribed but not encapsulated tumor. In both examples the tumor is noninvasive and entirely composed of a follicular growth pattern without papillae. **C**, Follicular growth with nuclear features diagnostic for PTC including **(D)** inclusions (arrowheads) confirms the diagnosis. The absence of invasion is associated with an indolent behaving tumor and the recent recommendation to rename this neoplasm as “noninvasive follicular tumor [NIFT] with papillary-like features”.

predicated on basis of cells showing nuclear features diagnostic for PTC:

- May be encapsulated or circumscribed but not encapsulated
- May be noninvasive
- May be invasive

Noninvasive FVPTC (Fig. 28-49)

- Arguably among more contentious diagnosis in surgical pathology
- Lack of consensus in diagnosis among experts in thyroid pathology, including:
 - Low interobserver reproducibility
 - No consensus regarding how many florid nuclear atypia there must be or how many atypical nuclei there must be in a follicular lesion to classify it as FVPTC
- Diagnosis fraught with much subjectivity
- Molecular analysis shows presence of:
 - *RAS* mutation and *PAX8/PPAR γ* translocation similar to follicular adenoma/carcinoma rather than *BRAF* mutation or *RET/PTC* translocation identified in PTCs
 - High frequency of aneuploidy
 - Exhibit patterns of chromosomal gains and losses similar to follicular neoplasms (adenoma, carcinoma)
- Identified by The Cancer Genome Atlas (TCGA) Research Network to be among *RAS*-like tumors rather than *BRAF* V600E-like tumors (see [General Considerations](#))
- Overall biologic behavior more similar to follicular adenoma than to carcinoma (papillary or follicular)

- Based on molecular genetics and prognosis nomenclature evolving and in near future may be classified among other RAS-like tumors (follicular adenoma/follicular carcinoma) rather than within spectrum of papillary thyroid carcinoma (*BRAF* V600E-like tumors)
- With above in mind, at present this entity still regarded as papillary thyroid carcinoma and so this is discussed in this portion of the chapter. However, a recent conference on the re-examination of the (noninvasive) FVPTC recommended replacing this terminology with “noninvasive follicular tumor (NIFT) with papillary-like features” reflecting the subjectivity among pathologists in establishing the diagnosis of PTC, its RAS-like molecular profile and its extremely indolent biology not warranting the designation as “cancer.”

Synonym: Lindsay tumor

Clinical

- Common variant representing from 20% to 30% of all PTCs
- Demographics, presentation, laboratory findings essentially similar to the usual type of PTC

Pathology

Gross

- Well circumscribed to overtly encapsulated
- Tend to be solid
- Varying sizes

Histology

- Encapsulated or circumscribed without complete encapsulation:
 - Capsule tends to be thin.
 - Absence of invasive growth
- Follicular growth pattern:
 - Follicles may vary in size and shape.
 - Readily identifiable colloid, which may appear darker than colloid in normal thyroid parenchyma
 - Absence of well-formed papillae
- Despite absence of papillary growth, other architectural features of PTC may be seen, including:
 - Elongated and/or twisted follicles
 - Internal irregular fibrosis
 - Presence of psammoma bodies in interfollicular stroma but less common as compared to more typical PTCs:
- Diagnosis predicated on cytomorphologic (nuclear) features in particular:
 - Nuclear enlargement
 - Variation in nuclear size and shape with irregularities of nuclear contour
 - Identifying nuclear membrane irregularities by emerlin immunohistochemistry may be useful as an adjunct diagnostic tool.

- Above findings:
 - Should be well developed
 - Should be seen in many areas of many sections
 - Should not be diagnostically equivocal and/or very limited in extent
- Presence of so-called “sprinkling sign” characterized by admixture of multiple small cellular dark appearing tumor foci scattered in a background of larger follicles resulting in “sprinkling” appearance.
- No objective criteria for diagnosis:
 - No diagnostic threshold established above which diagnosis of FVPTC can be rendered or below which it should not be rendered
 - Given varying thresholds, there is a wide variation in diagnosis and high interobserver variability in diagnosis among pathologists, including experts in thyroid pathology.
- If findings felt to be sufficient for diagnosis of FVPTC, then entire nodule should be so classified (and measured accordingly) even if significant portions do not show diagnostic nuclear features.
- Immunohistochemistry:
 - Lesional cells are immunoreactive for:
 - Thyroglobulin (cytoplasmic and luminal colloid), TTF-1 (nuclear), PAX8 (nuclear):
 - Cytokeratins including AE1/AE3, CAM 5.2, CK7
 - CK20 negative
 - Expression of HBME1 (strong membranous staining with apical accentuation), galectin 3, cytokeratin 19, and CITED-1 suggested as differentiating PTC (positive reactivity) from lesions other than PTC:
 - Such stains are not sensitive or specific.
 - Similar staining may be present in normal thyroid follicles, follicular cells in non-neoplastic lesions (e.g., chronic lymphocytic thyroiditis), and benign follicular neoplasms.
 - Calcitonin, chromogranin, and synaptophysin negative
- Cytogenetics and molecular biology:
 - *RAS* mutation:
 - Identified by The Cancer Genome Atlas (TCGA) Research Network to be among RAS-like tumors rather than *BRAF* V600E-like tumors, although some noninvasive FVPTC had *BRAF* mutation
 - *PAX8/PPARγ* rearrangements (1% to 5%)
 - Absence of *RET/PTC* translocation and *BRAF* mutation

Differential Diagnosis

- Follicular adenoma
- Follicular carcinoma

Treatment and Prognosis

- Surgical resection is preferred treatment
- Excellent prognosis with biologic behavior akin to that of follicular adenoma
 - Absence of nodal or distant metastasis
 - Purportedly lymph node and/or distant metastasis may occur even in absence of invasion, but generally risk in absence of invasion is essentially zero.
 - Tumors prone to metastasis:
 - Thick capsule
 - Significant intratumoral fibrosis
 - Invasion (capsular and/or vascular invasion)
 - Better classified as invasive FVPTC
 - Invasive FVPTC has potentially more aggressive behavior; see below.

Invasive FVPTC (Fig. 28-50)

Definition: Characterized by follicular pattern growth with absence of well-formed papillae and diagnosis predicated on basis of cells showing nuclear features diagnostic for PTC.

- Similar to encapsulated noninvasive counterpart (clinical, histology and immunohistochemistry) except for:
 - Presence of invasion, including capsular and/or vascular invasion
 - Tendency to show:
 - Greater degree of intratumoral fibrosis
 - Extrathyroidal extension
 - Presence of *BRAF* mutation and *RET/PTC* translocation:
 - Identified by The Cancer Genome Atlas (TCGA) Research Network to be among *BRAF* V600E-like tumors rather than *RAS*-like tumors
 - *RAS* mutation occasionally identified

Differential Diagnosis

- Follicular carcinoma

Treatment and Prognosis

- Surgical resection is preferred treatment.
- Excellent prognosis but in contrast to noninvasive FVPTC:
 - Greater tendency to develop nodal metastasis

Classification of Encapsulated Follicular Tumor

- Classification of an encapsulated follicular tumor showing equivocal cytomorphologic features for papillary thyroid carcinoma or isolated limited foci diagnostic for papillary thyroid carcinoma remains controversial:

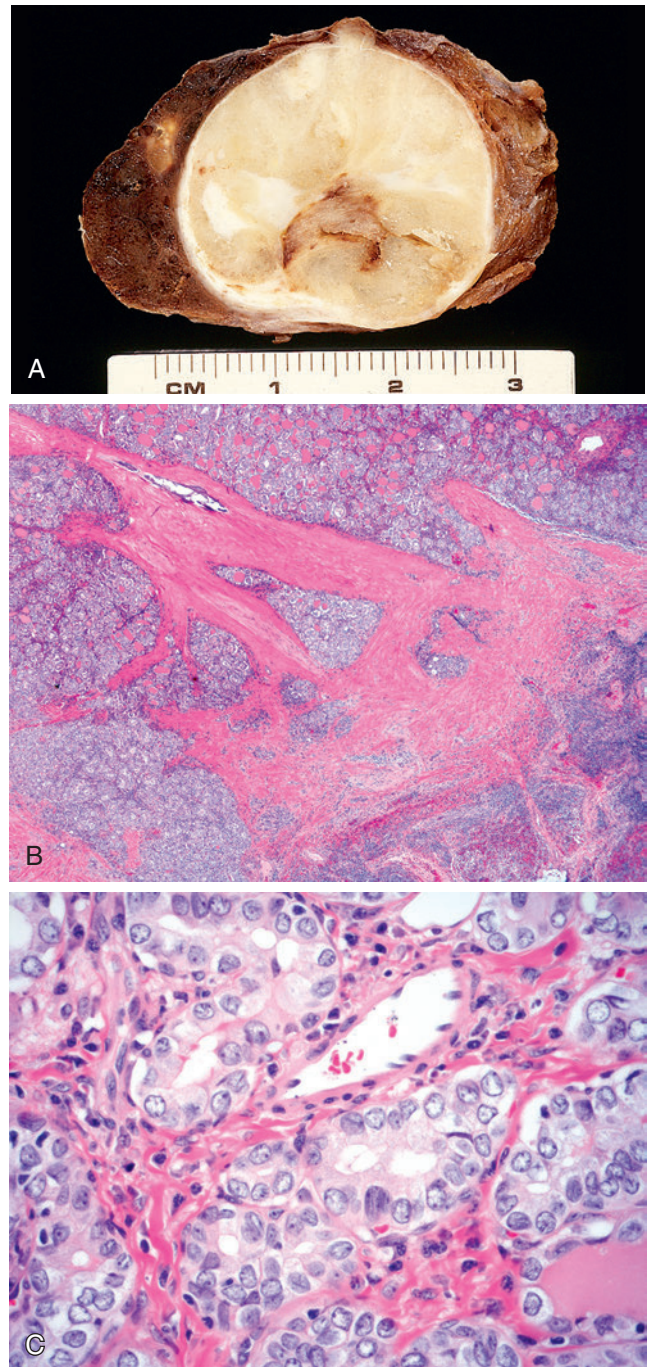


Fig. 28-50. Follicular variant of papillary thyroid carcinoma, invasive.

A, The tumor is predominantly circumscribed to encapsulated with an area of grossly evident invasive growth (violation of the capsule) at the superior aspect of the resection specimen. **B,** Histologically the tumor entirely composed of a follicular growth pattern invades through and beyond its capsule. **C,** Nuclear features diagnostic for PTC. The presence of invasion generally confers a more aggressive biologic behavior to the tumor.

- If extent of change is significant/widespread (to date there is no clear definition of what constitutes “significant” or “widespread”), then the diagnosis of encapsulated papillary thyroid carcinoma, follicular variant can be made.
 - If features are equivocal and there is no invasion, then this tumor can be termed as a follicular adenoma (with or without atypical features).
 - If features are equivocal but there is definitive evidence of invasion, then tumor can be diagnosed as carcinoma:
 - In such circumstances specific designation of type of carcinoma (i.e., papillary versus follicular) is academic because treatment should be the same.
 - Depending on one’s level of confidence following designations can be used:
 - Carcinoma, favor thyroid papillary carcinoma, follicular variant
 - Carcinoma, favor follicular carcinoma, minimally invasive
 - Well-differentiated carcinoma, not otherwise specified or well-differentiated (follicular) tumor of uncertain malignant potential
 - Not favored, given no link to defined clinical management, frustrating to clinicians and patients with such tumors
 - As previously indicated, reclassification of follicular variant of PTC is inevitable. A recent recommendation by a panel of expert thyroid pathologists (Nikiforov Y, et al—to be published) is to replace the term (noninvasive) FVPTC with an alternative nomenclature based on the facts that: in contrast to classic and many variants of PTC, this tumor has a RAS-like molecular profile; and given its extremely indolent biologic behavior the designation as “carcinoma” is not warranted. The proposed term recommended by that panel was “noninvasive follicular tumor (NIFT) with papillary-like features” which may be retained or may be slightly altered in the final recommendation.
 - Irrespective of specific designation, in such examples prognosis is excellent.
- At low magnification, bears resemblance to adenomatoid or hyperplastic nodules requiring high magnification to evaluate nuclear morphology
 - Macrofollicular growth predominates:
 - Admixture of smaller (nonmacrofollicles) follicles
 - Readily apparent colloid-filled follicles present
 - A potential hint suggesting diagnosis is presence of cellular foci seen throughout neoplasm in central and peripheral locations:
 - Cellular foci show characteristic nuclear features of PTC (see [Box 28-4](#)).
 - Cells lacking PTC-like nuclei are present, including cells with clear nuclei and coarse chromatin, as well as low cuboidal cells with hyperchromatic nuclei may be identified.
 - Given variably nuclear features as well as presence of abundant colloid, macrophages, macrofollicular follicular cell arrangement, and/or absence of widespread cytologic features associated with papillary carcinoma, erroneous diagnosis of goiter can be rendered on FNAB.
 - Presence of papillae not required for diagnosis but abortive papillary structures can usually be found
 - Treatment and prognosis same as that of conventional PTC:
 - Most behave in indolent manner
 - Few cases associated with aggressive behavior, unresponsive to radioactive iodine therapy and poor prognosis
 - May metastasize including to:
 - Regional lymph nodes:
 - Reported to occur in 20% of cases
 - Histology in metastasis often is similar to primary tumor with a macrofollicular architecture
 - In some reported cases no evidence of invasion in spite of nodal metastatic disease
 - Distantly:
 - 6% of cases
 - Most commonly to lung
 - Other sites may include bone.
 - Rare example reported of anaplastic transformation

Diffuse (Multinodular) Follicular Variant

Macrofollicular Variant ([Fig. 28-51](#))

- Rare variant
- In all regards, essentially similar to follicular variant except:
 - Neoplastic follicles are large (macrofollicles) measuring >200 μ m in diameter.
 - Macrofollicles represent >50% of neoplasm.
- Majority are encapsulated or circumscribed.
- Rare reported aggressive form of PTC
- More common in men than women; tends to occur in younger patients (second to third decades)
- Characterized by diffuse replacement of one lobe or entire thyroid gland that may include:
 - Multiple nodules
 - Diffuse involvement of gland without apparent nodules and/or associated sclerosis

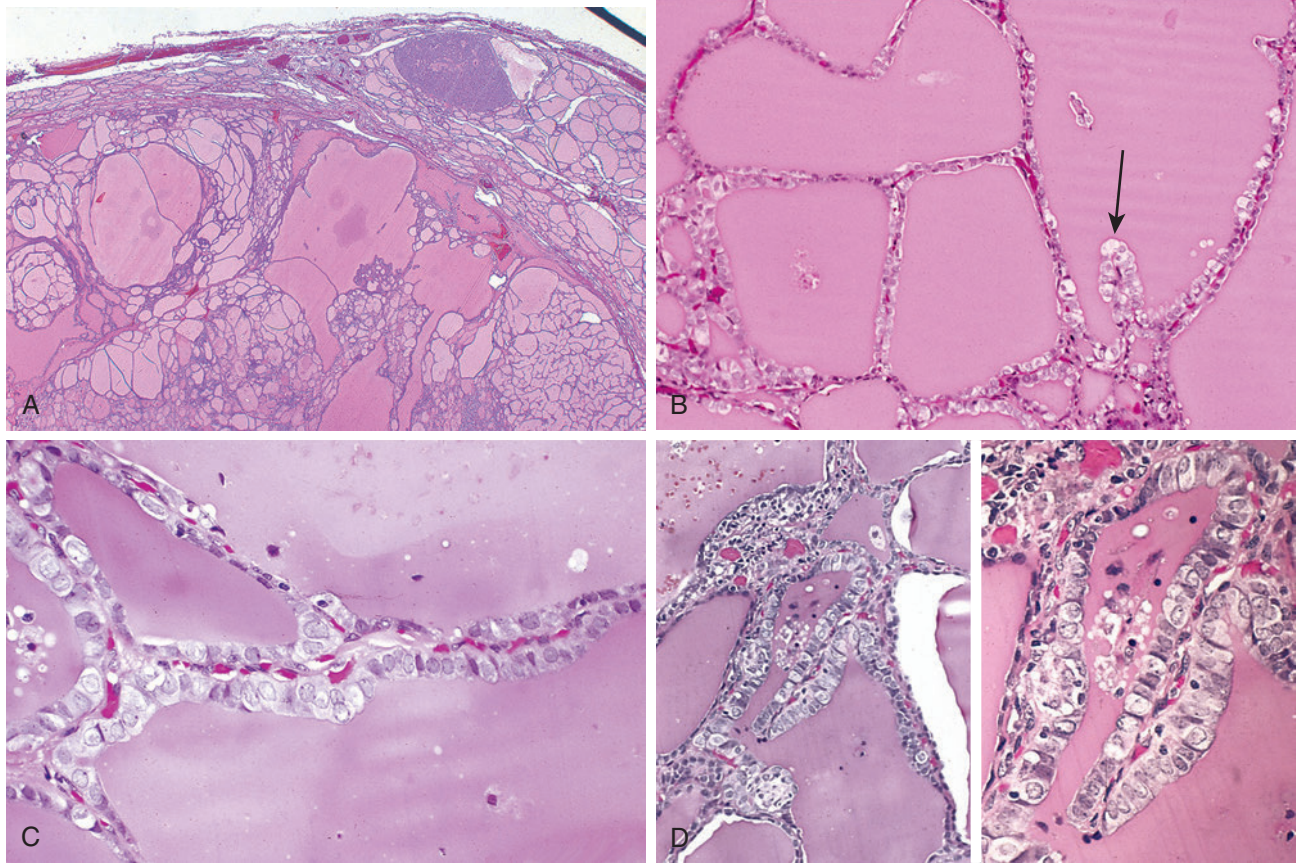


Fig. 28-51. Macrofollicular variant of thyroid papillary carcinoma.

A, At low magnification, the lesion is circumscribed but unencapsulated, and noninvasive with an appearance suggesting a diagnosis of an adenomatoid nodule including enlarged/widened follicles (macrofollicles). **B**, At this magnification the cells lining the macrofollicles appear unremarkable; focally an aborted papillary structure is seen (arrow). **C**, At higher magnification the cells lining the follicles show nuclear features diagnostic for PTC. **D**, Left and right, areas of the tumor show papillary architecture with diagnostic nuclear features. The key to the diagnosis is the nuclear alterations whether papillae are or are not identified.

- Follicular pattern growth predominantly small follicles but may be comprised other growth patterns including:
 - Macrofollicles
 - Solid
 - Trabecular
- Irrespective of growth pattern(s), characteristic nuclear features of PTC present but usually lack sclerosis and psammoma bodies
- Associated with invasive growth, including:
 - Lymph-vascular invasion
 - Extrathyroidal extension with invasion of tracheal cartilage and esophagus
 - Nodal metastasis (approximately 88%)
 - Distant (visceral) metastasis including to lungs (75%) and bone (25%)
- Prognosis is favorable due to younger age of patients and excellent response to radioactive iodine therapy,

although (older) patients reported with more aggressive and fatal outcome.

Oncocytic (Oxyphilic, Hürthle Cell) Variant (Fig. 28-52)

- Rare variant
- Gross:
 - Tumors tend to be circumscribed or encapsulated, measuring from 0.5 to 6 cm in greatest dimension.
 - Consistency varies from soft to fleshy to firm and appear yellow to orange to brown in color.
 - Cystic change can be seen.
- Architecturally, tumors show prominent papillary growth with complex configurations and fibrovascular cores:

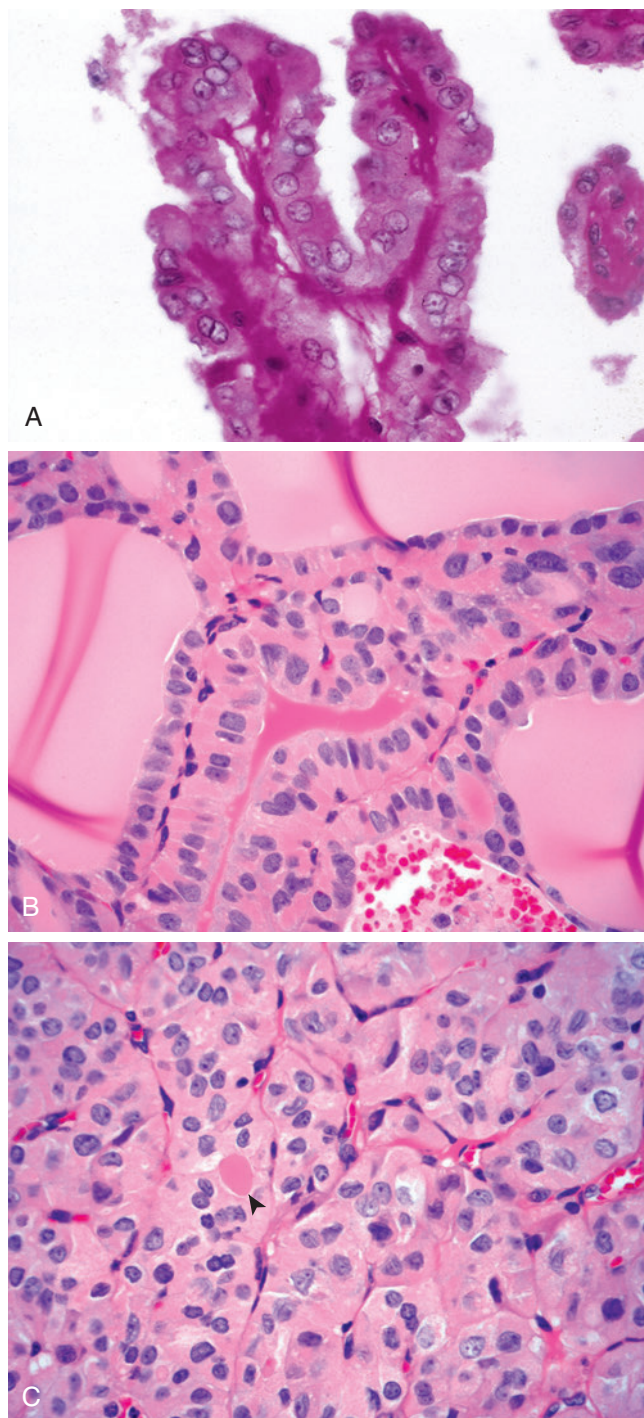


Fig. 28-52. Oncocytic papillary thyroid carcinoma.

Oncocytic variants of papillary thyroid carcinoma characterized by cells with brightly eosinophilic, granular cytoplasm and diagnostic nuclear features with (A) papillary growth, (B) follicular growth, and (C) predominantly solid growth with a colloid-filled follicle (arrowhead).

- Other growth patterns may include:
 - Follicular growth (oncocytic follicular variant of PTC)
 - Solid growth
- Characteristic cytomorphologic feature is dominance of cells with an abundant eosinophilic, finely to coarsely granular cytoplasm representing increased cellular mitochondria:
 - Focally, clear cytoplasmic change may be seen.
 - Cells are enlarged but are not twice as tall as they are wide and do not have distinct cell membranes (features of tall cell variant, see later).
- Nuclear alterations are those of PTC:
 - Although not seen in all cases, nuclei may have tendency to localize to apical (“tips”) portion of cell
 - Psammoma bodies may be identified.
- Background chronic lymphocytic (Hashimoto) thyroiditis may be present from one third to more than 85% of cases:
 - When prominent overall features resemble those of Warthin tumor-like variant of PTC (see below)
- Immunohistochemistry:
 - Thyroglobulin, TTF-1, cytokeratin, and vimentin reactivity present
- Cytogenetics and molecular genetics:
 - High prevalence of *BRAF* V600E mutations
 - Frequent *RET/PTC* rearrangements
- Must be differentiated from oncocytic follicular adenomas with papillary hyperplasia, which lack characteristic nuclear features associated with PTC
- May invade into adjacent thyroid parenchyma:
 - Extrathyroidal extension may occur but it is uncommon.
- Treatment and prognosis same as conventional PTC

Warthin-Like Variant (Fig. 28-53)

- Rare variant of PTC showing histologic similarity to salivary gland Warthin tumor
- More common in women than in men (10:1); occur over a wide age range from third to seventh decades with mean patient age in fifth decade
- Fine-needle aspiration biopsy:
 - Cellular smears, mostly in large and small papillary clusters of oncocytic-appearing cells
 - Nuclear grooves and rare nuclear inclusions
 - Lymphoplasmacytic cell background
- Tend to be circumscribed and solid but (central) cystic change may be present
- Overlapping features with oncocytic variant of PTC of which it may be considered a subvariant
- Histologic findings include:
 - Papillary architecture with papillae lined by cells with eosinophilic granular (oncocytic) cytoplasm
 - Characteristic nuclear features of PTC

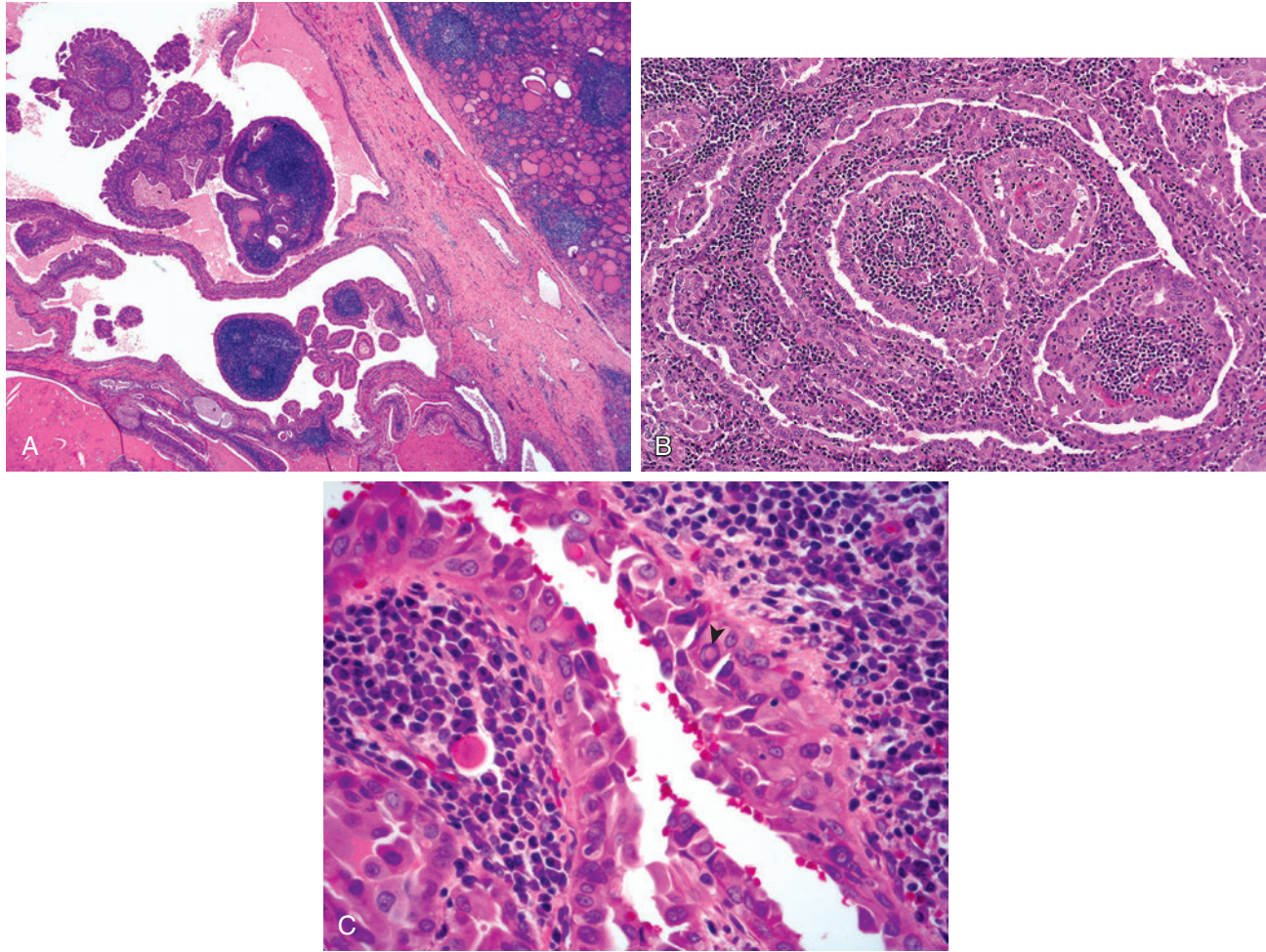


Fig. 28-53. Warthin-like variant of papillary thyroid carcinoma.

A, This thyroid tumor is characterized by similar features to parotid gland Warthin tumor (also referred to as papillary cystadenoma lymphomatosum), including cyst formation, papillary architecture, and presence of associated lymphoid infiltrate; note the presence of chronic lymphocytic (Hashimoto) thyroiditis in the adjacent thyroid parenchyma (*upper right*). **B,** Papillae are lined by cells with eosinophilic cytoplasm with a dense lymphoid infiltrate in the cores of the papillae. **C,** At high magnification the cells show eosinophilic granular (oncocyctic) cytoplasm, characteristic nuclear features of PTC including intranuclear inclusion (*arrowhead*), and a lymphoplasmacytic cells infiltrate in the core of the papillae.

- Lymphoplasmacytic cells infiltrate in core of papillae:
 - Admixture of T- and B-cells
 - Germinal centers may be present.
- Often occurs in background of chronic lymphocytic (Hashimoto) thyroiditis
- Cytogenetics and molecular genetics:
 - *BRAF* mutations
 - *RET/PTC* translocation
- Treatment and prognosis similar to conventional PTC:
 - Generally good prognosis but nodal metastasis and extrathyroidal extension may be identified
- Rare reports of dedifferentiated and/or anaplastic transformation

Clear Cell Variant (Fig. 28-54)

- Histologic variant in which predominant cell type (>50%) has clear-appearing cytoplasm and nuclear features diagnostic for PTC:
 - Other than distinct clear cell features, architecture and nuclear morphology are those of the conventional PTC
 - Presence of clear cytoplasm primarily due to accumulation of glycogen (intracytoplasmic diastase-resistant, PAS-positive) but may also be due to lipid, thyroglobulin, and distended mitochondria
 - Cells with oncocyctic cytoplasm may be present but represent minor component.

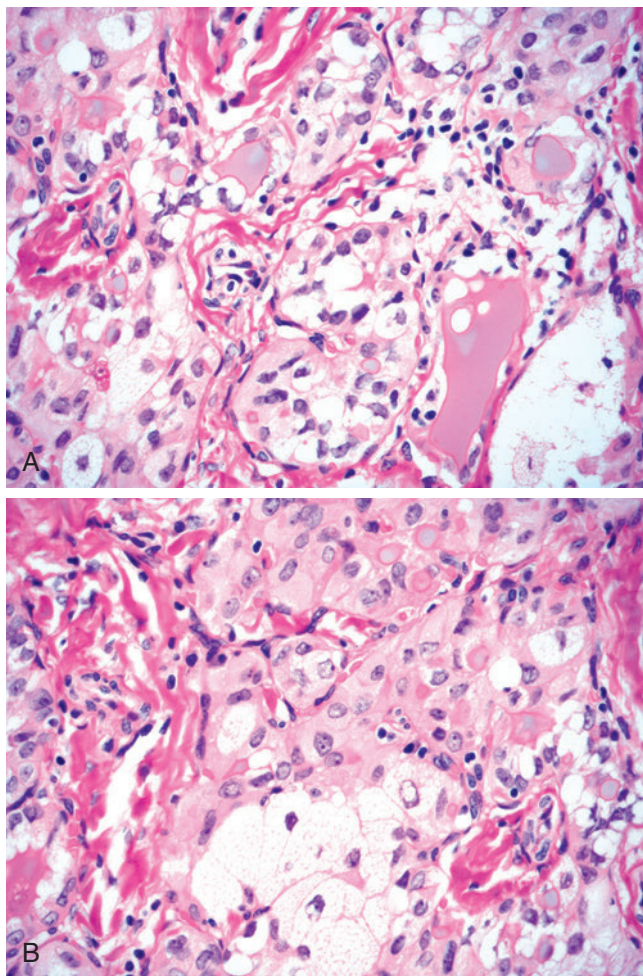


Fig. 28-54. Clear cell variant of PTC.

A, Papillary thyroid carcinoma with clear cells in which cells with distinct clear-appearing cytoplasm show nuclear morphology diagnostic for PTC. **B**, In association with the clear cells (lower) there are cells with oncocytic cytoplasm.

- May require immunohistochemistry to confirm follicular epithelial, cell origin, including:
 - Thyroglobulin, TTF-1 (nuclear), PAX8 (nuclear) reactivity
 - Calcitonin, synaptophysin, and chromogranin negative (differentiates from medullary thyroid carcinoma, clear cell variant)
 - CD10, renal cell carcinoma antibody, and PAX2, PAX8, CAIX negative (differentiates from metastatic renal cell carcinoma)
 - PAX8 (nuclear) reactivity not a discriminator between thyroid follicular cell origin and renal cell carcinoma because both are reactive for this marker
- Treatment and prognosis similar to those of conventional PTC

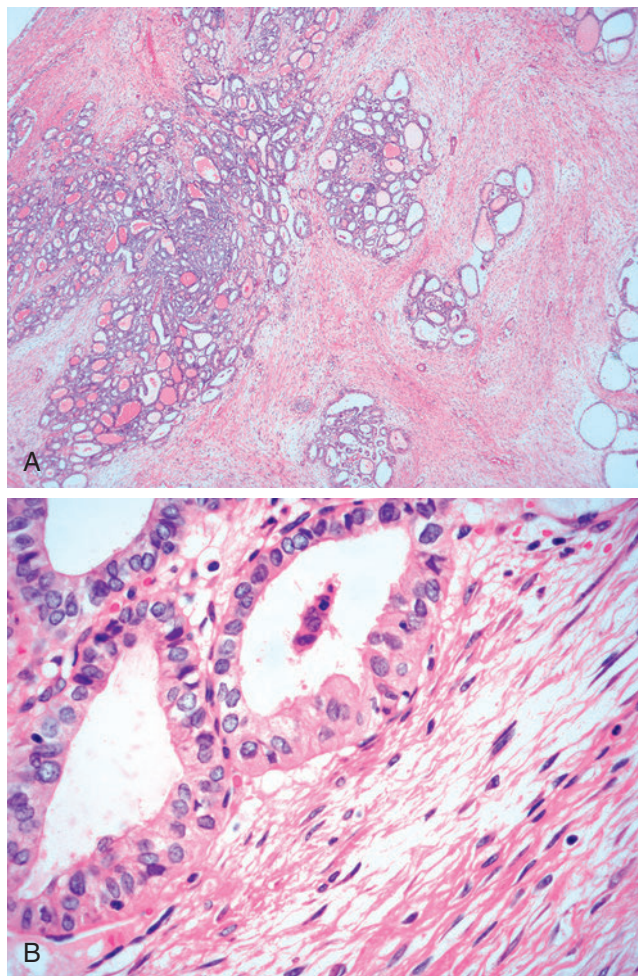


Fig. 28-55. PTC with fasciitis-like or fibromatosis-like stromal component.

A, PTC component includes anastomosing cords and tubules set in a spindle-shaped cellular proliferation with fibromyxoid stroma. **B**, At higher magnification the follicles include cells with nuclear features diagnostic for PTC, and adjacent spindle cells that are cytologically bland.

PTC with Nodular Fasciitis-Like or Fibromatosis-Like Stroma

(Fig. 28-55)

- Unusual histologic variant of PTC characterized by presence of a fasciitis-like or fibromatosis-like stromal component:
 - Confined to thyroid gland and likely represents an exaggerated stromal response to presence of invasive carcinoma
 - Stromal component may be exuberant and obscure diagnostic foci of PTC.
- Stromal component composed of:
 - Spindle-shaped cells with irregular fascicular growth, fibromyxoid stroma, and extravasated red cells

- But may also include:
 - Less dense cellularity with looser arrangement of spindle cells and associated myxoid stroma
 - Keloid-like fibrosis
- Spindle cells:
 - Cytologically bland with vesicular chromatin, small nucleoli, and low nuclear-to-cytoplasmic ratio
 - Mitotic figures may be identified but atypical mitoses not present
 - Immunoreactive for:
 - Vimentin and actins (support myofibroblastic nature of cells)
 - Beta-catenin (nuclear) reported in a single case to date
 - Cytokeratins, thyroglobulin, TTF-1, and PAX8 negative
- PTC component:
 - Arranged in anastomosing cords, tubules, and papillae
 - Nuclear features characteristic for PTC are present.
 - Associated squamous metaplasia may be identified.
- Treatment and prognosis are similar to those of conventional PTC.
- Nodal metastasis may occur and typically includes only carcinomatous component and not nodular fasciitis-like component.
- Differential diagnosis may include:
 - Undifferentiated (anaplastic) thyroid carcinoma
 - Presence of PTC with exuberant spindle cell proliferation may suggest diagnosis of undifferentiated (anaplastic) carcinoma but absence of cytologically high-grade features in spindle cell component of nodular fasciitis-like stroma should allow for differentiation.
 - Reactive fibrosis:
 - PTC component may not be readily apparent, owing to limited sampling or obscuring of neoplastic proliferation by spindle cell proliferation

Solid Variant (Fig. 28-56)

- PTC in which >50% of tumor has solid or trabecular growth
- Occurs in adults as well as in children and may be predominant pattern in very young children, especially those exposed to ionizing radiation:
 - Radiation-induced:
 - Along with diffuse sclerosing variant (see later in this chapter) represents most common growth pattern identified in children following Chernobyl accident
 - Higher radiation doses associated with higher frequency of solid and diffuse

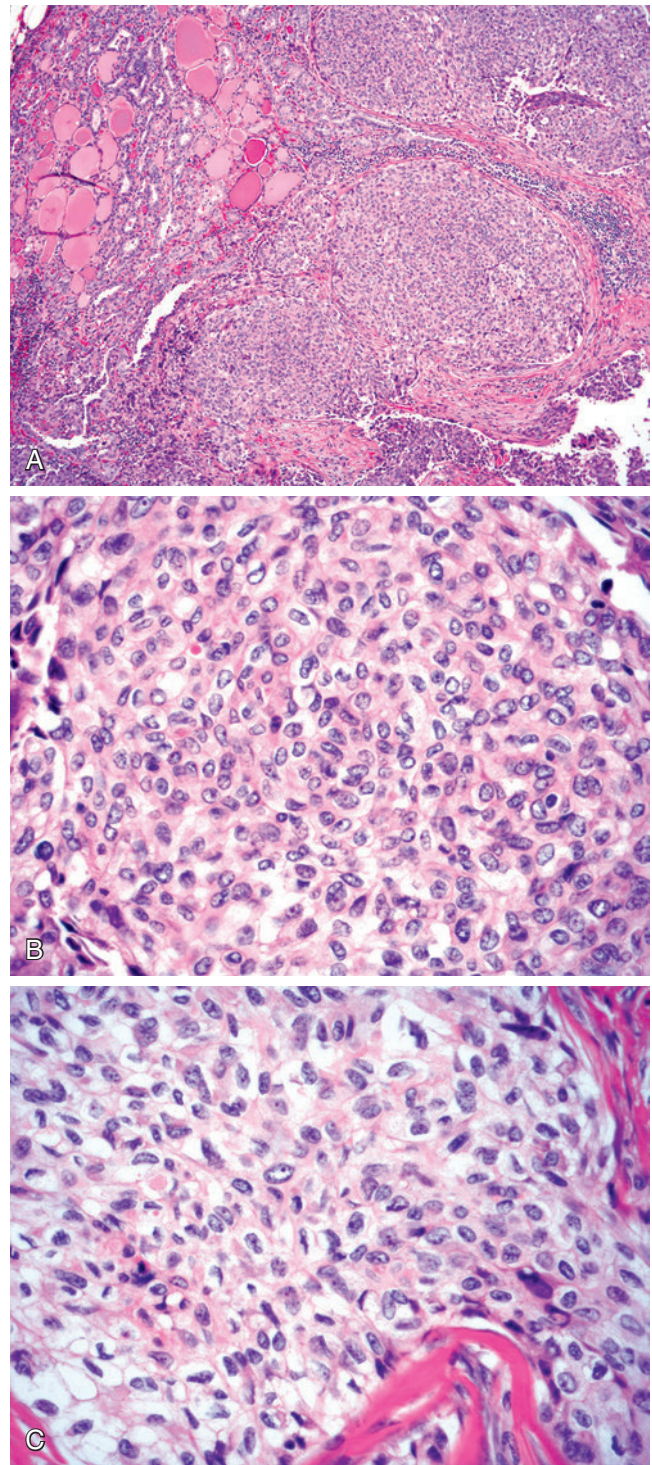


Fig. 28-56. Solid variant of thyroid papillary carcinoma.

A, Solid (diffuse) growth that comprises greater than 50% of the tumor. **B** and **C**, Nuclear features are diagnostic for papillary thyroid carcinoma. In contrast to poorly differentiated thyroid carcinoma, there is an absence of necrosis and increased mitotic activity.

- sclerosing variants as well as histologic features of cancer aggressiveness, including lymph-vascular invasion, intrathyroidal infiltration, multifocality
 - Other growth patterns may be seen in this setting, including follicular and papillary (classic).
- Solid nests may be separated by thin fibrovascular stroma, creating “insular” or nested/organoid pattern of growth:
 - Stromal component may vary from thin fibrous strands to thick fibrous bands.
 - Fibrovascular stroma with separation artifact may be seen in association with insular pattern.
- Follicular and papillary growth patterns can be focally identified:
 - Microfollicles (with or without colloid) as well as larger colloid-filled follicles may be identified.
 - Abortive papillae or well-formed papillae can be seen.
- Nuclear features diagnostic for PTC present
- No increase in mitotic activity and no necrosis
- Immunohistochemical staining includes:
 - Reactivity for thyroglobulin (may be very focal and/or limited in extent), TTF-1 (nuclear), PAX8 (nuclear)
 - Absence of calcitonin, synaptophysin, chromogranin
- Cytogenetics and molecular genetics:
 - Presence of *RET/PTC3* in most pediatric (postradiation exposure) cases but absent in adult patients without radiation exposure
- Differential diagnosis includes:
 - Poorly differentiated thyroid (“insular”) carcinoma (PDTC) (see later in this chapter):
 - Rare tumor type in children, adolescents, and young adults
 - Shares growth patterns with solid variant
 - Diagnosed primarily on basis of increased mitotic activity and presence of tumor necrosis findings not identified in solid variant of PTC
 - Medullary thyroid carcinoma:
 - Absence of colloid-filled follicles
 - Presence of immunoreactivity for calcitonin, synaptophysin, chromogranin
 - Absence of immunoreactivity for thyroglobulin, TTF-1, PAX8
- Prognosis:
 - In adults tends to have more aggressive behavior, including:
 - More frequently associated with distant metastasis
 - Slightly higher mortality rates
 - Post-Chernobyl radiation induced found to be:
 - Associated with higher frequency of lymph node metastases

- Associated with higher frequency of angioinvasion
- Associated with higher frequency of extrathyroidal invasion

Cribiform-Morular Variant (CMV-PTC) (Fig. 28-57)

- Rare variant of PTC representing less than 1 % of all PTCs
- May occur in association with familial adenomatous polyposis (FAP) or independent of FAP
- In setting of FAP:
 - Striking female predominance
 - Mean age at diagnosis in third decade of life; may occur in pediatric ages
 - Tend to be multifocal
 - Thyroid carcinoma may be identified prior to diagnosis of FAP.
 - Patients with CMV-PTC should be referred for colonoscopy and/or genetic evaluation for FAP because up to 40% will prove to have FAP.
 - Patients show germline mutation in adenomatous polyposis coli (*APC*) gene that frequently affects codon 15
- In non-FAP setting:
 - Sporadic occurrence
 - Also tend to occur in young females
 - Solitary lesion
 - Do not carry germline *APC* mutation
 - Frequently have somatic mutation in *APC* gene or in *CTNNB1* gene coding for β -catenin
- Histology:
 - Multiple or solitary circumscribed to encapsulated nodules:
 - Multifocality represents strong indicator of familial disease.
 - Invasion (capsular, vascular) may or may not be present.
 - Characterized by presence of prominent cribriform growth with interspersed squamoid islands referred to as morules
 - Cribriform:
 - Closed packet and fused follicles
 - Typical without identifiable colloid (empty spaces)
 - Morules:
 - May be absent in any given case
 - No evidence of squamous differentiation in form of keratinization and intercellular bridges
 - Additional growth characteristics may include:
 - Papillary architecture
 - Trabecular pattern with associated hyalinization

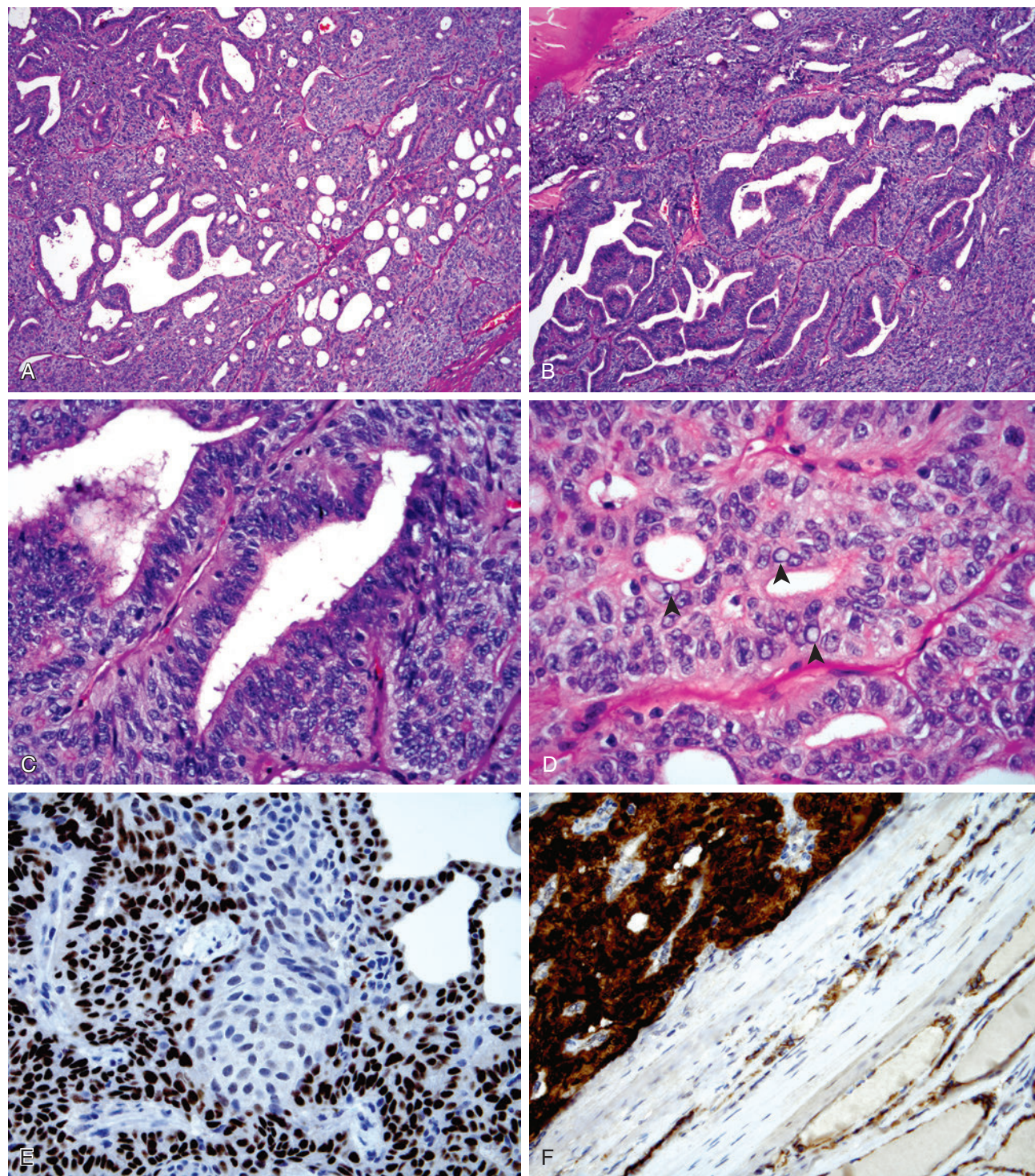


Fig. 28-57. Cribriform-morular variant of papillary thyroid carcinoma.

A, B, Cribriform growth includes closely packed and/or fused follicles that appear empty without colloid. Papillary growth pattern (*lower left*) may be present. **C,** Tumor cells appear columnar. **D,** Nuclei show nuclear (chromatin) clearing or inclusions appearing homogeneous and lightly eosinophilic and represent biotin-rich inclusions (*arrowheads*). **E,** Lesional cells are strongly TTF1 (nuclear) positive although a morular appearing focus is negative. **F,** Lesional cells (*top left*) show strong β -catenin nuclear and cytoplasmic staining in contrast to the normal (*non-neoplastic*) thyroid cells that show membranous (and not nuclear) staining (*bottom right*).

- Tumor cells may appear columnar or cuboidal:
 - Oncocytic cytoplasmic changes may be present.
- Nuclear features characteristic for PTC present but may only be focally found
- Nuclei show nuclear (chromatin) clearing or inclusions:
 - Appear homogeneous and lightly eosinophilic
 - Represent biotin-rich inclusions
- Psammoma bodies may be identified but are uncommon.
- Immunohistochemistry:
 - Neoplastic cells are:
 - Strongly immunoreactive for cytokeratins and TTF-1 (nuclear)
 - Tend to be focal and weakly thyroglobulin positive
 - β -catenin reactive (strong nuclear and cytoplasmic staining)
 - Normal (non-neoplastic) thyroid cells show membranous staining pattern for β -catenin, which changes to nuclear and cytoplasmic staining in neoplastic cells:
 - β -catenin staining supportive of diagnosis and may prove useful in cases with equivocal diagnostic features in cytologic and/or surgical material
 - In familial cases germline inactivating mutation of *APC* tumor suppressor gene and in sporadic cases somatic *APC* mutations or somatic mutations of *CTNNB1* gene that stabilize β -catenin prevent cytoplasmic degradation and promote accumulation in nuclei
 - Rare example reported with neuroendocrine differentiation including reactivity for synaptophysin and chromogranin but absence of calcitonin
 - Cytogenetics and molecular genetics:
 - *RET/PTC* rearrangement common
 - *BRAF* mutations not identified
 - Prognosis:
 - Nodal metastases occur in up to 20% of patients
 - Survival similar to that of classic PTC
 - Rare example of coexisting poorly differentiated thyroid carcinoma reported
- Generally are large, measuring more than 5 cm
- Often present with extrathyroidal extension
- Tend to disseminate early in disease course with regional lymph node metastasis as well as distant metastasis (particularly to lung)
- Are treated more aggressively than conventional PTC or less aggressive variants of PTC
- Some of tumors included within aggressive variants of PTC have been designated according to a particular cell type (e.g., tall, columnar), whereas others have been designated according to a growth pattern (e.g., insular); fact that these tumors are included within the spectrum of aggressive variants, and treated accordingly, should not be predicated solely on basis of a particular cell type or growth pattern; rather, each tumor should be evaluated as any other papillary carcinoma based on other potential prognostic parameters, including:
 - Patient age, tumor size, and extent of invasion (i.e., the presence or absence of extrathyroidal extension)
- Given tendency for these tumors as a group to be large, they may also have a tendency to have extrathyroidal extension; this finding, perhaps with some additional features associated with these tumors (e.g., older age at presentation), probably play a much more significant role than cell type or growth pattern in predicting aggressiveness of tumor.
- Exception to this would be the undifferentiated (anaplastic) thyroid carcinoma, which by definition is a high-grade, aggressive tumor

BIOLOGICALLY AGGRESSIVE VARIANTS OF PTC

See Box 28-6.

General Considerations

- These variants of PTC:
 - Tend to occur in older-age patients (except for the diffuse sclerosing variant)

Diffuse Sclerosing Variant (DSV)

(Figs. 28-58 and 28-59)

Clinical

- Uncommon variant representing less than 1% to 2% of PTCs
- Occurs more commonly in women than in men; tends to occur in younger age groups typically in second and third decades
- Clinical presentation most often as bilateral goiter or diffuse enlargement of thyroid gland rather than as a single mass; however, some patients may present with a “dominant” nodule with diffuse involvement of single lobe
- Delay in diagnosis may be due to fact that clinical presentation similar to that of chronic thyroiditis, including presence of serum antithyroid antibodies, including antithyroglobulin and antimicrosomal antibodies
- No known etiologic factors:
 - May occur in patients with radiation exposure

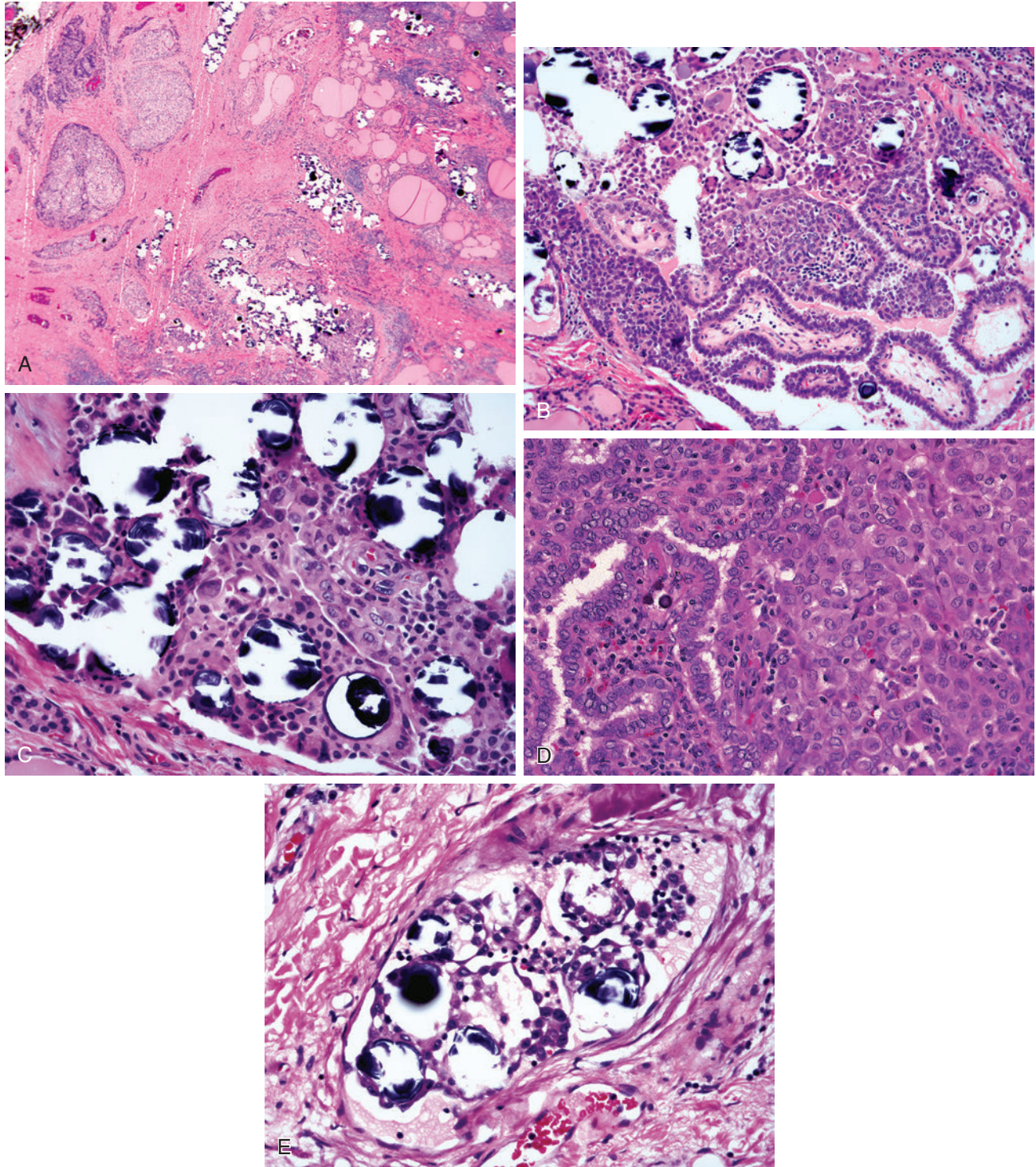


Fig. 28-58. Diffuse sclerosing variant of papillary thyroid carcinoma.

A, Diffusely infiltrative tumor with associated sclerosis including solid nests (*left*) as well as tumor nests with associated calcifications and a background of chronic lymphocytic thyroiditis. **B** and **C**, Papillary and solid growth with associated psammoma bodies. **D**, Associated squamoid squamous metaplasia including squamous morules is frequently present. **E**, Lymph-vascular space invasion is another feature commonly identified. Although not illustrated, extrathyroidal extension was present.

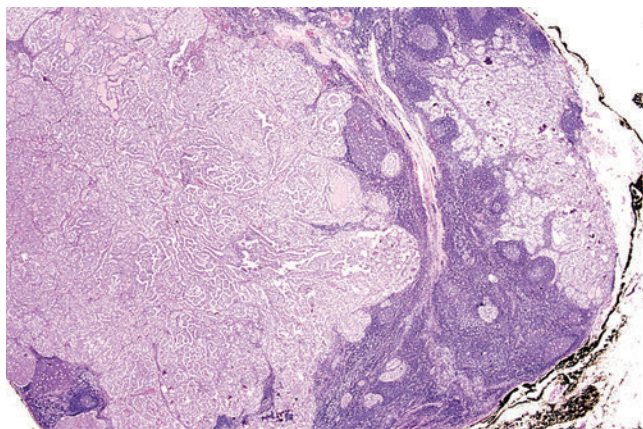


Fig. 28-59. Metastatic DSV.

The diffuse sclerosing variant of papillary thyroid carcinoma is associated with an increased incidence of cervical lymph node metastasis. The metastatic foci may include the presence of (numerous) psammoma bodies.

Pathology

Gross

- Bilateral diffusely enlarged thyroid gland or a discrete dominant mass or nodule may be present.
- Irrespective of extent of involvement, mass is firm, tan-white to gray in appearance with ill-defined borders and marked fibrotic change.
 - Identifiable mass may measure 5 cm (or more) in greatest dimension.
- Due to presence of innumerable psammoma bodies (see below), these tumors characteristically have a gritty consistency on cut section.

Histology

- Diffuse involvement of one lobe or entire gland:
 - At low magnification findings include:
 - Readily apparent background of chronic lymphocytic thyroiditis, including germinal centers
 - Dense sclerotic bands
 - Numerous psammoma bodies
- Tumor nests appear solid with associated squamous metaplasia, including squamous morules and islands:
 - Neoplastic cells in foci of squamous metaplasia lack nuclear features of PTC but in other foci diagnostic nuclear features can be found.
 - Innumerable psammoma bodies, including concentric laminations, seen in association with or separate from neoplastic foci
 - Prominent papillary growth with solid areas
- Pronounced fibrosis seen throughout gland
- Lesional cells have propensity to invade the intrathyroidal lymphatic spaces as well as the tendency to show extrathyroidal extension.
- A dense lymphoplasmacytic cell infiltrate is present that may include germinal centers.

- Immunohistochemistry:
 - Lesional cells are variably reactive for:
 - Cells of papillary carcinoma and squamous metaplasia are immunoreactive for thyroglobulin, TTF-1 (nuclear), and cytokeratins
 - Thyroglobulin staining may be weakly positive to absent in squamous metaplastic cells
 - p63 reactivity in squamous metaplastic cells
- Cytogenetics and molecular genetics:
 - *RET/PTC* rearrangement frequently found
 - *BRAF* mutation rarely found

Differential Diagnosis

- Chronic lymphocytic thyroiditis with squamous metaplasia

Treatment and Prognosis

- Total thyroidectomy or near total thyroidectomy is preferred treatment often supplemented by postoperative radioactive iodine therapy.
- Associated with more adverse prognostic findings, including:
 - Higher incidence of extrathyroidal extension
 - High incidence (greater than 80%) of cervical lymph node metastasis (uni- and bilateral)
 - Greater incidence of distant metastasis (approximately 10% to 15%) primarily (but not exclusively) to lung and may also include brain, bone, and liver
 - Shorter periods of disease-free survival
- Despite greater incidence of distant (pulmonary) metastases, mortality rates comparable to those of conventional PTCs possibly owing to ameliorating effects of younger age with:
 - 93% disease-specific survival at 10 years

Tall Cell Variant (TCV)

(Figs. 28-60 through 28-62)

Definition: Type of PTC characterized by presence of tall cells with the following combination of features:

- “Tall” defined as cells whose heights are at least three times greater than their widths:
 - Depending on plane of sectioning cells may be wider than tall
 - Not unique cell type to this variant and may be seen in conventional PTC as well as in other variants—in particular, columnar cell variant (see below)
- Presence of cells with eosinophilic cytoplasm (not quite to level of oncocytes or so-called Hürthle cells)
- Presence of distinct cell borders
- Above finding should be present in at least 50% of a given tumor to be diagnostic for TCV.
 - Those PTCs with tall cells in less than 50% of a given tumor have been referred to as papillary

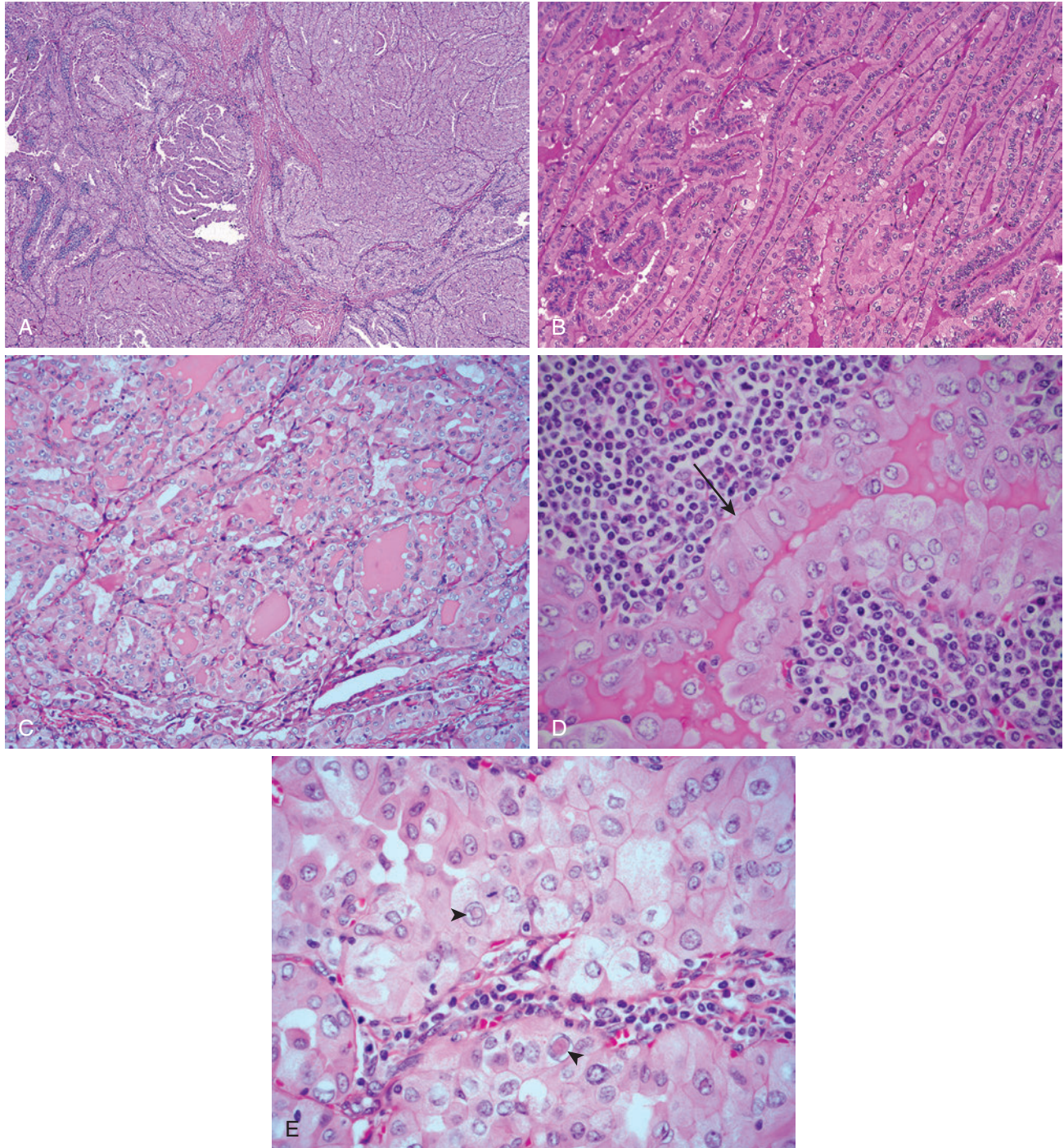


Fig. 28-60. Tall cell variant of papillary thyroid carcinoma.

A, At low magnification this variant of PTC tends to be extensively infiltrative and characterized by prominent papillary architecture. In addition to papillary architecture, this tumor also shows **(B)** elongated follicles arranged in parallel alignment ("railroad track"-like) and **(C)** follicular growth; **(D)** lesional cells are "tall" (*arrow*), defined as at least three times greater than their widths with eosinophilic cytoplasm (not quite to level of oncocytes or so-called Hürthle cells) and the presence of distinct cell borders. Depending on the plane of sectioning the lesional cells may be wider than tall, emphasizing the other criteria, including slightly eosinophilic cytoplasm and distinct cell borders. **E**, Nuclear features diagnostic for PTC are present, including readily identifiable nuclear inclusions (*arrowheads*).

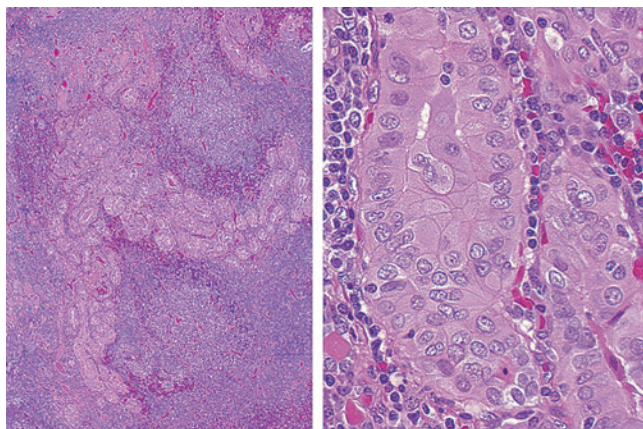


Fig. 28-61. Tall cell variant of papillary microcarcinoma.

Left, An incidental focus of papillary microcarcinoma is present in association with chronic lymphocytic (Hashimoto) thyroiditis identified in a thyroid gland resected for multinodular goiter. *Right*, At higher magnification the histologic features are those of the tall cell variant of thyroid papillary carcinoma. In general, microscopic foci of PTC do not convey any more aggressive behavior than more usual foci of PTC, but microscopic foci of the tall cell variant are reported as potentially being associated with aggressive biologic behavior.

thyroid carcinoma with tall cell features (see [Treatment and Prognosis](#) below)

Clinical

- Represents up to 10% of all PTCs
- More common in women than men; generally occurs in older age groups (\geq sixth decade of life):
 - May occur but uncommon in pediatric and young adult ages
- Clinical presentation includes asymptomatic or enlarging neck mass.
- Appear as “cold” nodules on thyroid scanning
- Etiology:
 - Unknown

Pathology

Fine-Needle Aspiration Biopsy

- Cytomorphologic features may include presence of papillary fronds, oncocyctic cells with prominent nuclear grooves, and intranuclear cytoplasmic inclusions.
- Multiple inclusions within same nucleus impart a “soap bubble appearance” to nucleus, a finding rarely seen in conventional PTC.

Gross

- Tend to be large, measuring >5 cm in greatest dimension

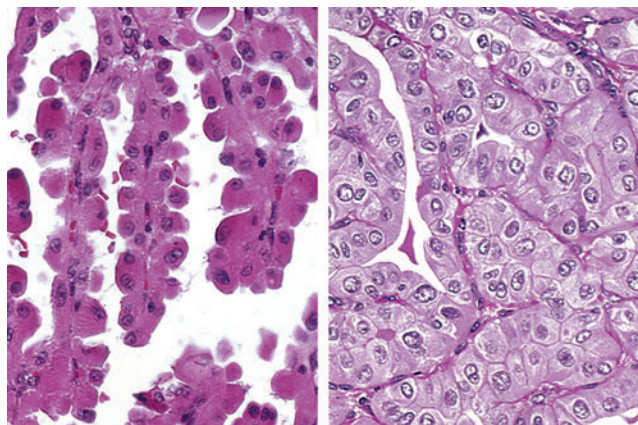


Fig. 28-62. Oncocyctic variant versus tall cell variant of PTC.

Left, The cells in the oncocyctic variant are not “tall,” have a more intensely eosinophilic cytoplasm, and lack distinct cell membranes. *Right*, Tall cell variant composed of “tall” cells with lightly eosinophilic cytoplasm and distinct cell membranes.

- Extrathyroidal extension may be grossly apparent.

Histology

- Tend to be unencapsulated and infiltrative with prominent papillary architecture:
 - Other growth patterns include trabecular, cord-like, and follicular.
 - Colloid-filled follicles are readily identifiable.
 - Marked fibrosis is present.
 - Another pattern of growth includes markedly elongated follicles arranged in parallel (“railroad track–like”) with minimal colloid content.
- Nuclear features diagnostic for PTC well developed, including:
 - Variation in size and shape
 - Nuclear grooves and pseudoinclusions readily apparent and prominently present
 - However, optically clear nuclear chromatin may not be readily apparent.
- Cytoplasmic features include distinct cell borders and presence of abundant or dense cytoplasmic eosinophilia:
 - Likely due to increased mitochondrial content
 - Less abundant as compared to oncocyctic (so-called Hürthle) cells
- An associated lymphocytic infiltrate not commonly seen but may be present in and around tumor.
- Psammoma bodies may be present but are uncommon.
- Mitotic figures may be present but generally are not significantly increased.
- Extrathyroidal extension and lymph-vascular space invasion not infrequently identified.

- Micropapillary carcinoma, tall cell variant (see Fig. 28-61)
 - Represent PTCs predominantly composed of tall cells measuring less than 1.0 cm in greatest dimension reported to potentially be associated with aggressive biologic behavior (see previous discussion under Micropapillary Carcinoma).
- Immunohistochemistry:
 - Thyroglobulin, TTF-1, and cytokeratin (including CK19) positive
 - Calcitonin, chromogranin, and synaptophysin negative
 - Higher rate of p53 staining as compared to conventional TPC
- Electron microscopy: but not as abundant or showing morphologic abnormality as seen in oncocytic (so-called Hürthle cell) tumors
- Cytogenetics and molecular genetics:
 - *BRAF* V600E mutation very common (approximately 80%)
 - *RET/PTC* translocation (in approximately 33%):
 - Associated with *RET/PTC3*
 - Telomerase reverse transcriptase (*TERT*) promoter mutations identified in TCV
 - Associated with more aggressive behaving thyroid cancers, including:
 - Poorly differentiated thyroid carcinoma
 - Undifferentiated (anaplastic) thyroid carcinoma
 - Greater expression of c-Met
- Higher incidence of cervical lymph node metastasis
- Higher incidence of distant metastasis (lung and bone)
- Higher recurrence rates in neck (approximately 22%) often with invasion into the trachea
- Higher tumor-related mortality rates (approximately 25%)
- Lower 5-year disease-specific survival
- May transform (dedifferentiate) to higher grade malignant neoplasms, including:
 - Spindle cell squamous carcinoma
 - Undifferentiated (anaplastic) carcinoma
- In most reported studies, tall cell variant more aggressive than conventional PTC:
 - Some studies reported no difference in behavior except for presence of extrathyroidal extension.
 - However, TCV without extrathyroidal extension reported to be biologically more aggressive than classical PTC without ETE independent of age, gender, and tumor size
- Papillary thyroid carcinoma with tall cell features:
 - PTCs with 30% to 49% tall cells reported to have:
 - Similar disease-specific survival and distant recurrence-free survival as tall cell variant (i.e., greater than 50% tall cells)
 - Higher rates of high-grade transformation than conventional PTC
 - Poorer outcomes than conventional PTC
 - Based on above findings suggestion made to lower threshold for diagnosis of TCV to 30% of a given tumor
- Microscopic tall cell variant:
 - Reported to be associated with aggressive features at presentation (except in rare pediatric cases), including:
 - Extrathyroidal extension (33%)
 - Lymph-vascular invasion (15%)
 - Multifocality (48%)
 - Metastasis to central compartment and lateral lymph nodes
 - Advanced stage (III/IVa0) (36%)
 - *BRAF* (V600E) mutation (approximately 93%)
 - Based on above findings recommendation made to differentiate microscopic TCV from other papillary microcarcinomas

Differential Diagnosis

- Columnar cell variant of papillary thyroid carcinoma (see below):
 - May be mistaken for tall cell variant given presence of “tall” cells
 - In contrast to tall cell variant, columnar cell variant characterized by:
 - Nuclear stratification
 - Nuclear hyperchromasia
 - Absence of eosinophilic cytoplasm and well-defined cell borders
- Oncocytic variant of papillary thyroid carcinoma
- Warthin-like variant of papillary thyroid carcinoma

Treatment and Prognosis

- Total thyroidectomy or near total thyroidectomy is preferred treatment, often supplemented by radioactive iodine therapy.
- As compared to conventional PTC, this variant has:
 - Tendency to occur in older patients
 - Tendency to be large (>5 cm)
 - Tendency to have extrathyroidal extension
 - Tendency to be refractory to radioactive iodine treatment

Columnar Cell Variant (CCV)

(Figs. 28-63 through 28-68)

Definition: Type of PTC characterized by columnar cells with nuclear stratification:

- Should be present in at least 50% of a given tumor
- Additional patterns can be seen (see below).

Synonym: Hypersecretory variant of PTC



Fig. 28-63. Columnar cell variant.

Columnar cell variant appearing as a large, circumscribed, solid tumor.

Clinical

- Rare tumor type representing less than 1% of all PTCs
- Demographics may vary depending on whether tumors are invasive or encapsulated/noninvasive:
 - Invasive:
 - More common in men than women
 - Most common in sixth decade of life
 - Encapsulated/noninvasive:
 - More common in women than men
 - Most common in sixth decade of life
- Clinical presentation includes asymptomatic or enlarging neck mass.
- Appear as “cold” nodules on thyroid scanning
- Etiology:
 - Unknown

Pathology

Fine-Needle Aspiration Biopsy

- Moderately cellular aspirate of sheets, papillary clusters, and microfollicles
- Cells with oval nuclei and uniform, finely granular chromatin arranged in a pseudostratified manner around well-defined fibrovascular cores
- Absence of intranuclear inclusions or well-defined nuclear grooves in the cells
- Absence to sparse colloid

Gross

- May be large, measuring >5 cm with invasive growth (intra- and extrathyroidal)
 - May be small (<5 cm), encapsulated, and even microscopic

Histology

- May be:
 - Circumscribed to encapsulated without invasion

- Circumscribed to encapsulated with limited invasive growth (capsular or vascular)
- Extensively invasive including into thyroid parenchyma and/or extrathyroidal extension
- Prominent papillary growth but other growth patterns may be seen, including:
 - Follicular, cribriform, and solid
 - Colloid may only focally be seen and can be absent.
 - Another pattern of growth includes markedly elongated follicles with minimal colloid content.
- Cells are tall but are columnar-appearing and have prominent nuclear stratification:
 - Nuclei tend to be elongated and hyperchromatic.
 - In areas of any given tumor, nuclei may show classic features of PTC.
- Cytoplasmic changes may vary and include:
 - Nondescript eosinophilic appearance
 - Clear or vacuolated appearance with subnuclear vacuolization similar to that seen in secretory-type endometrium
- Squamoid foci (morules) and spindle cells with fascicular growth may be present.
- Psammoma bodies may be present but are uncommon.
- Increased mitotic activity can be present; necrosis is generally not found.
- Immunohistochemistry:
 - Thyroglobulin and TTF-1 positive:
 - Marked variability in thyroglobulin reactivity including portions of tumor with intense thyroglobulin reactive, whereas other areas are completely negative or weakly positive, including foci adjacent to intensely thyroglobulin-positive foci
 - Cytokeratin and vimentin positive
 - No immunoreactivity with calcitonin, synaptophysin, and chromogranin
 - CDX2 (nuclear) reactivity purported to be selective marker for CCV, but this finding not substantiated
- Cytogenetics and molecular genetics:
 - *BRAF* V600E mutation (approximately 33%)

Differential Diagnosis

- Tall cell variant of papillary thyroid carcinoma
- Cribriform-morular variant of PTC
- Hyalinizing trabecular adenoma
- Medullary thyroid carcinoma
- Metastatic colonic adenocarcinoma or endometrioid adenocarcinoma

Treatment and Prognosis

- Thyroidectomy preferred treatment and may include:
 - Total thyroidectomy with postoperative radioiodine therapy for larger tumors with extrathyroidal extension

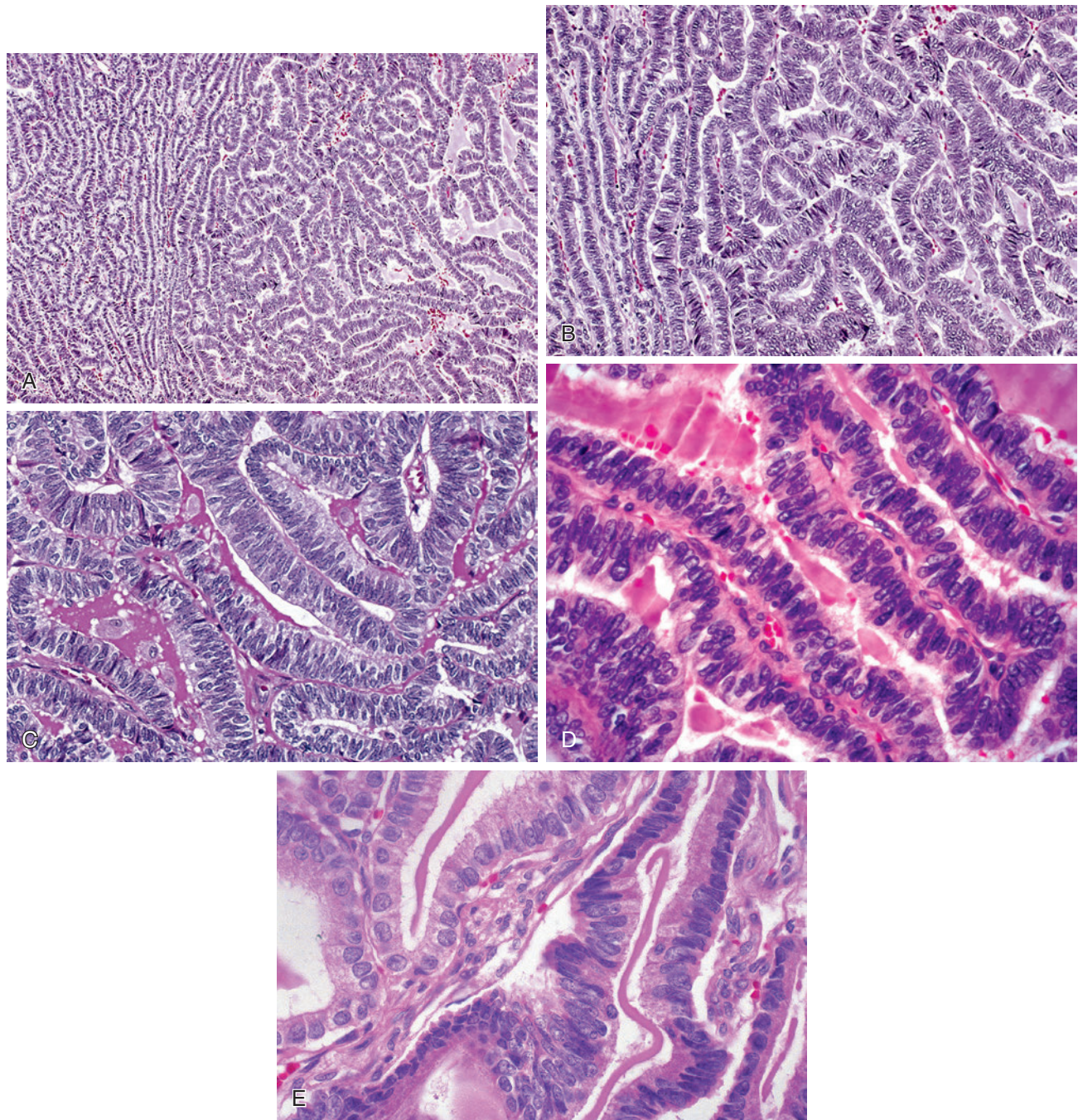


Fig. 28-64. Columnar cell variant.

Columnar cell variant of papillary thyroid carcinoma characterized by **(A and B)** papillary growth and markedly elongated follicles arranged in parallel ("railroad tracks") with minimal but identifiable colloid; **(C and D)** the nuclei are elongated (columnar) and hyperchromatic with stratification lacking the typical features seen in conventional papillary thyroid carcinoma; **(E)** in areas more typical nuclear features of papillary thyroid carcinoma (*upper left*) may be focally identified adjacent to and/or admixed within columnar cells (*lower right*).

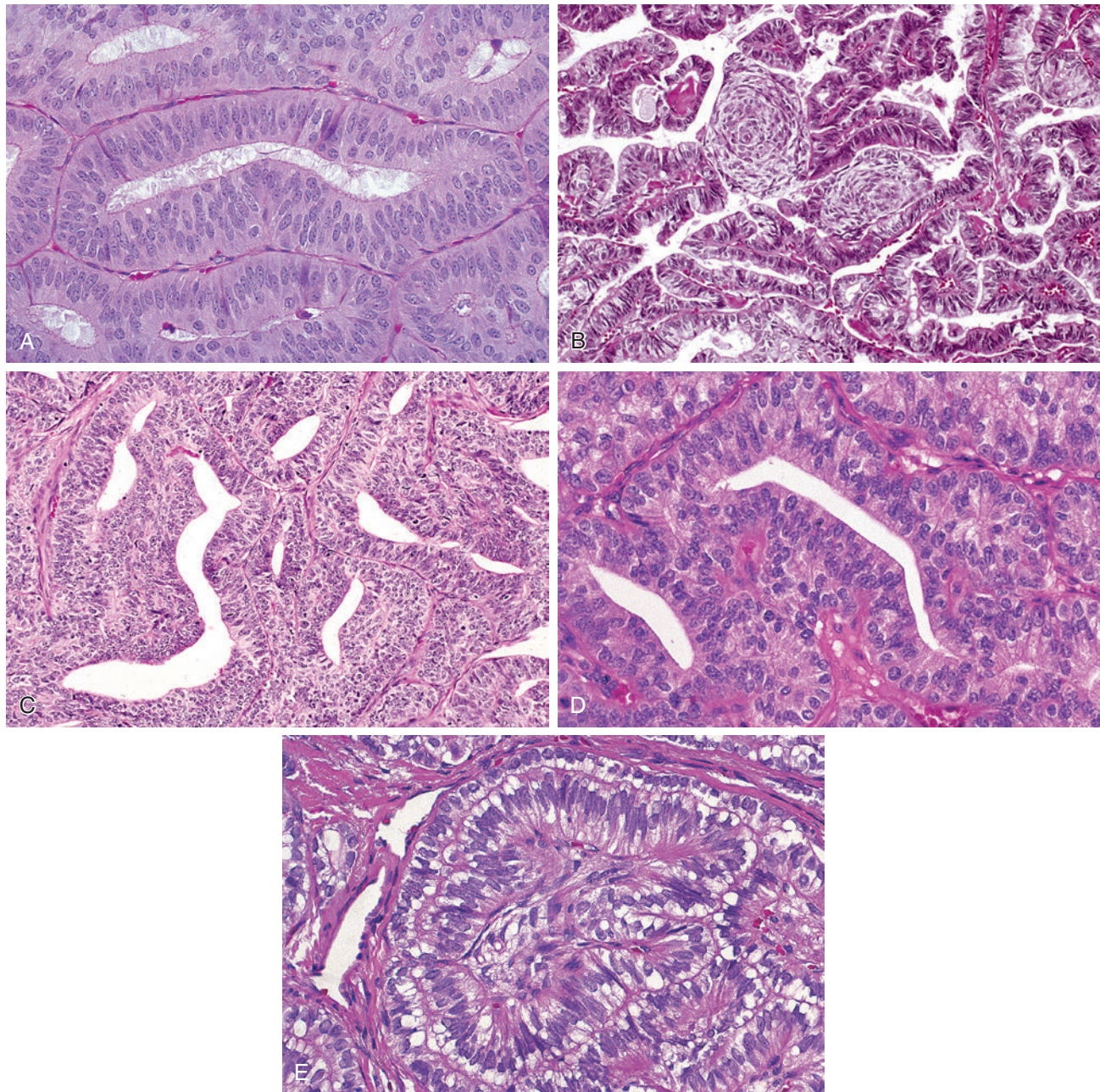


Fig. 28-65. Columnar cell variant.

Other findings that are seen in the columnar cell variant include **(A)** follicular growth with nuclear stratification; **(B)** squamoid morules; **(C and D)** cribriform growth devoid of colloid and composed of columnar cells with slightly eosinophilic cytoplasm and nuclear stratification; and **(E)** clear or vacuolated appearance with subnuclear vacuolization similar to features seen in secretory-type endometrium (hence the term hypersecretory variant of CCV).

- Lobectomy or subtotal thyroidectomy for tumor confined to thyroid gland without evidence of extrathyroidal extension
- May metastasize including to:
 - Cervical lymph nodes:
 - Histologic appearance of metastatic foci may include columnar cells, cells with clear-appearing cytoplasm (secretory endometrium-like), and/or cells with classic features of PTC
 - Metastatic foci may:
 - Not include cells with nuclear features of PTC
 - Be thyroglobulin negative or weakly positive

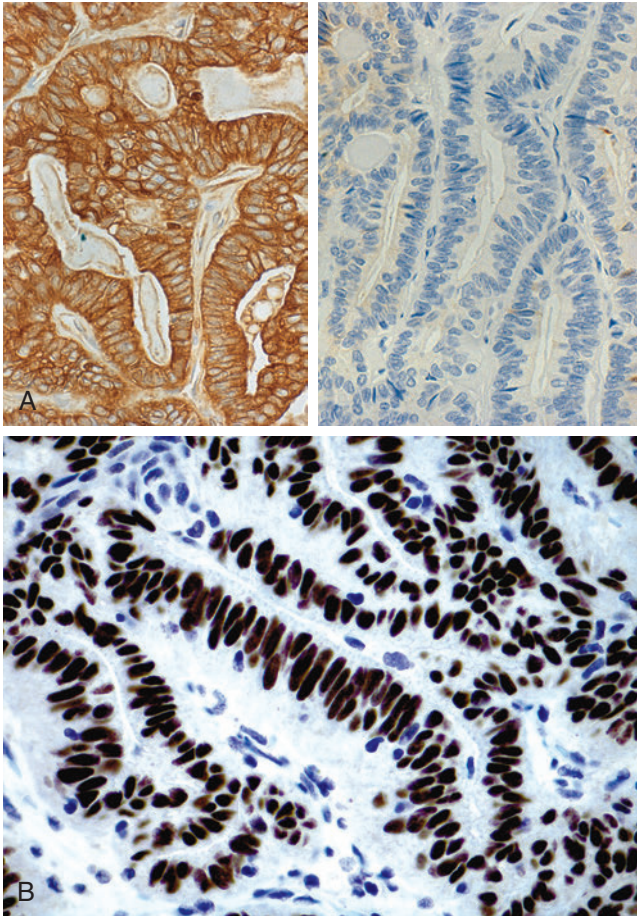


Fig. 28-66. Columnar cell variant.

Immunohistochemical staining in CCV includes thyroglobulin immunoreactivity that can vary from case to case and even within the same case, including (A) left, diffuse and intense thyroglobulin reactivity; right, areas completely thyroglobulin negative; (B) TTF-1 (nuclear) reactivity is typically diffuse and strong.

- TTF-1 staining should be used in conjunction with thyroglobulin to confirm thyroid gland origin
- Distant metastasis:
 - Include to lung and bone may occur
 - Usually occur in cases with extrathyroidal extension
- Associated with high mortality rates with death occurring within 4 years from diagnosis; however, prognosis not uniformly unfavorable but varies depending on presence or absence of extrathyroidal extension (ETE):
 - Large tumors with extrathyroidal extension:
 - Aggressive behavior with distant metastasis (e.g., lungs) and increased mortality rates over shorter follow-up periods

- Tumors confined to thyroid gland without extra-thyroidal invasion
 - Prognosis similar to conventional PTC even in presence of nodal metastatic disease

Hobnail Variant of PTC (HVPTC)

(Fig. 28-69)

Definition: Aggressive type of PTC characterized by cells with hobnail or micropapillary features:

- Should be present in at least 30% of a given tumor but even tumors with 10% hobnail (micropapillary) features may behave aggressively

Synonyms: Papillary carcinoma with prominent hobnail features; PTC with micropapillary features

Clinical

- Rare tumor type representing less than 1% of all PTCs
- More common in women than in men; occur over a wide age range from third to eighth decades of life but most common in the sixth decade
- Clinical presentation includes:
 - Neck mass associated with dyspnea owing to compression of trachea
 - Cervical lymphadenopathy
 - History of multinodular goiter

Pathology

Fine-Needle Aspiration Biopsy

- Highly cellular with bloody background and scant colloid
- Cells arranged in papillary-like clusters or micropapillary groups
- Cell population consists of medium-sized cells with “tear-drop” cytoplasm, apically placed nuclei, producing surface bulge resulting in hobnail appearance
- Nuclei may show variable degrees of atypia, occasional eosinophilic intranuclear pseudoinclusions, and grooves:
 - Nuclear stratification and mitotic figures, including atypical forms, may be present.

Gross

- Range in size from 1.0 cm to 5.0 cm
 - Mean 3.0 cm
 - Often include multiple nodules in one or both thyroid lobes
 - Less commonly may be a single encapsulated nodule with or without central degeneration and hemorrhage

Histology

- Findings include:

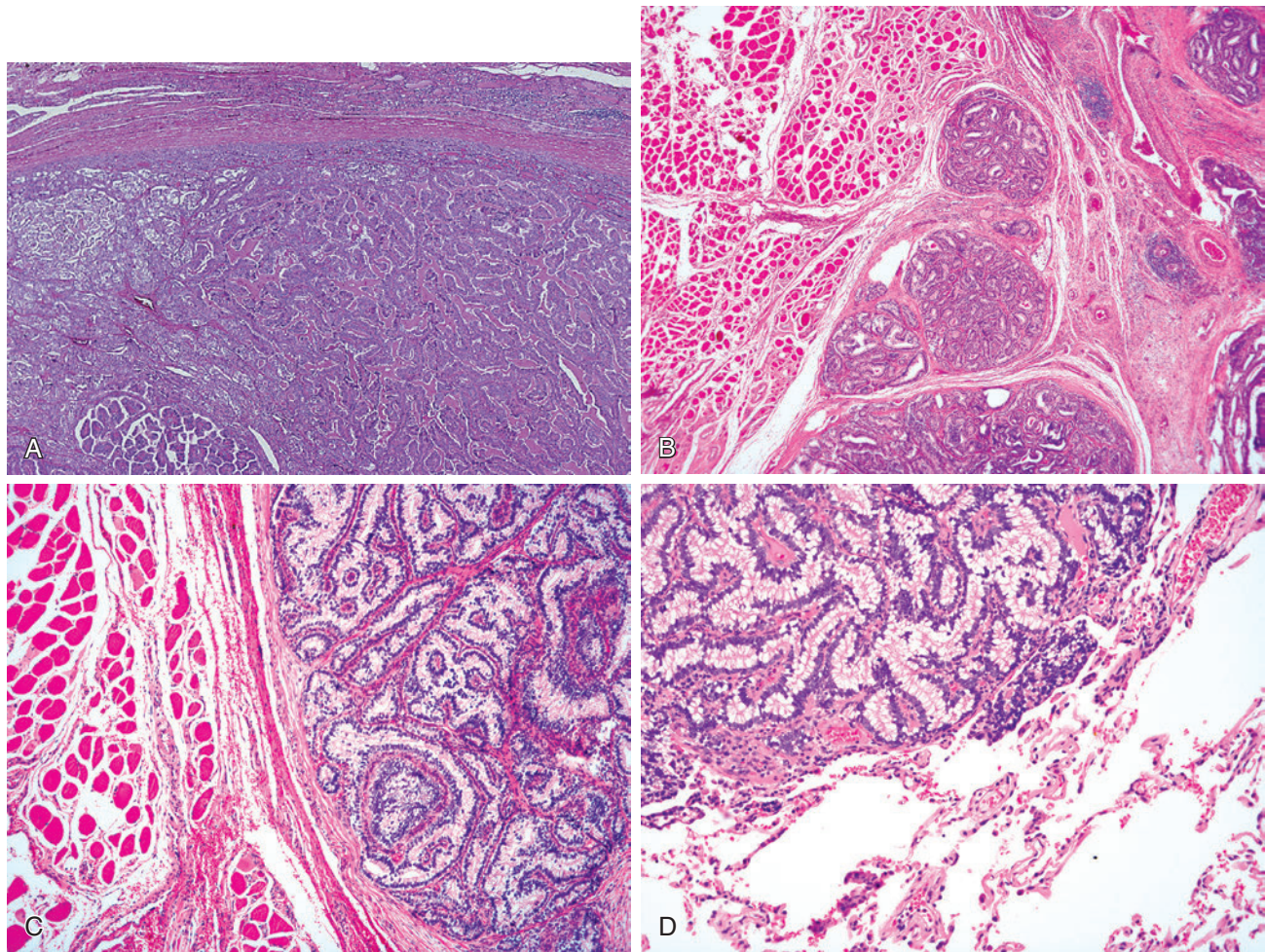


Fig. 28-67. Columnar cell variant.

The prognosis associated with the columnar cell variant correlates with the extent of invasion and not necessarily on the cell type. **A**, Tumors that are encapsulated without invasion (as shown here) or that are minimally invasive within the thyroid gland without extrathyroidal extension often have a favorable prognosis without metastasis and/or increased mortality. **B** and **C**, In contrast, this CCV with clear cytoplasmic change invaded perithyroidal soft tissues, approximating (but not extending into) skeletal muscle, and metastasized (**D**) to the lungs, showing similar clear cell change as the primary tumor and ultimately resulting in patient death.

- Papillary pattern without colloid characterized by variably sized complex papillary and micropapillary structures:
 - Papillae may contain prominent vascular cores covered by cuboidal or oval epithelium with:
 - Nuclei located in middle or in apex of cytoplasm with cellular discohesiveness and bulging of apical surface producing hobnail appearance
 - Increased nuclear-to-cytoplasmic ratio
 - Moderate to marked pleomorphism
 - Dense eosinophilic cytoplasm with well-defined borders
 - Cytomorphologic features of conventional PTC, including enlarged irregular-appearing and overlapping nuclei with clear chromatin, nuclear grooves, and pseudoinclusions may present in focal areas.
- Follicular pattern with limited amounts of colloid characterized by:
 - Variably sized follicles lined by neoplastic epithelium (two to four cells thick) with hobnail cytologic features similar to those in papillary pattern
- Clustered pattern characterized by clusters of cancer cells with hobnail nuclear features forming

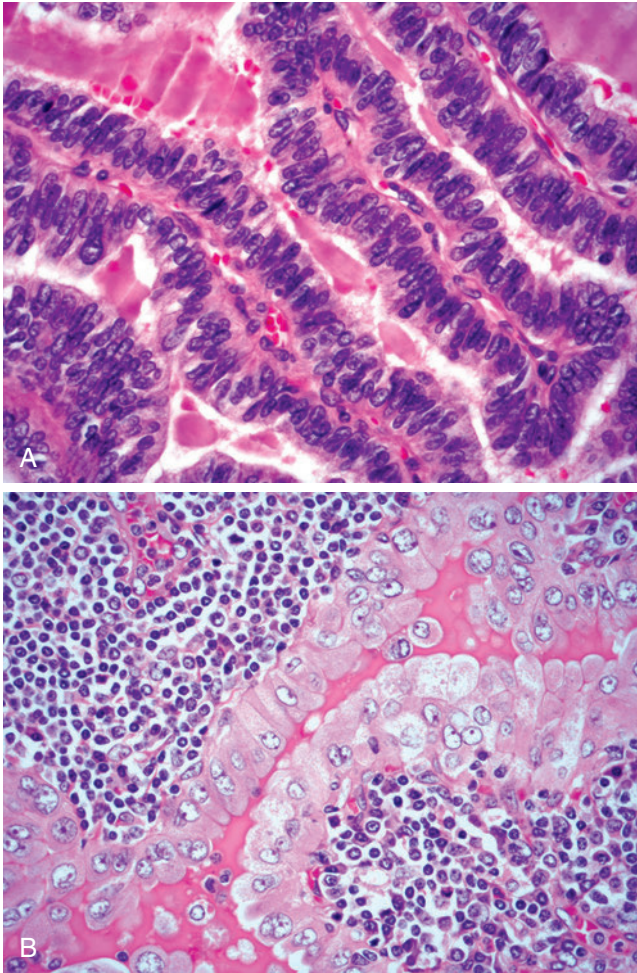


Fig. 28-68. Columnar cell versus tall cell.

Columnar cell variant versus tall cell variant of papillary thyroid carcinoma (PTC). The histologic distinction between these two variants of PTC characterized by “tall” cells is stark, allowing for ready differentiation. **A**, Columnar cell variant is characterized by (tall) columnar cells with nuclear stratification. **B**, Tall cell variant is characterized by cells that are three times as long as wide with pale eosinophilic cytoplasm and distinct cell membranes.

papillary structures without colloid and fibrovascular cores

– May be associated with angiolymphatic spaces

- Increased mitotic activity and atypical mitoses commonly seen:
 - Mitotic rate of ≥ 3 mitoses per 10 high-power fields
- Necrosis not present
- Psammoma bodies can be seen but usually are not numerous.
- Extensively invasive, including:
 - Vascular invasion
 - Extrathyroidal extension

- Concomitant foci with tall cell features, poorly differentiated thyroid carcinoma, and undifferentiated (anaplastic) thyroid carcinoma reported
- Immunohistochemistry:
 - Lesional cells reactive for:
 - Thyroglobulin, TTF1-1 (nuclear)
 - HBME-1 and nuclear expression of p53
 - Membrane staining for β -catenin and E-cadherin:
 - Patchy lateral and or basolateral membrane positivity
 - MUC1 reactivity with characteristic “inside-out” staining pattern in micropapillary component
 - Increase proliferative index by Ki67 staining:
 - Ranges from 2% to 20% (mean 10%)
- Cytogenetics and molecular genetics:
 - *BRAF* V600E mutation in majority of cases (>50% and as high as 80%)
 - *RET/PTC1* rearrangement:
 - In some reported not identified
 - In other reported found in up to 20% of cases

Treatment and Prognosis

- Treatment includes total thyroidectomy and cervical lymph node dissection
- Aggressive tumor often associated with:
 - Lymph node metastasis (75%) at presentation:
 - Metastases show hobnail pattern of growth similar to primary tumor
 - Advanced clinical stage (AJCC Stage III or IV) at presentation
 - Extrathyroidal extension
 - Recurrent disease
 - Distant metastasis most commonly to lung > brain, bone, liver, spinal cord, soft tissues, pancreas, psoas muscle, epiglottis, larynx, nasopharynx, base of tongue, and tonsils:
 - Metastases show hobnail pattern of growth similar to primary tumor.
 - Increased mortality rates in most but not all cases

POORLY DIFFERENTIATED THYROID CARCINOMA (PDTTC) (Figs. 28-70 through 28-75)

Definition: Malignant epithelial thyroid neoplasm showing histologic and biologic features that are intermediate between differentiated thyroid carcinomas and anaplastic (undifferentiated) thyroid carcinoma.

- Turin proposal established criteria for diagnosis including:
 - Presence of solid, trabecular, insular pattern of growth

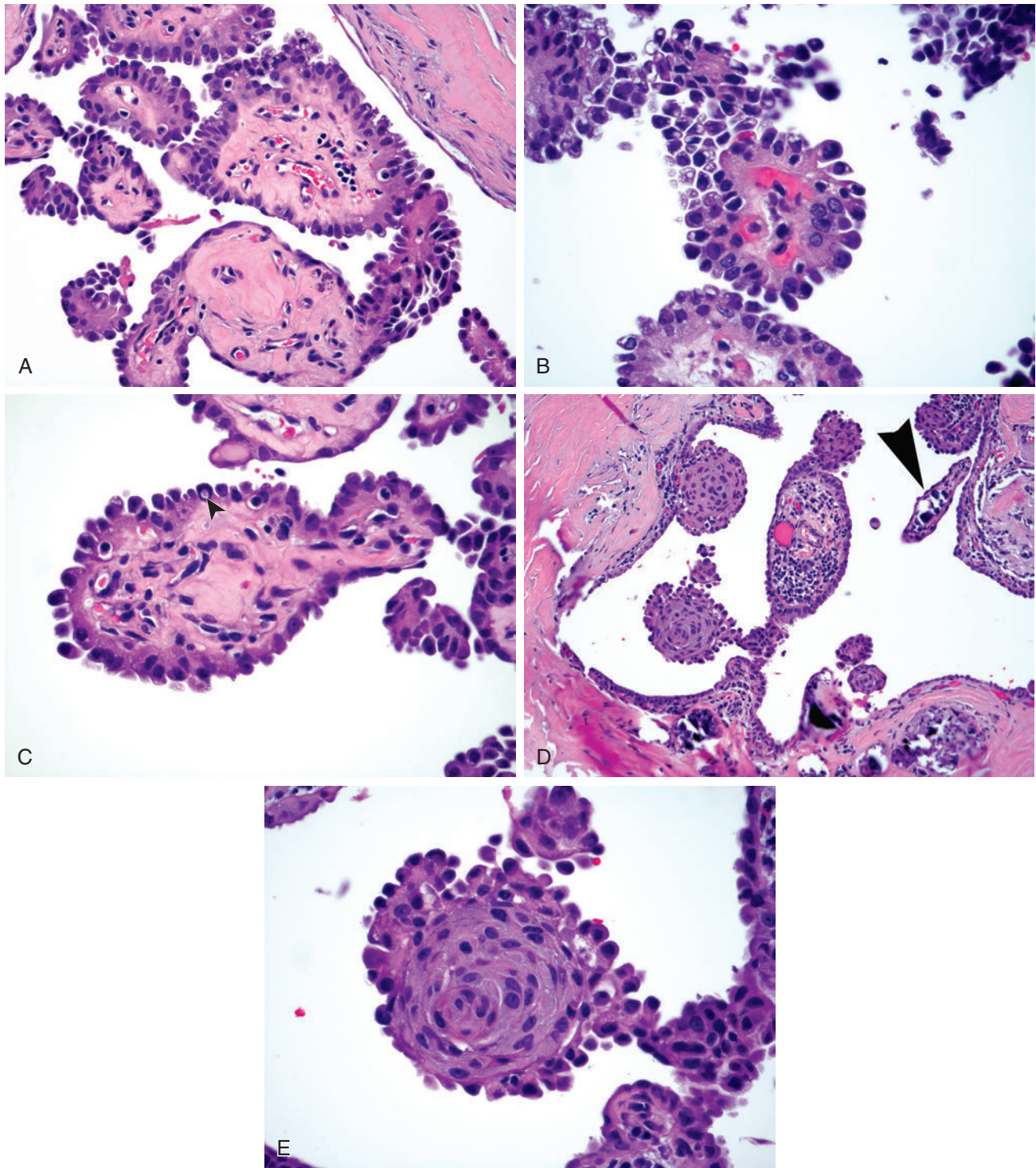


Fig. 28-69. Hobnail variant of PTC.

A, This variant of PTC is characterized by variably sized papillae with vascular cores covered by cuboidal or oval epithelial cells with surface bulge producing a hobnail appearance. **B**, Enlarged hyperchromatic nuclei with increased nuclear-to-cytoplasmic ratio and **(C)** intranuclear inclusions (*arrowhead*) are present. In addition, **(D)** psammoma bodies (*arrowhead*) and **(E)** squamous eddies may be identified.

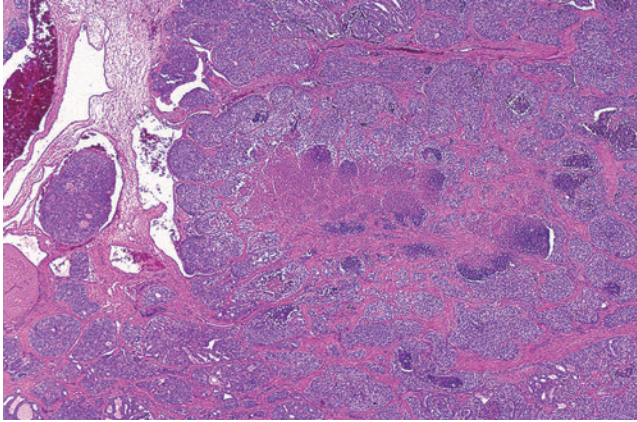


Fig. 28-70. PDTC.

Poorly differentiated thyroid carcinoma (PDTC) characterized by insular, trabecular, and solid growth, confluent area of necrosis and invasive growth (i.e., angioinvasion into large size vascular space [*left side of illustration*]). Uncommonly, PDTC may be encapsulated and noninvasive (*not shown*), which is associated with significantly improved overall survival compared to invasive tumors.

- Absence of conventional nuclear features of papillary thyroid carcinoma
- Presence of at least one of following features:
 - Mitotic activity ≥ 3 per 10 high-power fields
 - Tumor necrosis
 - Convoluted nuclei
- Growth pattern alone including insular, solid, trabecular do not define a given thyroid tumor as poorly differentiated because such growth patterns can be seen in differentiated thyroid tumors.
- Thyroid carcinomas with high-grade features:
 - Represent PDTC defined on basis of mitosis and necrosis
 - May be present in tumors with features of papillary thyroid carcinoma and follicular thyroid carcinoma (non-oncocyctic and oncocyctic).
 - Criteria include:
 - ≥ 5 mitoses per 10 high-power fields
 - Tumor necrosis
- Amount of poorly differentiated foci for diagnosis of PDTC:
 - Minor poorly differentiated features in differentiated thyroid carcinomas shown to portend more aggressive features:
 - In some studies reported as $<20\%$
 - In other studies $\geq 10\%$ poorly differentiated foci shown to affect prognosis significantly

Synonym: “Insular” carcinoma

Clinical

- Uncommon tumor representing less than 2% of all thyroid cancers:
 - In mountain region of northern Italy represents 4% to 7% of all thyroid malignant neoplasms
- More common in women than in men; most common in the sixth decade of life:
 - Typically occurs a decade later than differentiated thyroid cancers
 - May occur in children but rather rare occurrence
- Presentation includes presence of thyroid mass of varying duration:
 - Some are of recent duration (within 1 year)
 - Others occur in long-standing enlarged thyroid (e.g., goitrous thyroid gland)
 - Rarely, patients present with distant metastasis.
- At presentation often (but not always) associated with locally advanced disease, including extrathyroidal extension
- Patients are euthyroid.
- Appear as “cold” nodules on thyroid scanning:
 - Owing to loss of avidity for radioiodine, tumor may not be detected on scanning but may require FDG-PET.
- Usually arise de novo but may be associated with (transform from) differentiated thyroid carcinomas, including papillary or follicular carcinoma
- Etiology:
 - Unknown

Pathology Fine-Needle Aspiration Biopsy

- Cellular aspirates composed of discohesive, small, monotonous, round to oval cells that may include a plasmacytoid appearance with eccentric hyperchromatic nuclei, smooth nuclear contours, small to inconspicuous nucleoli, and finely granular, ill-defined cytoplasm; occasional binucleate cells may be identified.
- Nuclear atypia and pleomorphism are usually mild.
- Microfollicles are variably seen and scant colloid is present.
- Necrosis and mitotic figures may or may not be identified.

Gross

- Typically overtly infiltrative with extrathyroidal extension but may be encapsulated (partly or completely)
- Vary in size from 1 to 10 cm but most measure >5 cm
- Solid, firm, and tan-white with associated hemorrhage and necrosis

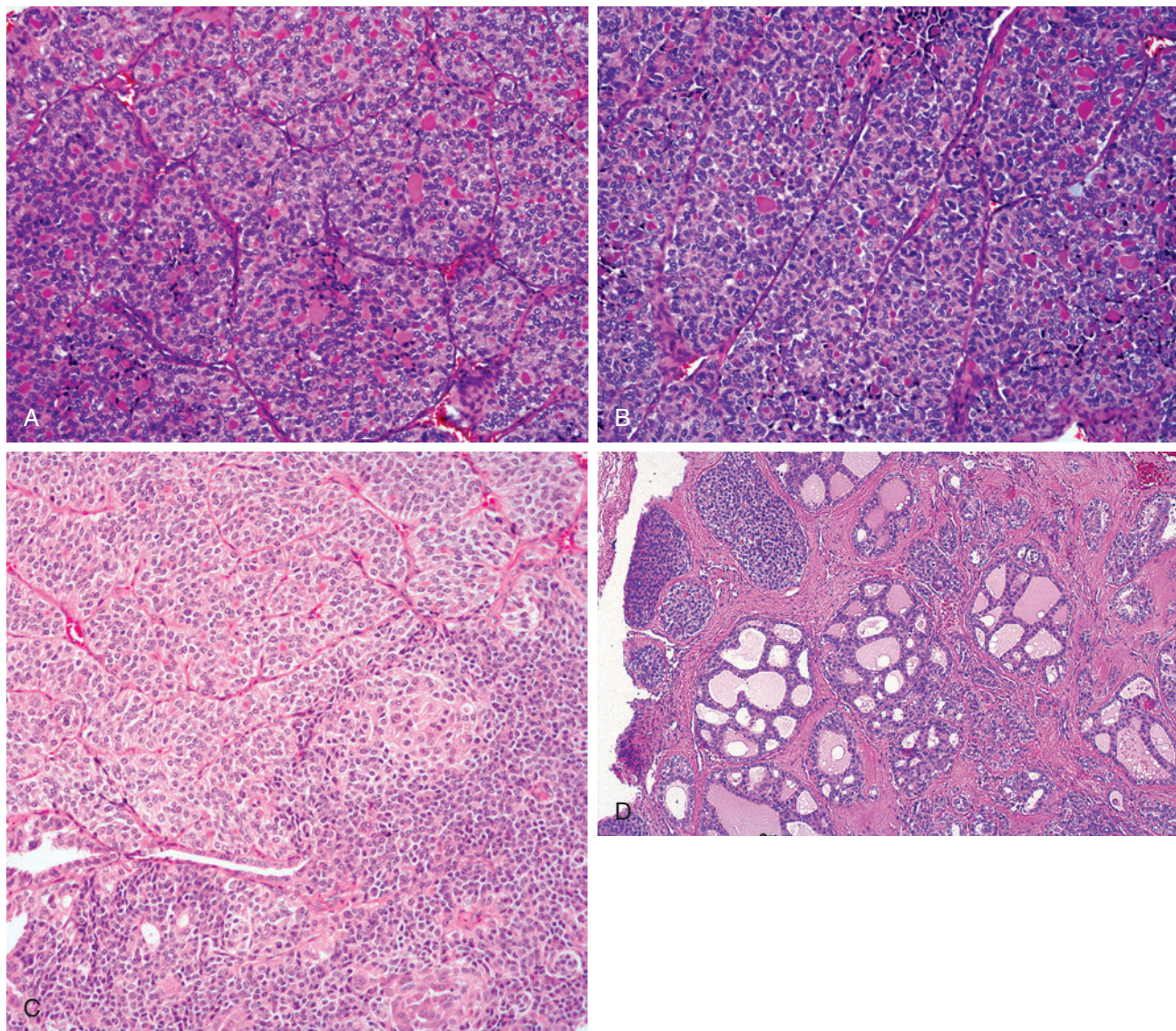


Fig. 28-71. Poorly differentiated thyroid carcinoma.

Growth patterns in poorly differentiated thyroid carcinoma include **(A)** insular, **(B)** trabecular, **(C)** solid (lower) juxtaposed to areas with insular pattern (*upper*). **D**, Cribriform may uncommonly be identified.

Histology

- Growth patterns:
 - Dominant growth patterns include solid, trabecular, and insular:
 - Solid growth characterized by diffuse sheets of tumor that may be separated by variable amount of fibrovascular stroma
 - Trabecular pattern characterized by elongated cords or ribbons of tumor
 - Insular growth arranged in well-defined round to oval cell nests or islands (“insulae”) separated by varying amount of fibrovascular stroma
 - Retraction artifact characterized by clear areas surrounding tumor nests may be present.
 - Papillary architecture may be focally identified.
 - Microfollicles containing dense colloid may be identified but typically follicular pattern with abundant colloid formation not present:
 - Presence of readily identifiable colloid-filled follicles in PDTC represent residual foci of differentiated thyroid tumor, including follicular adenoma/carcinoma, papillary carcinoma
- Cytomorphology:
 - Monotonous population of small cells with round, hyperchromatic to vesicular nuclei with

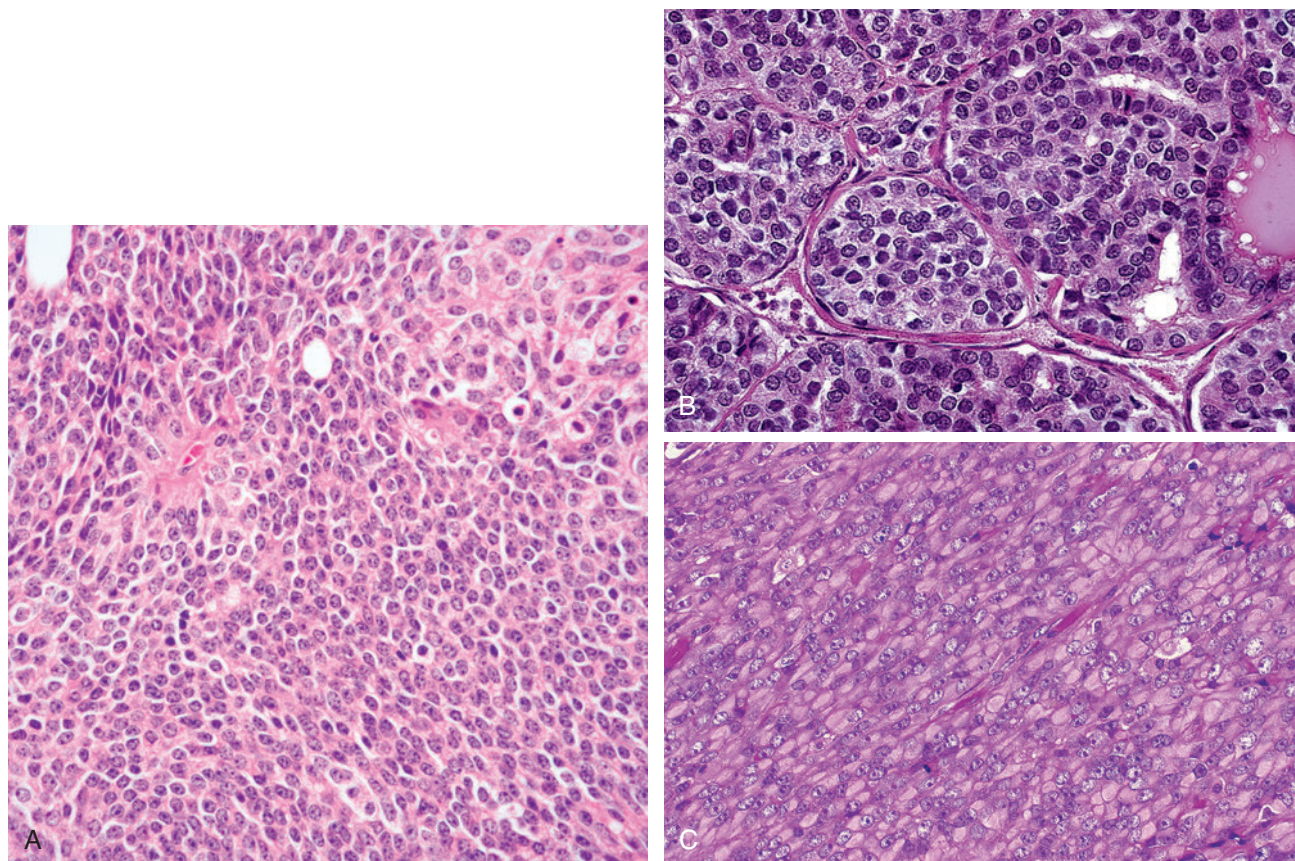


Fig. 28-72. Poorly differentiated thyroid carcinoma.

Whether associated with **(A)** solid growth or **(B)** insular growth the cytomorphic findings in poorly differentiated thyroid carcinoma include a rather monotonous population of small cells with round, hyperchromatic to vesicular nuclei with smooth nuclear contours, inconspicuous to small nucleoli and indistinct cytoplasm. Some of the cells are small and hyperchromatic, with irregularities in the nuclear contour referred to as so-called convoluted nuclei. **C**, Rhabdoid cells may infrequently be identified in poorly differentiated thyroid carcinoma. Overall, there is an absence of nuclear features diagnostic for PTC.

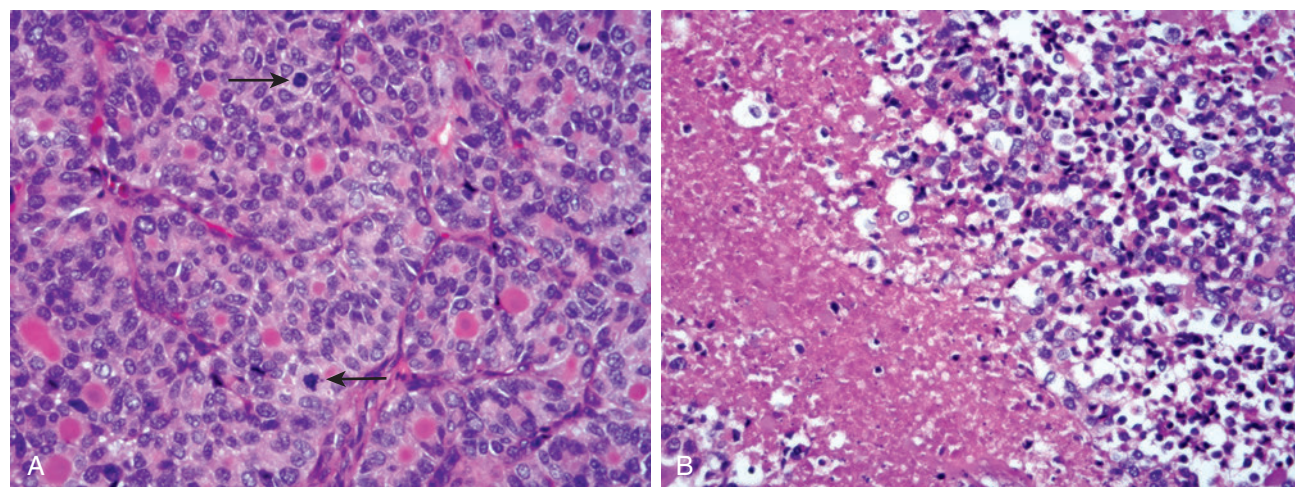


Fig. 28-73. Poorly differentiated thyroid carcinoma.

The diagnostic criteria for poorly differentiated thyroid carcinoma require the presence of **(A)** increased mitotic activity (*arrows*) and **(B)** necrosis (*left*). Mitotic activity should be on the order of more than 3 to 5 mitoses per 10 high-power fields; necrosis is coagulative type involving groups of tumor cells.

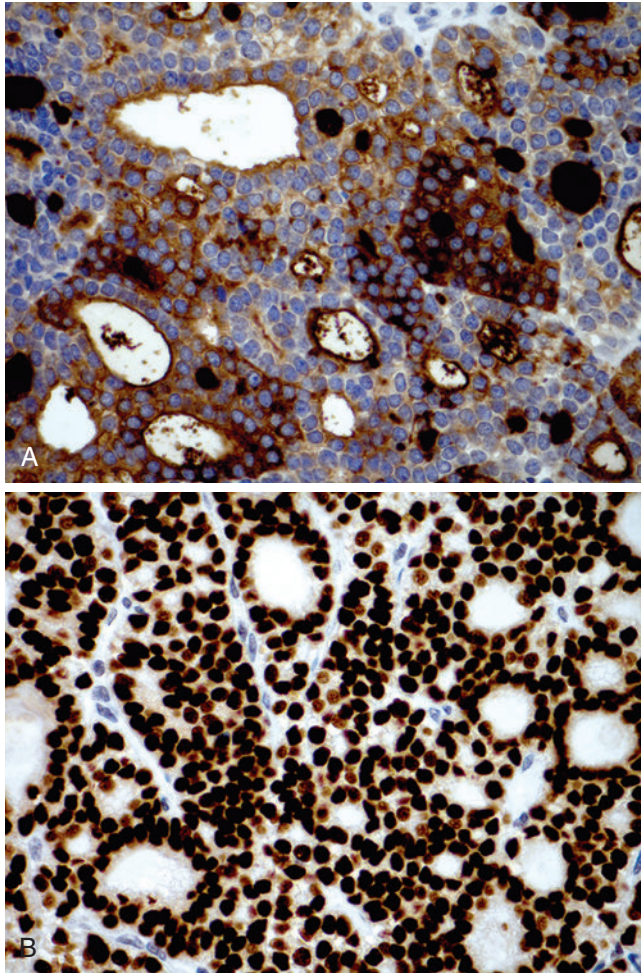


Fig. 28-74. IHC in PDTC.

Immunohistochemical staining in poorly differentiated thyroid carcinoma includes **(A)** thyroglobulin and **(B)** TTF-1 (nuclear). Typically, thyroglobulin reactivity may be focal limited to abortive or small follicles containing colloid, limited to isolated cells as paranuclear globules or vacuoles or may be completely absent; TTF-1 staining tends to be strong and diffuse.

- smooth nuclear contours, inconspicuous to small nucleoli, and indistinct cytoplasm
- Cells with larger nuclei, vesicular nuclear chromatin, smooth nuclear contours, and identifiable nucleoli may be identified.
- Convoluted nuclei
 - Small, hyperchromatic, raisin-like nuclei
 - Some irregularities in nuclear contour
- Absence of nuclear features diagnostic for PTC
- Other cell types seen in PDTC include:
 - Oncocytic cells
 - Rhabdoid cells
- Mitotic activity:
 - Increased mitotic activity identified

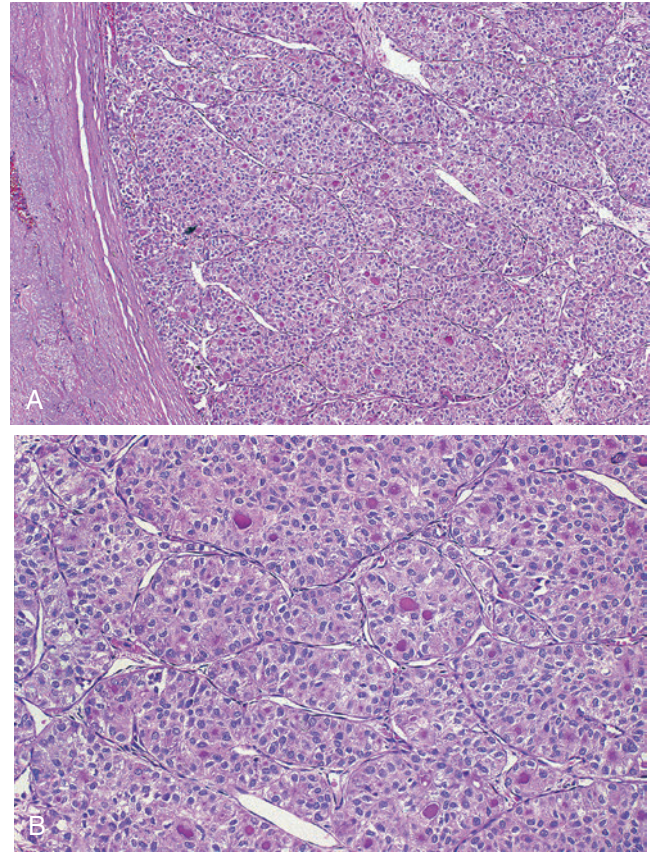


Fig. 28-75. Follicular adenoma with insular growth.

Insular growth can be seen in a variety of thyroid lesions that are not poorly differentiated thyroid carcinoma. As such, the presence of insular growth is not in and of itself an indicator of malignancy. This thyroid neoplasm with insular growth is encapsulated without evidence of invasive growth, necrosis, and/or increase in mitotic activity representing a follicular adenoma with an insular growth pattern. Other thyroid lesions that may have an insular growth pattern (in part or dominant) include adenomatoid nodules, papillary thyroid carcinoma, follicular thyroid carcinoma, and medullary thyroid carcinoma (not shown).

- Turin criteria is ≥ 3 per 10 high-power fields
- ≥ 5 mitoses per 10 high-power fields proposed in criteria associated with thyroid carcinomas with high-grade features
 - Atypical mitoses may be found.
- Necrosis:
 - Commonly found
 - Represents coagulative-type necrosis involving groups of tumor cells and not individual cell necrosis
 - May be focal, appearing as small foci in center of solid nests or insulae
 - May be more extensive, appearing as confluent foci

- In this setting may spare areas around blood vessels, creating peritheliomatous appearance
- Invasiveness:
 - Most PDTCs are extensively invasive, including:
 - Intrathyroidal invasion with capsular invasion, vascular invasion, and invasion into adjacent thyroid parenchyma
 - Extrathyroidal extension
 - May be noninvasive (noninvasive PDTC or non-invasive thyroid carcinoma with high-grade features)
 - Encapsulated without evidence of invasion
 - Entire tumor should be submitted to exclude presence of invasion.
- Hobnail features:
 - Papillary thyroid carcinoma with hobnail features (>10%) reported in association with poorly differentiated thyroid carcinoma (22% of cases)
 - Suggest that hobnail features may be manifestation of higher-grade transformation
- Immunohistochemistry:
 - Thyroglobulin, TTF-1 (nuclear), and PAX8 (nuclear) positive:
 - Thyroglobulin reactivity may vary from case to case and even within same case showing:
 - Very focal limited to abortive or small follicles containing colloid
 - Limited to isolated cells as paranuclear globules or vacuoles
 - Completely negative
 - Typically not diffusely/strongly reactive
 - TTF-1 tends to be diffuse.
 - Cytokeratin reactivity including AE1/AE3, CAM 5.2, CK7
 - p53 reactivity (focal or diffuse)
 - Calcitonin, synaptophysin, and chromogranin negative
 - High proliferation indices as determined by Ki67 (MIB1) staining
 - Rhabdoid cells negative for thyroglobulin but are vimentin positive owing to presence of intermediate filaments.
- Cytogenetics and molecular genetics:
 - Limited utility owing to absence of specific mutations
 - β -catenin gene mutation (*CTTNB1*) may be identified.
 - Point mutations of *RAS* oncogene in significant proportion of cases
 - *BRAF* mutations uncommon unless arising in association with PTC
 - *RET/PTC* rearrangement uncommon
 - *PAX8/PPAR γ* rare
 - Telomerase reverse transcriptase (TERT) promoter mutations identified

- Associated with more aggressive behaving thyroid cancers, including (other than PDTC):
 - Tall cell variant of PTC
 - Undifferentiated (anaplastic) thyroid carcinoma
- *PIK3CA*, *PTEN*, and *CDKI* mutations present in 14% to 20% of PDTCs

Differential Diagnosis

- Medullary thyroid carcinoma (MTC):
 - Presence of immunoreactivity for calcitonin, synaptophysin, and chromogranin
 - Absence of immunoreactivity for thyroglobulin and PAX8
 - TTF-1 may be positive in MTC and PDTC.
- Undifferentiated (anaplastic) carcinoma (see below).
- Papillary thyroid carcinoma, solid variant:
 - Typical nuclear features of PTC
 - Absence of increased mitotic activity and necrosis
 - Presence of more diffuse thyroglobulin reactivity as might be seen in PDTC

Treatment and Prognosis

- Multimodality therapy including:
 - Total thyroidectomy
 - Neck dissection for patients with lymph node disease
 - Postoperative radioactive iodine:
 - Advocated for all patients with PDTC owing to high mortality rates
 - However, conflicting data in literature on avidity for radioactive iodine
 - Adjuvant external beam radiation advocated for patients with:
 - T3 tumors without distant metastases
 - T4 tumors
 - Unresectable or incompletely excised tumors
 - Locoregional recurrence
 - Regional lymph node metastases
- Recurrence and metastasis following treatment occur in a high proportion of cases (>60%)
- Lymph node and distant metastases occur in approximately 60% and 70% of cases, respectively.
- Death from disease is common:
 - Caused by uncontrolled local or distant metastatic disease
 - In contrast to rapid demise typically associated with undifferentiated (anaplastic) carcinoma, death from PDTC occurs after several years.
- Survival rates:
 - 5-year survival rate of 50% to 72%
 - 10-year survival rate of 46%
- Findings associated with worse outcome include:
 - Patients ≥ 45 years of age
 - Tumor measuring greater than 4 cm (decreased progression-free survival)

- Presence of extrathyroidal extension into perithyroidal soft tissues (correlates with decreased overall survival)
- Presence of metastasis
- RAS mutation
- Presence of insulin-like growth factor II messenger RNA protein-3 (IMP3) immunoreactivity
- Noninvasive (encapsulated) PDTC:
 - Significantly improved overall survival compared to invasive tumors
 - Indolent behavior even in presence of extensive tumor necrosis
 - Recent report of widely metastatic disease in noninvasive follicular carcinoma with high-grade features, including presence of focal necrosis (<5%) and 14 mitoses per 10 high-power fields.

UNDIFFERENTIATED (ANAPLASTIC) THYROID CARCINOMA (UTC) (Figs. 28-76 through 28-85)

Definition: Highly aggressive, undifferentiated thyroid malignant neoplasm with immunohistochemical and ultrastructural evidence of epithelial differentiation arising from follicular epithelial cells.

Synonyms: Sarcomatoid carcinoma; pleomorphic carcinoma; metaplastic carcinoma; spindle cell carcinoma; giant cell carcinoma

Clinical

- Uncommon thyroid malignant tumor representing less than 5% of thyroid malignancies.
- More common in women than in men; typically occur in older patients usually >seventh decade of life; rarely occurs in patients younger than 50 years of age
- Clinical presentation classically includes:
 - Rapidly enlarging neck or thyroid mass occurring over short periods of time (weeks to months):
 - Rapid thyroid enlargement most common in patients with long-standing goiter
 - Less often, rapid enlargement may be associated with a differentiated thyroid carcinoma (papillary or follicular carcinoma).
 - Often, neck enlargement associated with dyspnea, dysphagia, hoarseness, vocal cord paralysis
 - Locoregional and/or distant (e.g., lungs, bone, brain) metastases at presentation may be identified:
 - Unusually, metastatic disease may occur in absence of overt thyroid or neck mass.
- Tumors are large, bulky, firm to hard masses distorting appearance of neck and may cause reddening of the overlying skin.
 - Owing to presence of extrathyroidal extension at presentation, a rather common finding (up to 50% of patients), fixation present to adjacent structures, including:
 - Skin, trachea, larynx, esophagus, extrinsic skeletal muscles, and nerves (e.g., recurrent laryngeal nerves, others)
 - Invasion and/or occlusion of jugular vein or carotid artery may occur.
 - Cutaneous ulceration with necrosis may be seen and tumors may grow through skin.
 - Owing to tendency for these tumors to be very large, cervical adenopathy may be difficult to appreciate.
- Most patients are euthyroid, although both thyroid hypofunction and hyperfunction may uncommonly occur:
 - Thyroid hyperfunction due to destruction of thyroid follicular epithelium with release of colloid and thyroid hormone into circulation
 - May be associated with humoral hypercalcemia of malignancy due to parathyroid hormone-related protein secretion
- Radiology:
 - Hypofunctioning (“cold”) lesion on thyroid scanning
 - Uptake in either primary tumor or in metastatic foci may represent remnants of better differentiated component.
 - CT scan (preferred diagnostic modality):
 - Large infiltrative mass with irregular borders of low attenuation with cystic areas
 - Punctate calcifications and necrosis frequently present
 - Diffuse enlargement and replacement of thyroid gland by hypodense tumor may be identified.
 - Extensive spread outside thyroid gland with infiltration into soft tissue of neck as well as into adjacent structures (trachea, larynx, jugular vein, carotid artery, other) may be identified.
 - Nodal metastasis (cervical neck, mediastinal) may be identified.
 - Ultrasonography:
 - Hypoechoic
- Etiology:
 - Association with pre- or coexisting thyroid disease:
 - In majority of cases, develops in setting of pre-existing thyroid neoplasm, the majority of which are differentiated follicular-derived tumors, including:
 - Conventional papillary thyroid carcinoma and variants thereof:
 - Most common “precursor” neoplasm (>80% of cases showing differentiated and undifferentiated components)
 - Follicular carcinoma and variants thereof (e.g., oncocytic variant)

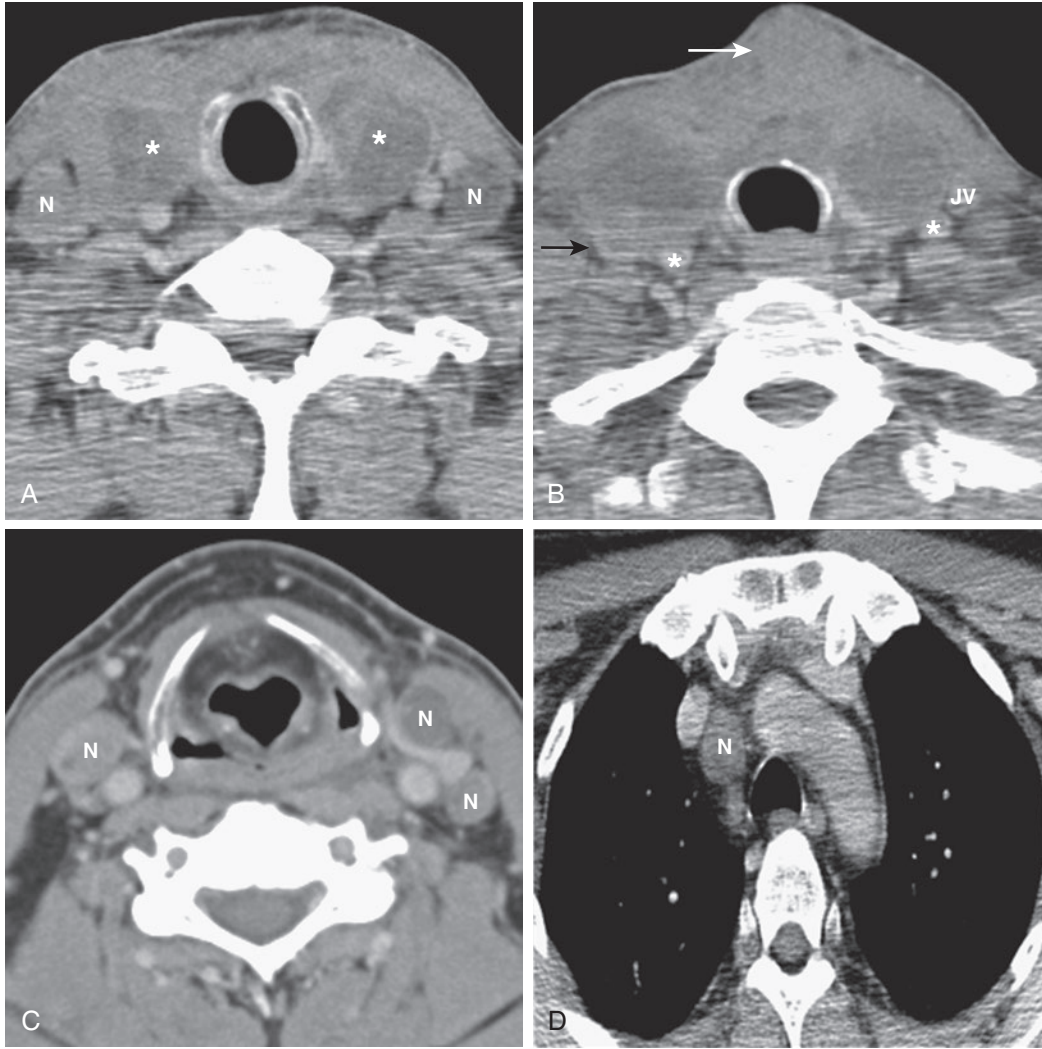


Fig. 28-76. Anaplastic thyroid cancer on contrast-enhanced CT.

A, Axial CT image at the level of the cricoid cartilage shows diffuse enlargement and replacement of the thyroid gland with hypodense tumor (*). There are necrotic bilateral cervical lymph node metastases (N). **B**, Axial CT scan inferior to **A** at the level of the trachea shows extensive involvement of the thyroid gland with anaplastic carcinoma. There is extensive spread outside the thyroid capsule into adjacent soft tissues of the neck anteriorly (white arrow), as well as laterally with invasion into the right jugular vein (black arrow), which is occluded. *Common carotid arteries; JV, patent left jugular vein. **C**, Axial CT image shows multiple bilateral necrotic metastatic lymph nodes (N) in the midcervical lymph chains. **D**, Axial CT scan of the chest shows mediastinal lymph node metastasis (N). (From Som and Curtin: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Figure 41-77, p 2646.)

- Follicular adenoma
- Less often, may develop from pre-existing poorly differentiated thyroid carcinoma
 - May develop from pre- or coexisting adenomatoid nodule(s) in patients with history of longstanding (decades-long) goitrous thyroid
 - In spite of development in setting of antecedent thyroid disease, probability of anaplastic transformation of a pre-existing follicular lesion is considered low.
- Iodine deficiency:
 - Higher incidence in areas of dietary iodine deficiency and endemic goiter
- Includes alpine regions
- Reduction in incidence with iodine supplementation
 - Radiation exposure (external and radioactive iodine)
 - Implicated as potential causative factor
 - Approximately 10% have history of radiation exposure, and 10% to 12% have history of another malignant neoplasm.
 - Probability of anaplastic transformation occurring is so low that it should not play any role in considering whether to use radiation in treatment.

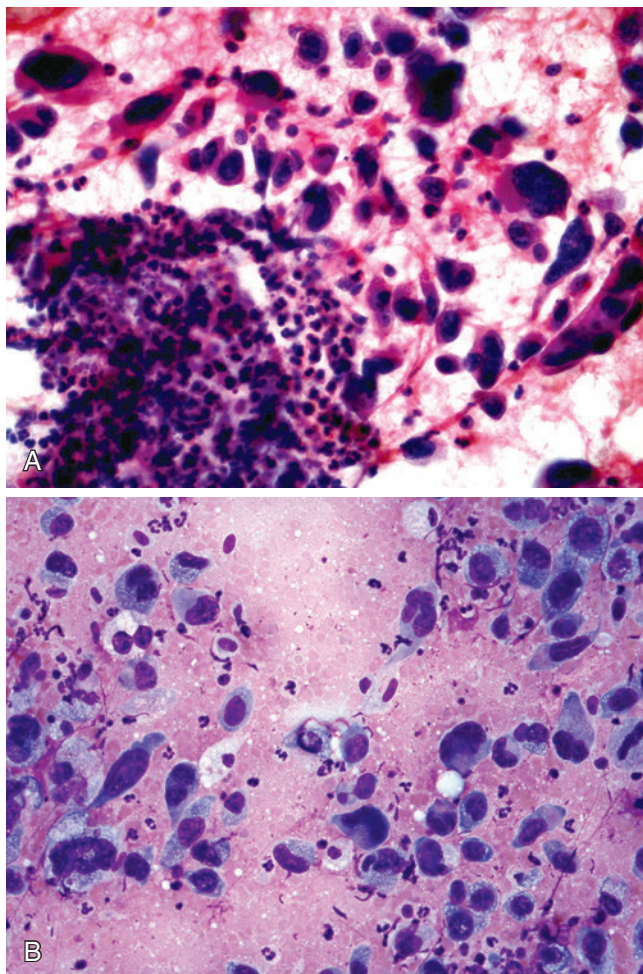


Fig. 28-77. Undifferentiated (anaplastic) thyroid carcinoma, fine-needle aspiration biopsy (FNAB).

Thyroid-related neck mass showing (A) cellular smear characterized by markedly pleomorphic cells with highly atypical hyperchromatic nuclei and associated necrosis and inflammation (Papanicolaou stain). B, Round to oval, spindle-shaped, and multinucleated highly malignant cells (Diff-Quik stain). Immunohistochemical staining on a cell block (not illustrated) showed the lesional cells to be reactive for cytokeratins and PAX8 but negative for thyroglobulin and TTF-1. The FNAB diagnosis would be “malignant; poorly differentiated carcinoma consistent with undifferentiated (anaplastic) thyroid carcinoma (Bethesda VI).”

Pathology

Fine-Needle Aspiration Biopsy

- Cellular aspirates with sheets, cell clusters, or isolated cells
- Large pleomorphic cells with bizarre hyperchromatic nuclei, prominent single or multiple nucleoli, and abundant cytoplasm
- Spindle-shaped cells are commonly seen.
- Mitoses and necrotic background are present.



Fig. 28-78. UTC.

Undifferentiated (anaplastic) thyroid carcinoma appearing as tan-white tumor with foci of necrosis replacing most of the thyroid gland. The tumor is grossly invading outside the confines of the thyroid gland (left).

Gross

- Large and widely invasive tumors that vary in appearance:
 - Often tan-white and firm to hard but may appear as mottled soft to rubbery due to extensive hemorrhage and necrosis
 - Rarely, anaplastic foci may appear as small firm to hard solid areas in a nodule or differentiated neoplasm.
 - Remnant of non-neoplastic thyroid gland may be limited in extent or absent due to replacement by anaplastic carcinoma.
- Range in size from 1 to 20 cm:
 - Usually measure >5 cm
 - Mean size 6.4 cm
- Extrathyroidal invasion commonly present

Histology

- Wide variation in histologic findings between tumors and even within same tumor
- Growth patterns include solid, fascicular, and storiform:
 - Admixtures of different growth patterns can be seen in any one case.
- Cytologically, irrespective of cell type (see below) features common to all tumors include presence of:
 - Marked nuclear pleomorphism
 - Increased mitotic activity with atypical mitoses
 - Extensive coagulative tumor necrosis
 - Extensive invasive growth, including:
 - Within thyroid parenchyma, into adjacent (extrathyroidal) tissues including skeletal muscle, adipose tissue
 - Vascular invasion, neurotropism

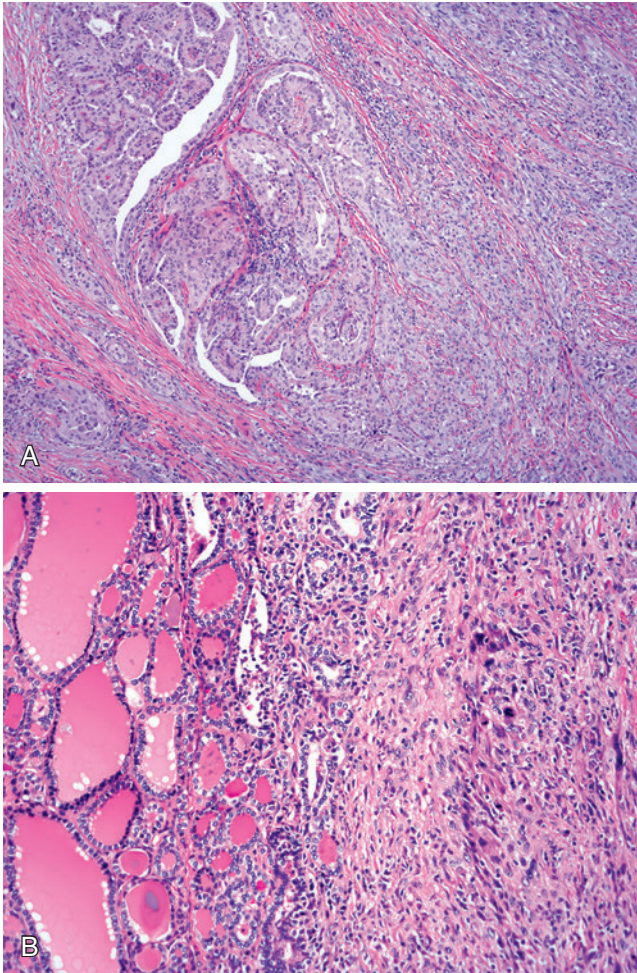


Fig. 28-79. UTC.

Undifferentiated (anaplastic) thyroid carcinoma characterized by fascicular growth and cells with high-grade nuclear features associated with remnants of **(A)** papillary thyroid carcinoma and **(B)** differentiated follicular neoplasm.

- Absence of follicular differentiation (in undifferentiated component)
- Among the cell types the most common are spindle-shaped, giant cell, and squamoid:
 - Spindle-shaped (sarcoma-like):
 - Most common
 - Composed of elongated and/or pleomorphic and hyperchromatic nuclei
 - Storiform and fascicular (long fascicles) growth
 - Heterologous elements may be present, including malignant bone and cartilage.
 - May include staghorn (hemangiopericytoma-like) vascularity
 - Giant cells:
 - Pleomorphic, round to oval cells characterized by bizarre-appearing nuclei
 - Often multinucleated with abundant eosinophilic to granular-appearing cytoplasm
 - Intracytoplasmic hyaline globules may be identified.
 - May represent only neoplastic cellular component or may be admixed with spindle-shaped (sarcomatous) foci
 - Pseudoglandular and pseudoangiomatous foci may be present.
- Squamoid (epithelioid):
 - Least common
 - Retention of epithelial appearance in form of nested or cohesive growth pattern suggestive of an epithelial neoplasm
 - Predominantly nonkeratinizing
 - Squamous differentiation including keratinization (keratin pearls, individual cells) may be present but usually does not make up majority of tumor.
 - Squamoid cell foci generally are devoid of giant cells but may be admixed with spindle-shaped (sarcomatous) foci.
- Histologic variants are rare and include:
 - Paucicellular variant:
 - Gross appearance may simulate features of Riedel disease, including homogenous, firm, tan-white
 - Characterized by relatively hypocellular proliferation with prominent associated fibrosis and hyalinization
 - Scattered lesional cells, often spindle-shaped, embedded in fibrous stroma show cytomorphic features of malignancy, including marked nuclear atypia with increased mitotic activity, necrosis, and vascular invasion:
 - Vascular invasion assists in differentiating the paucicellular variant from Riedel disease.
 - Lesional cells typically are cytokeratin positive.
 - Rhabdoid cell type (rhabdoid tumor of thyroid gland):
 - Thyroid tumors predominantly (approximately 30% to 40% of total tumor content) composed of rhabdoid cells
 - Controversial cell type infrequently seen in thyroid tumors with a limited number of cases reported in the world literature
 - Predominantly occurs in women (6:1); occur over a wide age range from the fifth to seventh decades of life (mean age, 55 years)
 - Occurs in association with differentiated thyroid carcinoma (i.e., follicular carcinoma or thyroid papillary carcinoma)
 - Some authorities categorize rhabdoid tumors of thyroid within category of undifferentiated

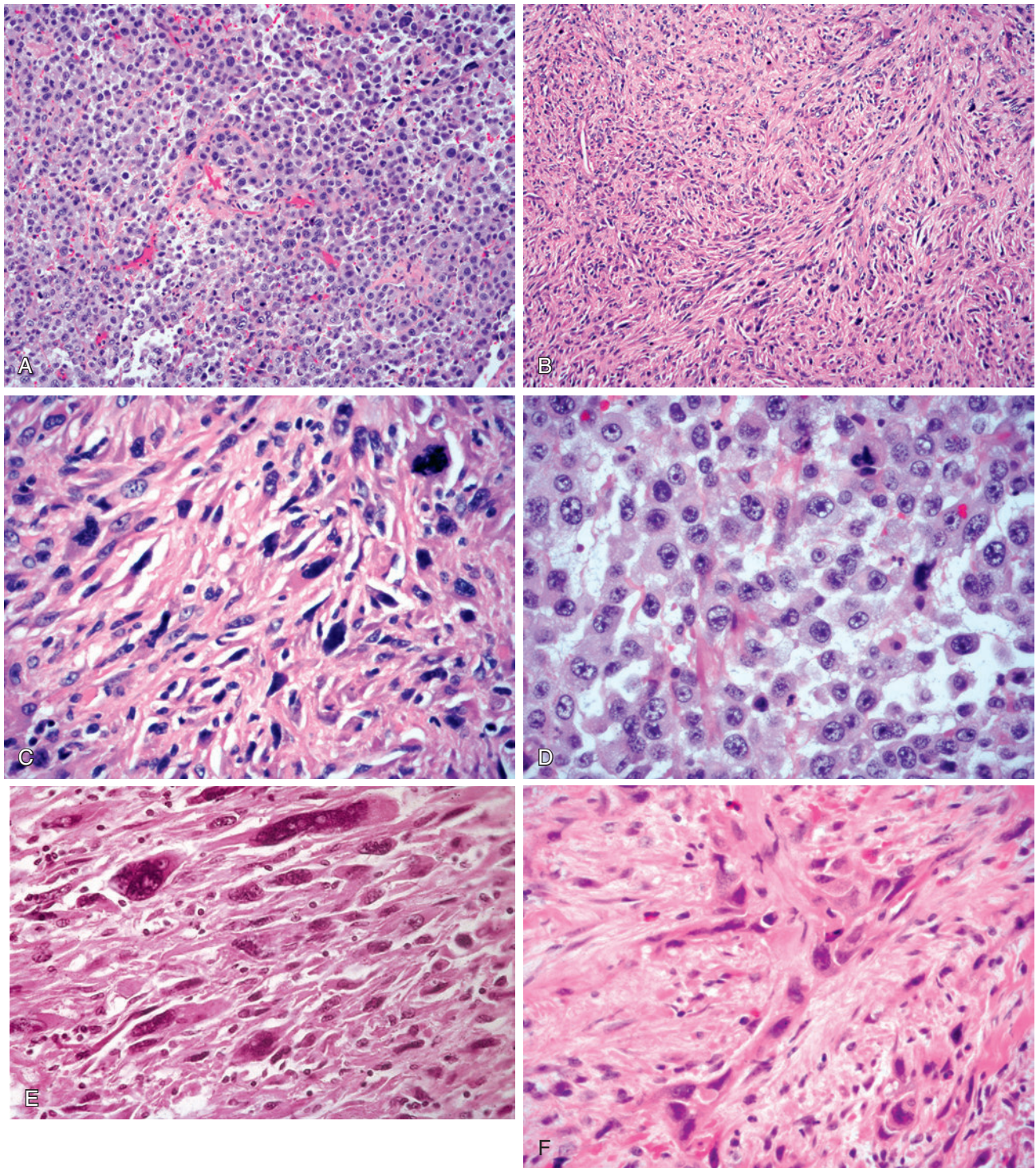


Fig. 28-80. Undifferentiated (anaplastic) thyroid carcinoma.

Undifferentiated (anaplastic) thyroid carcinoma. Growth patterns include **(A)** solid and **(B)** fascicular to storiform (sarcoma-like). Lesional cells include **(C)** spindle-shaped; **(D)** pleomorphic; **(E)** giant cells; **(F)** squamoid. Irrespective of the cell type, there is marked nuclear pleomorphism and increased mitotic activity with absence of cellular differentiation.

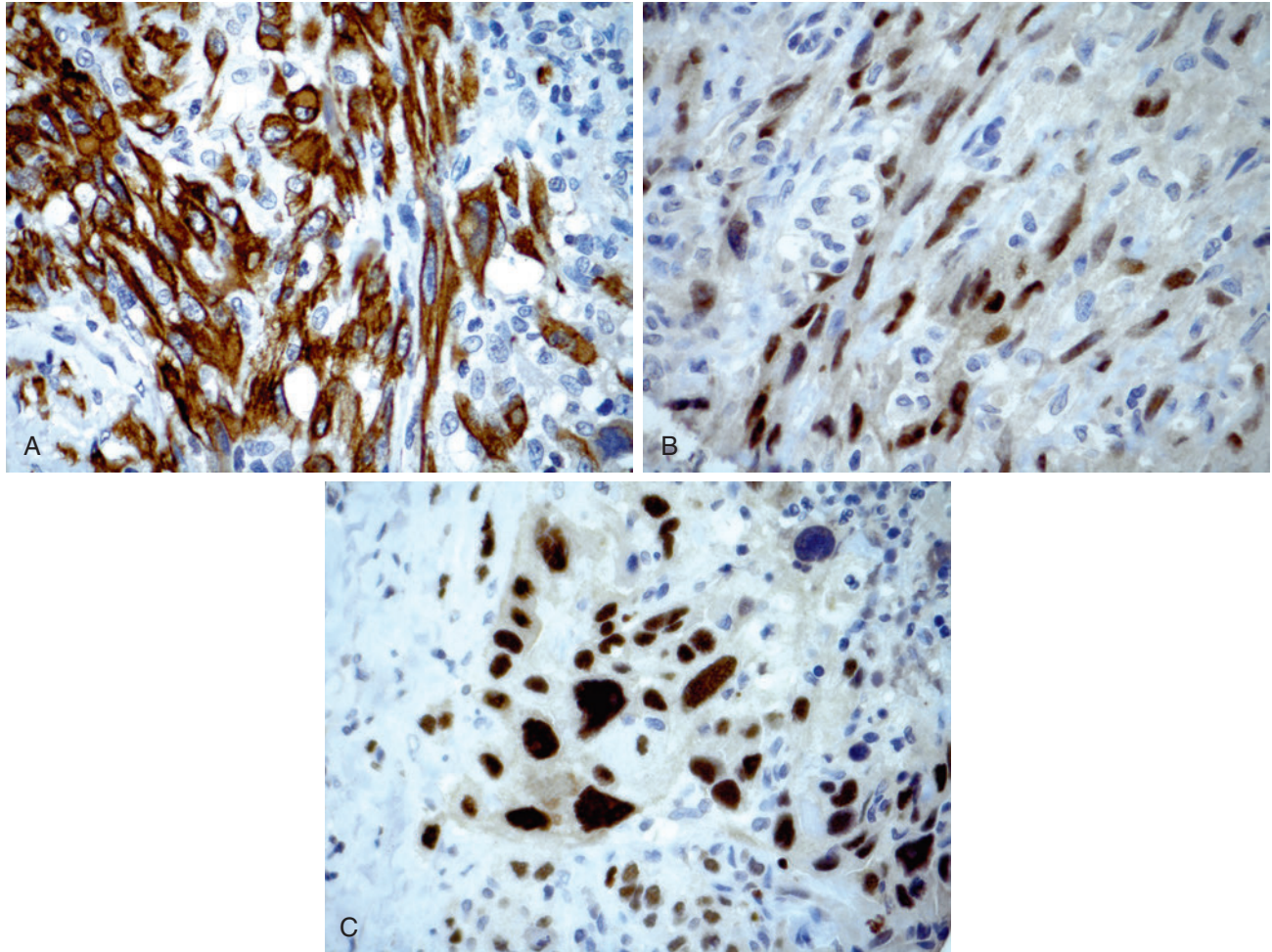


Fig. 28-81. Undifferentiated (anaplastic) thyroid carcinoma.

Immunohistochemical staining in undifferentiated (anaplastic) thyroid carcinoma typically includes an absence of thyroglobulin and TTF-1. **A**, Cytokeratins are typically patchy with scattered positive cells although in any given case may be diffuse and strong (AE1/AE3). PAX8 (nuclear) staining represents the most useful thyroid follicular epithelial cell marker in the diagnosis and is present in the majority of cases reactive in **(B)** spindle-shaped and **(C)** pleomorphic cells.

- (anaplastic) carcinomas, whereas other authorities classify it within category of poorly differentiated carcinoma (see later)
- Invasive, solid, and highly cellular composed of rhabdoid cells characterized by:
 - Presence of large cells with abundant eosinophilic to amphophilic cytoplasm, eosinophilic cytoplasmic inclusions, eccentric nuclei with prominent eosinophilic nucleoli
 - Increased mitotic figures and necrosis are present.
- Rhabdoid cells are:
 - Immunoreactive for cytokeratins, PAX8, vimentin, sarcomeric actin, and myoglobin
 - Tend to be nonreactive for thyroglobulin, TTF-1, desmin, smooth muscle actin, and S100 protein
- One case of rhabdoid tumor of the thyroid reported to have *RET/TPC3* rearrangement, a finding that:
 - Confirms an underlying papillary thyroid carcinoma
 - Indicates a direct relationship of rhabdoid tumor to the differentiated carcinoma.
- Lymphoepithelioma-like:
 - Unusual variant resembling undifferentiated-type carcinoma of other sites (lung, nasopharynx)
 - Composed of sheets or islands of cells with large round to oval nuclei with vesicular chromatin and prominent eosinophilic nucleoli
 - Associated lymphoplasmacytic infiltrate may be present.
 - Absence of Epstein-Barr virus

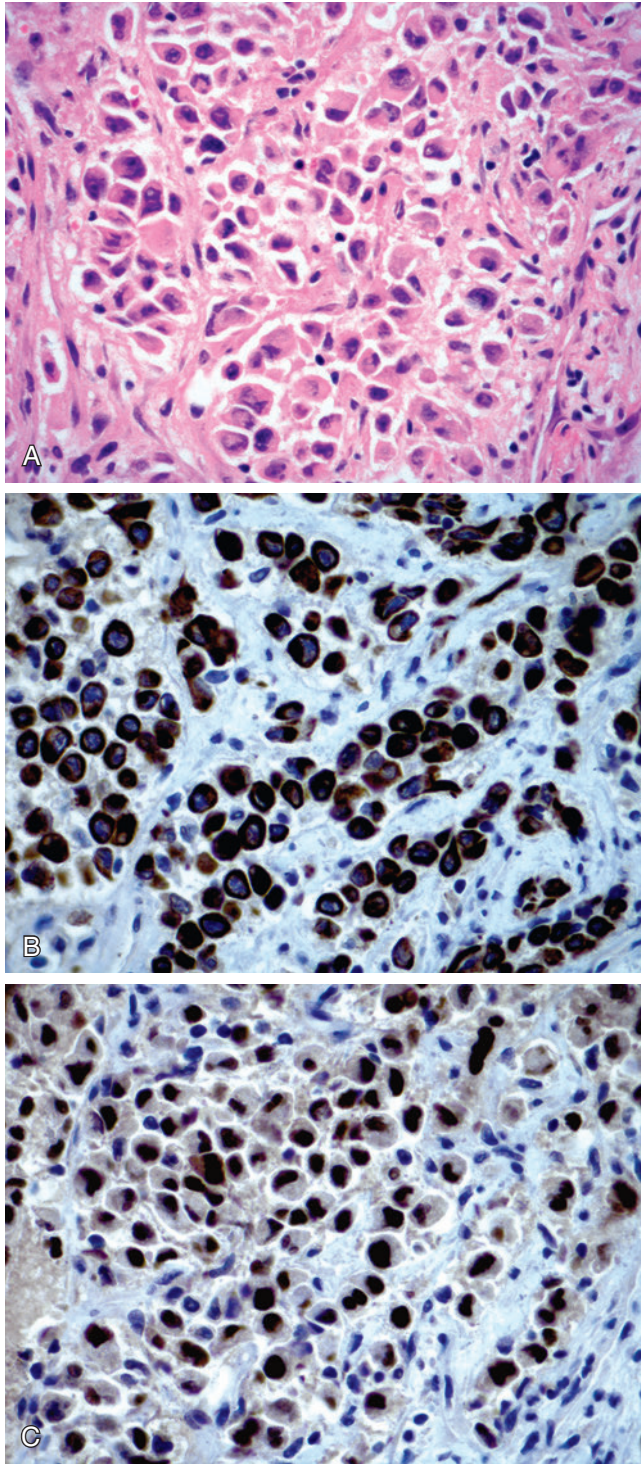


Fig. 28-82. Rhabdoid cells.

Rhabdoid cell type is characterized by **(A)** presence of large cells with abundant eosinophilic cytoplasm, eosinophilic cytoplasmic inclusions, and eccentric nuclei. Rhabdoid cells are immunoreactive for **(B)** cytokeratins (CAM 5.2) and **(C)** PAX8 (nuclear).

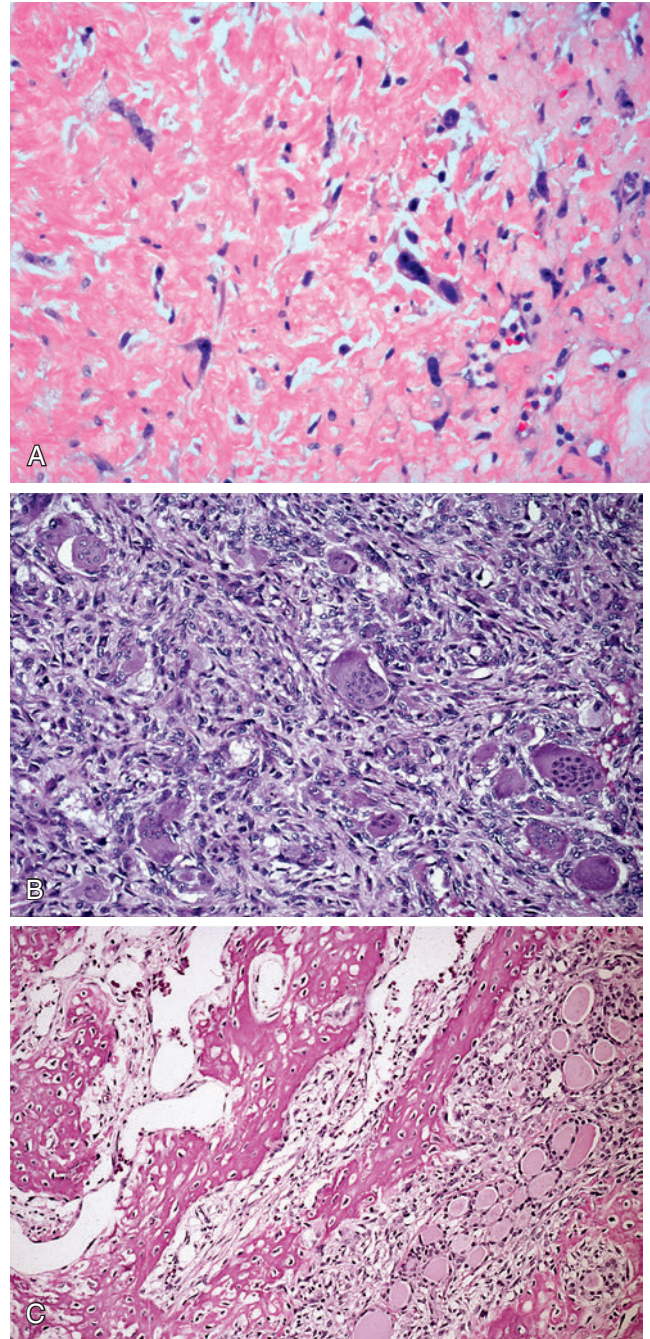


Fig. 28-83. Histologic variants of UTC.

Other findings that can be seen in undifferentiated (anaplastic) thyroid carcinoma include **(A)** paucicellular, **(B)** osteoclastic giant cells, and **(C)** heterologous bone.

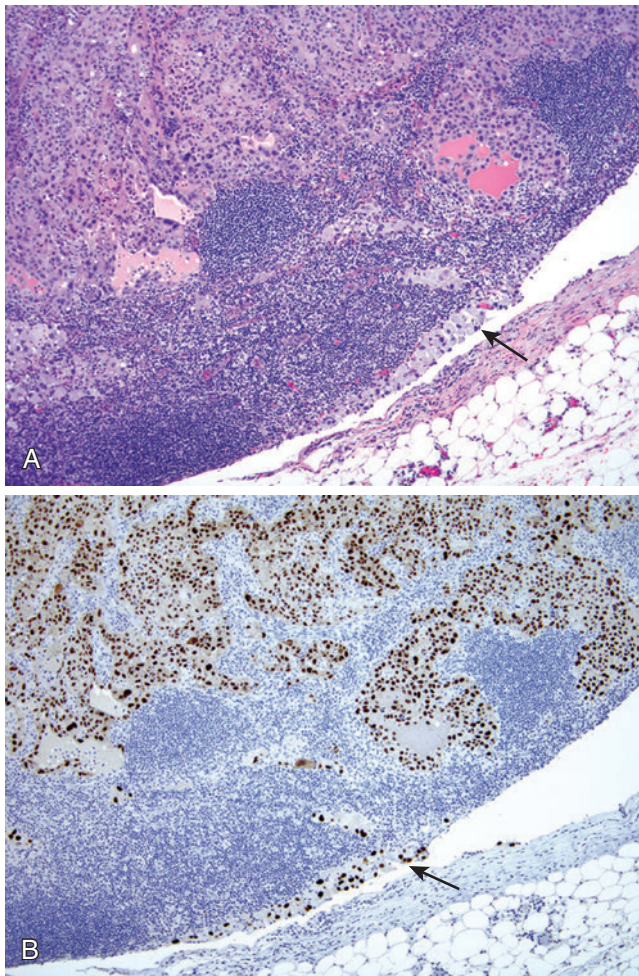


Fig. 28-84. Metastatic UTC.

In undifferentiated (anaplastic) thyroid carcinoma metastatic disease often occurs early in the disease course including **(A)** to regional lymph nodes with tumor in the subcapsular sinus (*arrow*) and in node parenchyma; **(B)** lesional cells are strongly and diffusely PAX8 reactive (nuclear), including cells in subcapsular sinus (*arrow*).

- Absence of CD5 reactivity would differentiate this tumor type from carcinoma showing thymus-like element (CASTLE)
- Angiomatoid:
 - Presence of anastomosing tumor cell-lined clefts that may contain blood simulating histology of angiosarcoma
- Small cell type:
 - Has been considered a type of undifferentiated carcinoma
 - Existence of a true small cell type of carcinoma in the thyroid is questionable.
 - These tumors more likely represent lymphoma, a variant of medullary carcinoma, a variant of

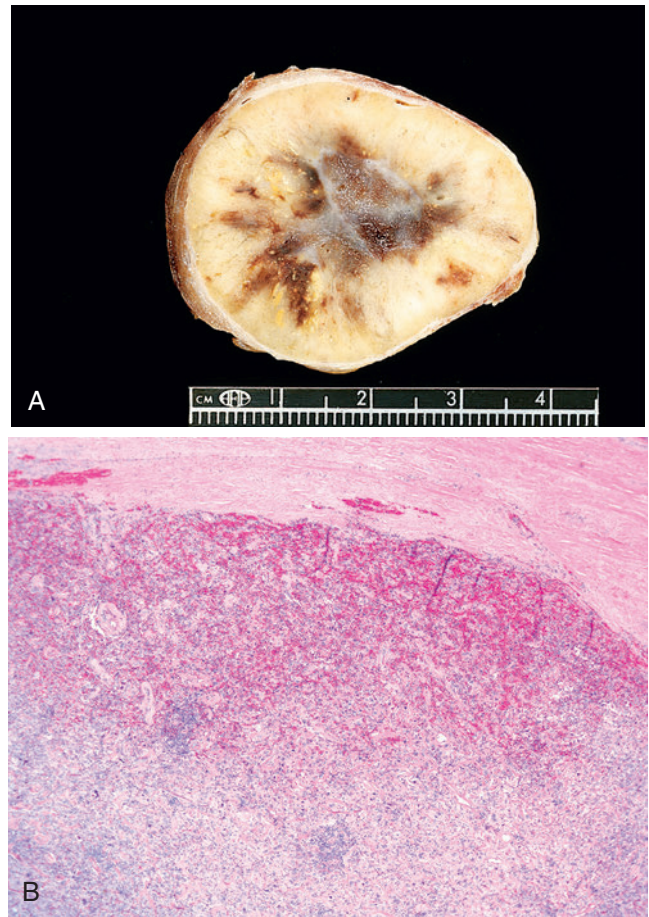


Fig. 28-85. Noninvasive UTC.

In rare examples, undifferentiated (anaplastic) thyroid carcinoma may be encapsulated without invasion both by **(A)** macroscopic and **(B)** microscopic evaluation. The absence of invasion is uncommon, requiring submission of the entire tumor to exclude invasive growth. Patients with noninvasive undifferentiated (anaplastic) thyroid carcinoma may experience longer survival periods as compared to the rapid demise typically associated with the majority of patients whose cancers are invasive.

- follicular carcinoma (e.g., insular carcinoma), metastatic small cell carcinoma.
- Hobnail features:
 - Presence of foci with hobnail features reported in 1 of 26 anaplastic carcinomas (3.8%) (more frequently in poorly differentiated thyroid carcinoma)
 - Findings suggest that hobnail features may be manifestation of higher-grade transformation.
- Osteoclastic-type giant cells:
 - Characterized by numerous nuclei with limited atypical cytologic features that may be present in a small percentage of cases

- Typically osteoclastic-type giant cells are seen in or near hemorrhagic areas.
- Nature of osteoclastic giant cells remains uncertain but likely represent reactive cells of macrophage/histiocyte origin rather than neoplastic cells as evidenced by their ability to phagocytize inflammatory cells, immunoreactivity with CD68 (KP-1), ultrastructural features, and presence of high levels of acid phosphatase activity.
- As noted previously:
 - In any given tumor mixed growth patterns and mixed cell types can be seen.
 - Irrespective of cell type, neoplastic cellular infiltrate:
 - Is undifferentiated without evidence of colloid formation
 - Is markedly pleomorphic with an increase in nuclear to cytoplasmic ratio; prominent eosinophilic nucleoli may be present
 - Has high mitotic rate with numerous atypical forms
 - Has associated foci of confluent necrosis and individual cell necrosis
- Stroma may have myxoid change or may have prominent collagen deposition.
 - An associated inflammatory cell infiltrate including many neutrophils may be present.
- Prominent vascularity is present, which may have a pericytic (“staghorn”) growth or resemble appearance of an angiosarcoma (interconnecting vascular channels lined by neoplastic cells)
- Heterologous elements, including bone and cartilage, may be present.
 - When present, these elements are usually seen in association with sarcomatous foci but can also be seen admixed with epithelial and giant cell infiltrates.
- Invasiveness:
 - Most UTCs are extensive invasion, including:
 - Intrathyroidal invasion of thyroid parenchyma, vascular invasion, peri- and intraneural invasion
 - Vascular space invasion (veins, arteries, and lymphatics) with replacement of endothelial cells and the development of tumor thrombi is often present.
 - Extrathyroidal infiltration including:
 - Perithyroidal soft tissues (muscle, vessels, nerves), invasion into larynx, trachea, and esophagus
 - May be noninvasive (noninvasive undifferentiated thyroid carcinoma)
 - Encapsulated without evidence of invasion
 - Entire tumor should be submitted to exclude presence of invasion.
- Differentiated thyroid lesion/neoplasm:
 - Remnants of a pre- or coexisting differentiated thyroid follicular-derived lesion may or may not be present.
 - Differentiated thyroid lesion includes:
 - Papillary thyroid carcinoma
 - Most common
 - May include follicular or tall cell variants
 - Less commonly may include:
 - Adenomatoid nodule
 - Follicular neoplasm (carcinoma, adenoma)
 - Poorly differentiated thyroid carcinoma
 - Presence of identifying differentiated thyroid lesion/neoplasm may be function of sampling
- Immunohistochemistry:
 - Undifferentiated component:
 - Reactivity with cytokeratins is most useful marker:
 - Identified in majority of cases
 - May vary but most often focally identified in scattered lesional cells
 - Should include array of cytokeratins including AE1/AE3, CAM 5.2, OSCAR
 - Epithelial membrane antigen (EMA):
 - Usually positive but with variable reactivity
 - Carcinoembryonic antigen (CEA) reactivity
 - Usually is limited to focal areas and/or scattered cells (epithelial, spindle-shaped, giant cells, paucicellular cells)
 - p63 (nuclear) reactivity:
 - Positive in majority of cases
 - Based on limited number of reported cases
 - PAX8 (nuclear) reactivity:
 - Most useful among thyroid follicular epithelial cell markers
 - Reported positive in up to 79% of cases
 - Thyroglobulin and TTF-1 (nuclear) reactivity:
 - Extremely variable and usually absent
 - Generally not helpful in diagnosis
 - Reactivity due to diffusion of thyroglobulin from destroyed non-neoplastic cells or thyroglobulin expression in entrapped differentiated tumor or non-neoplastic thyroid parenchyma can be seen and should not be interpreted as expression in undifferentiated component
 - Vimentin reactivity is usually present in all cellular components but is most reactive with spindle-shaped cells.
 - High proliferation indices as determined by Ki67 (MIB1) staining
 - Calcitonin, synaptophysin, and chromogranin negative
 - Evidence of epithelial-to-mesenchymal transition markers reported, including decreased expression of E-cadherin and increased

expression of Zinc Finger E-Box Binding Homeobox 1 (ZEB1):

- Epithelial mesenchymal transition (EMT) is major pathologic mechanism in tumor progression and is linked to acquisition of stem-like properties of cancer cells
- Electron microscopy:
 - Evidence of epithelial (follicular cell) differentiation, including specialized cell junctions (desmosomes) or microvilli may be present (approximately 50% of cases), but due to the poorly differentiated nature of these tumors evidence of epithelial differentiation may not be identified.
- Cytogenetics and molecular genetics:
 - Mutations of p53 gene found in high percentage of cases
 - A significant percentage of anaplastic carcinomas harbor *BRAF* mutations:
 - Consistent sharing of the same *BRAF* profile is present in cases in which thyroid papillary carcinoma and UTC occur together; this finding supports the notion that UTCs represent progressive malignant degeneration of a pre-existing, well-differentiated thyroid carcinoma
 - Given the high frequency of *BRAF* mutations in UTC, anti-*BRAF* therapy may offer potential benefits for these patients.
 - β -catenin gene mutation (*CTTNB1*) common occurrence
 - *RAS* and *BRAF* mutations may be present in approximately a third of cases.
 - Low prevalence of *RET/PTC* rearrangement and *PAX8/PPAR γ* fusion
 - Telomerase reverse transcriptase (TERT) promoter mutations identified
 - Associated with more aggressive behaving thyroid cancers, including (other than UTC):
 - Tall cell variant of PTC
 - Poorly differentiated thyroid carcinoma
 - *PIK3CA* and *PTEN* mutations may be present

Differential Diagnosis

- Poorly differentiated thyroid carcinoma
- Papillary thyroid carcinoma with:
 - Squamous metaplasia
 - Spindle cell metaplasia
 - Nodular fasciitis-like stroma
- Depending on the histologic variant, additional differential diagnoses may include:
 - Carcinoma showing thymus-like elements (CASTLE) for lymphoepithelial-like variant
 - Riedel disease for paucicellular variant
- Malignant lymphoma, diffuse, predominantly large cell type
- Malignant melanoma
- Angiosarcoma

- Other sarcomas (primary and secondary involvement from a neck soft tissue tumor), including:
 - Undifferentiated pleomorphic sarcoma
 - Malignant peripheral nerve sheath tumor
 - Leiomyosarcoma
- Medullary thyroid carcinoma
- Invasive carcinoma from non-thyroid origin (e.g., larynx, other)
- Parathyroid carcinoma

Treatment and Prognosis

- Multimodality therapy, including surgery, radiation, and chemotherapy
 - If possible, complete surgical excision is indicated.
 - Unfortunately, these tumors tend to be so large and extensively invasive at presentation that complete surgical excision is not possible, and debulking of tumor is all that can be done.
 - Postoperative external irradiation and chemotherapy administered but efficacy in treatment is questionable, at best
- Radioactive iodine therapy has no role in the management because undifferentiated thyroid carcinoma is not iodine avid.
- Combined surgical, external irradiation, and chemotherapy offer best chances of survival but, even with multimodality therapy, most patients die (owing to local relapse), with mortality rates of more than 95%:
 - Death often occurs within short periods of time (6 months).
 - Approximately 20% of patients survive for 1 year.
 - 5-year survival rate is <14% with median survival rates of 2.5 to 6 months.
 - Longer-term survival may occur in association with:
 - Patients under 60 years of age
 - Tumors with limited anaplastic foci in a predominantly differentiated neoplasm
 - Noninvasive tumors, tumors confined to thyroid (intrathyroidal), and/or tumors with limited invasive growth
 - Tumors less than 4 cm
 - Tumors amenable to complete surgical resection
- Metastatic disease occurs early (at presentation or soon thereafter):
 - Lymphatic (regional and distant) and hematogenous spread occur
 - Common metastatic sites include adrenal glands, lung, and gastrointestinal tract.
 - Histology of metastatic tumor resembles that of primary neoplasm, and all of the cellular components of primary tumor may appear in the

metastatic foci (except for the heterologous elements such as bone and cartilage).

- Targeted molecular therapy emerging as potentially promising in treatment and includes:
 - Tyrosinase inhibitors
 - Thailandepsin A (TDP-A), a histone deacetylase (HDAC) inhibitor
 - Mitotic kinases, including Polo-like kinase-1 (PLK1)
 - Combretastatin

UNUSUAL EPITHELIAL TUMORS OF THE THYROID GLAND

Primary Thyroid Mucoepidermoid Carcinoma

- Two entities included under designation of thyroid mucoepidermoid carcinoma, including:
 - Mucoepidermoid carcinoma
 - Sclerosing mucoepidermoid carcinoma with eosinophilia
- Literature appears to support separating these two tumor types as distinct entities based on apparent differences in light microscopic and immunohistochemical findings, although this issue has not been entirely resolved.
- Separation may be academic because both tumor types have a similar indolent biologic course.

Thyroid Mucoepidermoid Carcinoma (TMEC)

(Figs. 28-86 and 28-87)

Definition: Low-grade malignant thyroid tumor with histologic appearance similar to its low-grade salivary gland counterpart, including presence of epidermoid cells and mucous cells.

Clinical

- Rare thyroid malignant tumor
- More common in women more than in men; occurs over a wide age range (second through eighth decades), with most patients in the fifth through seventh decades of life
- Most common presenting complaint includes painless neck mass:
 - Less commonly, pain, hoarseness, and vocal cord paralysis may occur.
 - Extrathyroidal extension in approximately 20%:
 - Symptoms of tracheal, esophageal, and recurrent laryngeal nerve compression may be present.
- Patients are euthyroid.
- May occur in any portion of thyroid gland, including isthmus



Fig. 28-86. Thyroid mucoepidermoid carcinoma.

Thyroid mucoepidermoid carcinoma appearing as a circumscribed solid mass (upper) separated from adjacent thyroid gland.

- Radiology:
 - Hypoactive “cold” nodule on thyroid imaging
- Etiology:
 - No known etiologic factors
 - History of radiation exposure during childhood reported in limited cases
- Histogenesis:
 - Several theories for origin of TMEC, including:
 - Likely origin from squamous metaplasia of follicular epithelial cells (possibly as a metaplastic variant of papillary carcinoma); in support of this consideration includes:
 - Transitions from follicular epithelium or foci of papillary thyroid carcinoma
 - Occurrence in background of chronic lymphocytic (Hashimoto) thyroiditis:
 - ◻ Common setting in which to find squamous metaplasia including presence of keratinization and intercellular bridges
 - Presence of thyroglobulin, TTF-1, and PAX8 reactivity
 - Presence of psammoma bodies
 - Association with papillary thyroid carcinoma
 - Indolent biology
 - Tendency to metastasize to regional lymph nodes
 - Origin from ultimobranchial bodies or solid cell nests, but most associated findings (see immediately above) weigh against such origin
 - Origin from thyroglossal duct

Pathology

Fine-Needle Aspiration Biopsy

- Smears show epidermoid cells and mucus-secreting cells.
- Cellular sheets with a microcystic-like pattern containing hyaline bodies may be identified.

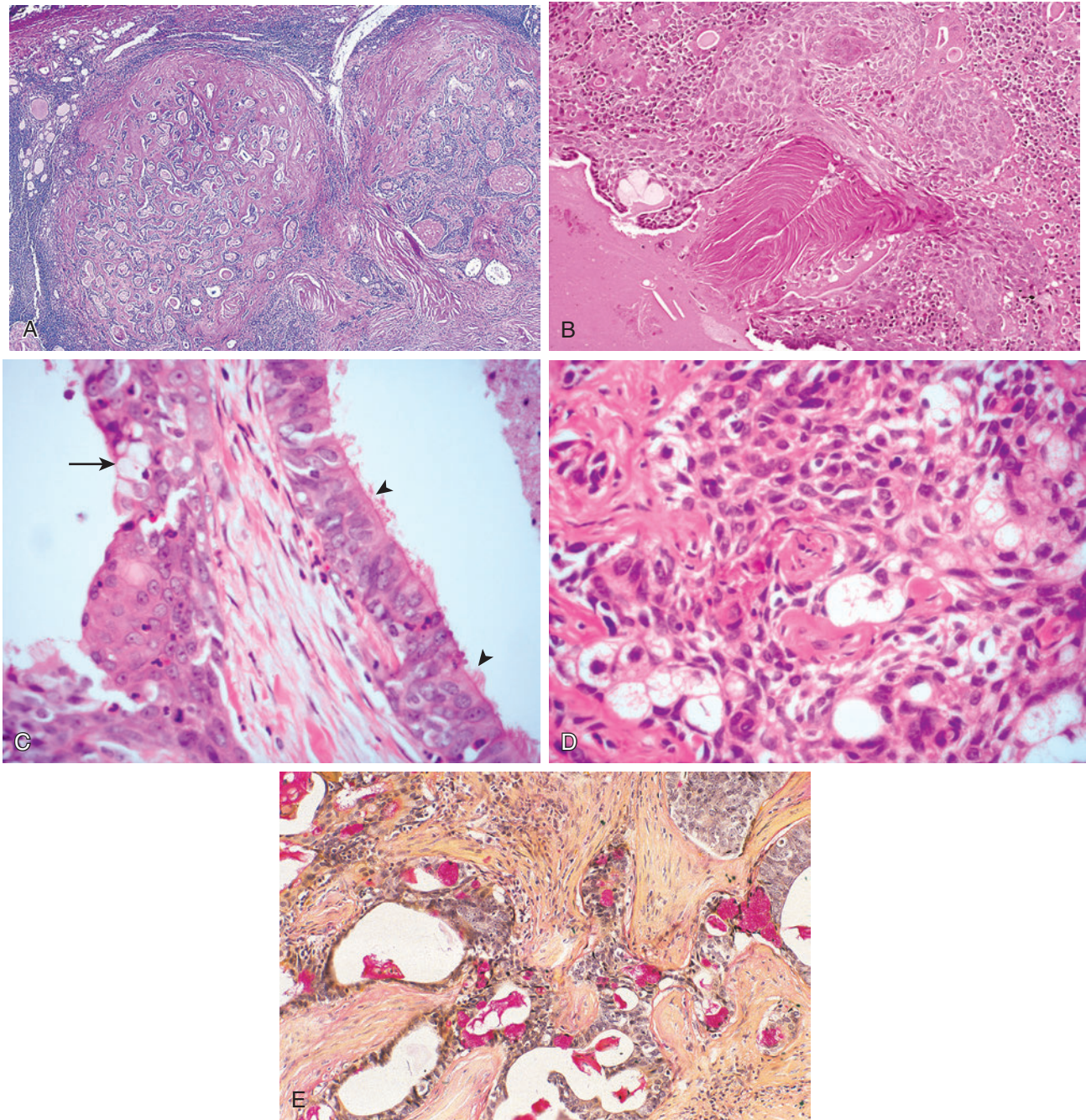


Fig. 28-87. Thyroid mucoepidermoid carcinoma.

A, Nodular proliferation that is delineated but unencapsulated composed of solid and cystic foci with associated fibrosis; chronic lymphocytic (Hashimoto) thyroiditis is seen in the adjacent non-neoplastic thyroid tissue (*upper left*). **B**, Squamous or epidermoid component may include horny pearl formation, as well as individual cell keratinization; a cluster of mucocytes (*left of center*) is seen intimately admixed with the squamous/epidermoid component. **C**, Cystic lesion including epidermoid cells and scattered mucocytes (*arrow*); note columnar-appearing cells with prominent cilia (*arrowheads*). **D**, Solid lesion composed of an admixture of squamous/epidermoid cells and scattered mucocytes. **E**, Mucicarmine staining shows the presence of intracytoplasmic and intraluminal mucin-positive (red) material.

Gross

- Solitary mass measuring up to 10 cm in greatest dimension
- Cut section shows solid, nodular-appearing tissue varying from tan-brown to yellow-orange and with a rubbery to firm consistency.
 - Cystic change can be seen.

Histology

- Circumscribed but unencapsulated predominantly solid mass:
 - Prominent cystic foci may be present.
- Neoplastic proliferation includes epidermoid cells admixed with mucocytes.
 - Epidermoid cells
 - Round to oval cells with round nuclei, prominent centrally located nucleoli, and eosinophilic cytoplasm
 - Horny pearl formation, individual cell keratinization, and intercellular bridges are seen.
 - Mild nuclear pleomorphism, slight increase in the nuclear to cytoplasmic ratio, and scattered mitotic figures can be seen.
 - Mucous cells
 - Cells with abundant clear to foamy-appearing cytoplasm and peripherally located hyperchromatic nuclei
 - Mucocytes are intimately admixed with epidermoid cells.
 - Extravasated mucinous material/pools may be present.
 - Psammoma bodies may be identified.
 - Columnar-appearing cells with prominent cilia resembling respiratory-type epithelium can be identified.
 - A mixed inflammatory cell infiltrate including mature lymphocytes and plasma cells can be seen within the neoplastic proliferation; eosinophils may predominate in any given tumor.
 - Intratumoral sclerosis composed of thick, acellular hyalinized bands of tissue can be seen and is not necessarily limited to those cases with abundant eosinophils (see below).
 - Chronic lymphocytic (Hashimoto) thyroiditis is commonly present in the surrounding non-neoplastic thyroid gland and may include foci of squamous metaplasia.
 - Associated lesions:
 - Papillary thyroid carcinoma (separate or admixed) including tall cell variant:
 - Undifferentiated (anaplastic) carcinoma reported in association with PTC
 - Follicular carcinoma, conventional, and oncocytic variant
 - Adenomatoid nodules may be seen.

- Generally confined to thyroid gland but extrathyroidal extension may occur.
- Histochemistry:
 - Mucocytes:
 - Presence of intracytoplasmic and intraluminal mucicarmine and diastase-resistant, PAS-positive material
 - Cystic spaces may also show mucicarminophilic material.
- Immunohistochemistry:
 - Cytokeratins positive including:
 - Low and high molecular weight
 - CK5/6
 - p63 reactivity may be present
 - Thyroglobulin, TTF-1, and PAX8 (nuclear):
 - Thyroglobulin staining may be focal or even absent.
 - Polyclonal carcinoembryonic antigen may be present in association with mucocytes.
 - Calcitonin, chromogranin, synaptophysin
- Cytogenetics and molecular genetics:
 - Marked abnormalities of the cadherin/catenin complex, including consistent neoexpression of P-cadherin and major alterations in the expression of E-cadherin
 - *CRTC1/MAML2* fusion transcript reported

Differential Diagnosis

- Metastatic mucoepidermoid carcinoma of salivary gland origin
- Primary thyroid squamous cell carcinoma
- Papillary carcinoma with squamous metaplasia
- Adenosquamous carcinoma: primary thyroid origin or (direct) invasion from a minor salivary gland mucoepidermoid carcinoma from the larynx or trachea
- Lymphocytic thyroiditis with epithelial-lined cysts
- Medullary carcinoma with squamous differentiation
- Branchial cleft-derived cysts

Treatment and Prognosis

- Surgery is preferred treatment:
 - May include lobectomy/subtotal thyroidectomy or total thyroidectomy
- Indolent tumor with excellent prognosis:
 - Rare cases associated with PTC with anaplastic transformation follow dire disease course associated with undifferentiated (anaplastic) carcinoma.
- Metastatic tumor:
 - Regional cervical lymph nodes metastasis common
 - Distant metastasis is uncommon but may occur (lung).
- Presence of extrathyroidal extension and metastatic disease considered adverse biologic factors in other

follicular epithelial-derived tumors, does not appear to adversely affect prognosis in TMEC

Sclerosing Mucoepidermoid Carcinoma with Eosinophilia (SMECE) (Fig. 28-88)

Definition: Low-grade malignant thyroid tumor with histologic appearance similar to its low-grade salivary gland counterpart, including epidermoid cells and mucous cell differentiation plus presence of prominent sclerotic stroma and eosinophil-rich inflammatory cell component.

- Considered distinct from thyroid mucoepidermoid carcinoma

Clinical

- Uncommon thyroid malignant tumor
- Demographics similar to mucoepidermoid carcinoma:
 - Affects women more than men
 - Occurs over a wide age range (second to eighth decades), with most patients in the fifth through seventh decades of life
- Most common presenting complaint that of painless neck mass:
 - Rarely associated with hoarseness, vocal cord paralysis
- Arises in thyroid glands affected by chronic lymphocytic (Hashimoto) thyroiditis, in particular, fibrous variant

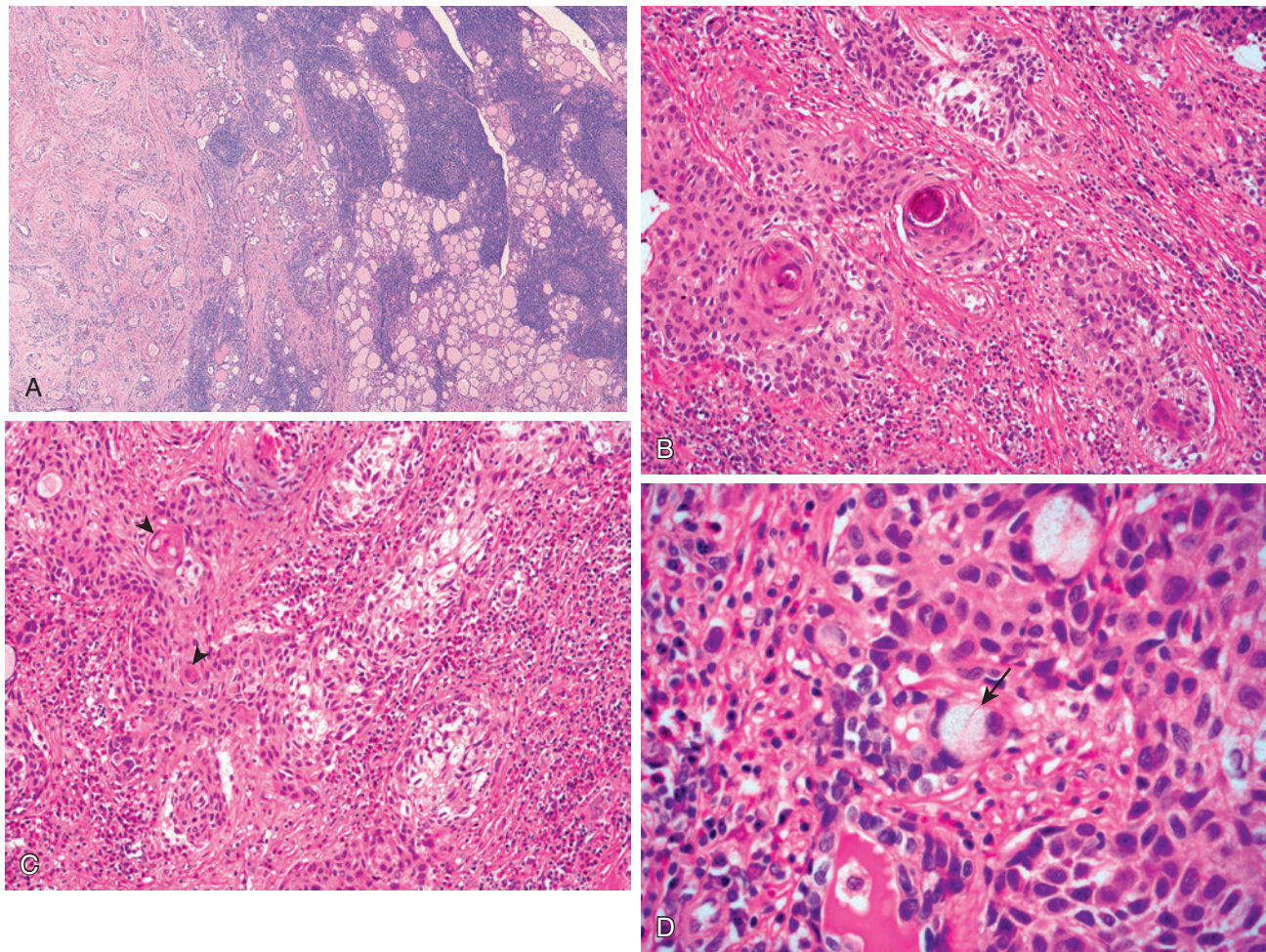


Fig. 28-88. Sclerosing mucoepidermoid carcinoma with eosinophilia.

A, At low magnification the tumor (*left*) appears unencapsulated with associated sclerosis (*left*) and infiltrates into the adjacent thyroid gland (*center*), which is characterized by the presence of chronic lymphocytic (Hashimoto) thyroiditis. **B and C,** Infiltrating cohesive cords of tumor with associated sclerosis and numerous eosinophils. The epidermoid/squamous cell component includes (**B**) foci with prominent squamous differentiation to (**C**) more subtle squamous differentiation in the form of individual cell keratinization (*arrowheads*). **D,** Admixture of squamous/epidermoid cells and scattered mucocytes (*arrow*) with associated eosinophilic cell infiltrate (*left*).

- Patients are euthyroid
- May occur in any portion of thyroid gland, including isthmus
- Radiology:
 - Hypoactive “cold” nodule on thyroid imaging
- Etiology:
 - No known etiologic factors
- Histogenesis:
 - Presumed to arise from metaplastic squamous epithelium

Pathology Fine-Needle Aspiration Biopsy

- Clusters of epidermoid or glandular cells in background of inflammatory cells, including eosinophils:
 - Mucinous material/debris may be present.

Gross

- Lesion with ill-defined borders, although may be circumscribed
- Measure from approximately 1.0 cm to 13 cm
- Cut section shows solid, firm lesion with white to yellow color.
 - Cystic change can be seen.

Histology

- Circumscribed but unencapsulated to infiltrative lesion:
 - Most are infiltrative including extrathyroidal extension
- Neoplastic proliferation includes:
 - Presence of anastomosing cords and narrow strands of tumor cells infiltrating sclerotic stroma with associated mixed inflammatory cell infiltrate that includes prominent eosinophilic cell component as well as lymphocytes and mature plasma cells
 - Neoplastic cells show squamous or epidermoid differentiation, including keratinization, as well as occasional mucocytes and/or mucin pools
 - Clear cells may be seen typically representing a minor component (10% to 30%) of tumor:
 - Clear cells appear to be glycogen-rich squamous cells.
 - Mucous pools may be present but are uncommon.
 - Pseudoangiomatous appearance may be identified owing to loss of cohesion of tumor cells.
- Chronic lymphocytic (Hashimoto) thyroiditis commonly present in surrounding non-neoplastic thyroid gland and may include foci of squamous metaplasia.
- Perineural invasion and vascular invasion common
- Rarely associated with conventional papillary thyroid carcinoma
- Histochemistry:

- Mucocytes:
 - Presence of intracytoplasmic and intraluminal mucicarmine and diastase-resistant, PAS-positive material
 - Cystic spaces may also show mucicarmino-philic material.
- Immunohistochemistry:
 - Cytokeratin and TTF-1 (nuclear) positive
 - p63 positive in squamous/epidermoid cells
 - Polyclonal carcinoembryonic antigen may be present in association with mucocytes.
 - Thyroglobulin negative
 - Calcitonin, chromogranin negative

Differential Diagnosis

- Metastatic mucoepidermoid carcinoma of salivary gland origin
- Primary thyroid squamous cell carcinoma
- Papillary carcinoma with squamous metaplasia
- Adenosquamous carcinoma: primary thyroid origin or (direct) invasion from a minor salivary gland mucoepidermoid carcinoma from the larynx or trachea
- Chronic lymphocytic (Hashimoto) thyroiditis with cyst formation and prominent eosinophilic infiltrate
- Medullary carcinoma with squamous differentiation
- Branchial cleft-derived cysts

Treatment and Prognosis

- Total thyroidectomy is preferred treatment.
- Indolent tumor with excellent prognosis
- Metastatic tumor:
 - Occurs to cervical lymph nodes in approximately one third of patients at presentation
 - Distant metastasis is uncommon but may occur to lung and bone.
- Extrathyroidal extension:
 - Occurs in approximately 50% of patients
- Presence of extrathyroidal extension and metastatic disease considered adverse biologic factors in other follicular epithelial-derived tumors, does not appear to adversely affect prognosis

OTHER SQUAMOUS CELL MALIGNANT TUMORS OF THE THYROID GLAND

Squamous Cell Carcinoma (SCC)

(Figs. 28-89 through 28-91)

- Extraordinarily rare primary thyroid follicular cell-derived tumor entirely composed of cells with squamous differentiation

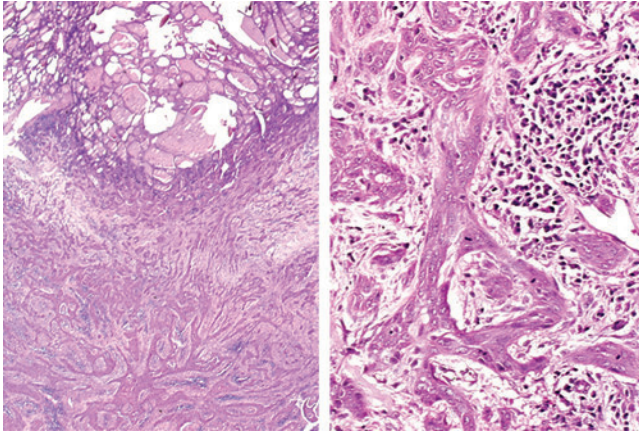


Fig. 28-89. Thyroid squamous cell carcinoma.

Primary squamous cell carcinoma of the thyroid may arise in association with (*left*) an adenomatoid nodule (*top*) with invasive growth composed of (*right*) squamous cells with nuclear pleomorphism and mitotic figures.

- Tend to arise in setting of long-standing thyroid disease, including goitrous thyroid and chronic lymphocytic (Hashimoto) thyroiditis:
 - Probably take origin from squamous metaplastic foci of follicular epithelial cells
 - Some classify within spectrum of undifferentiated (anaplastic) carcinoma.
- More common in women than men; wide age range from 20 to 90 years with mean age at diagnosis of 63 years
- Most common complaint is anterior neck mass that may be rapidly enlarging
 - Dyspnea or dysphagia may be present
 - Extension to adjacent structure found in majority of cases
- Spectrum of histologic changes includes well-, moderately, and poorly differentiated squamous cell carcinoma:
 - May be nonkeratinizing with features similar to nonkeratinizing carcinomas of the oropharynx and nasopharynx
 - In contrast to squamous metaplasia, squamous cell carcinomas show pleomorphism, increased nuclear to cytoplasmic ratio, hyperchromatic nuclei, increased mitotic activity, and invasive growth.
- Dense sclerotic stroma is present.
- Immunohistochemical staining includes:
 - Strong reactivity for cytokeratins (AE1/AE3 and CK19) and p63
 - Focal positivity for CK7 and CK18
 - Thyroglobulin and TTF-1 (nuclear) staining reactivity reported
- Negative staining, calcitonin, chromogranin, and synaptophysin
- Overexpression of p53
- High proliferative index as determined by Ki67 (MIB1)
- A spindle cell variant may occur either de novo or in relationship to papillary carcinoma variants (e.g., tall cell):
 - Occurs in older patients
 - Tumors are large, solid
 - Histology is similar to that of spindle cell squamous carcinoma of the upper aerodigestive tract, including differentiated squamous cell carcinoma and an associated pleomorphic spindle cell proliferation with increased mitotic figures, necrosis, and hemorrhage.
 - Extrathyroidal invasion is common.
 - Spindle and squamous cells are cytokeratin positive and thyroglobulin negative.
- Classification of these squamous cell tumors have been considered within the category of undifferentiated (anaplastic) thyroid carcinoma:
 - Histology of these tumors is readily recognizable as to merit its own classification separate from undifferentiated (anaplastic) carcinoma.
- Irrespective of into which category this tumor is placed, it behaves as a high-grade tumor akin to the behavior of anaplastic (undifferentiated) thyroid carcinoma:
 - Treatment should be similar to that of undifferentiated (anaplastic) thyroid carcinoma.
 - Survival:
 - Median survival 9 months
 - 3-year survival rate of 37.6%
 - Prognosis is very poor, but complete resection of disease may correlate with improved survival.
- In presence of squamous cell carcinoma in thyroid, a primary tumor originating elsewhere should be excluded:
 - Squamous carcinomas from mucosal site may directly invade into the thyroid or may metastasize to thyroid.
 - Rare collision tumors including papillary thyroid carcinoma and laryngeal squamous cell carcinoma reported

Mucinous Carcinoma

- Extremely rare characterized by clusters of neoplastic cells floating or surrounded by extracellular mucin deposition
- May present as either a slowly or rapidly growing lesion.
- Histologically similar to mucinous (colloid) carcinoma of other sites (e.g., breast, lung, salivary gland), including:

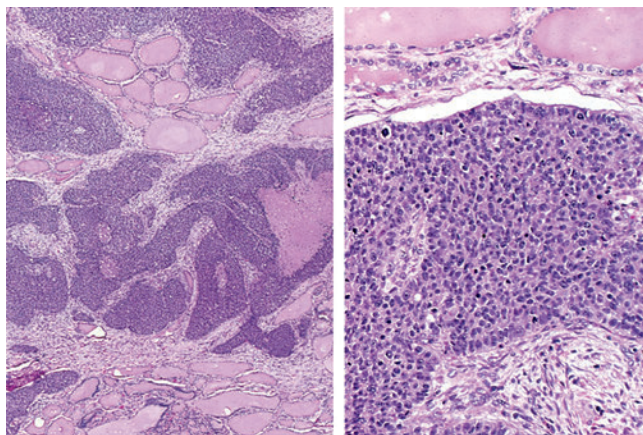


Fig. 28-90. Primary thyroid squamous cell carcinoma.

Left, tumor invading thyroid gland composed of solid interconnecting cords with foci of central necrosis. *Right*, At higher magnification the carcinoma is nonkeratinizing and has histologic features similar to nonkeratinizing carcinomas of the oro- and nasopharynx. In this case, the patient did not have a primary tumor in any other site. Material was unavailable to evaluate for human papillomavirus (p16) and Epstein-Barr virus (EBER).

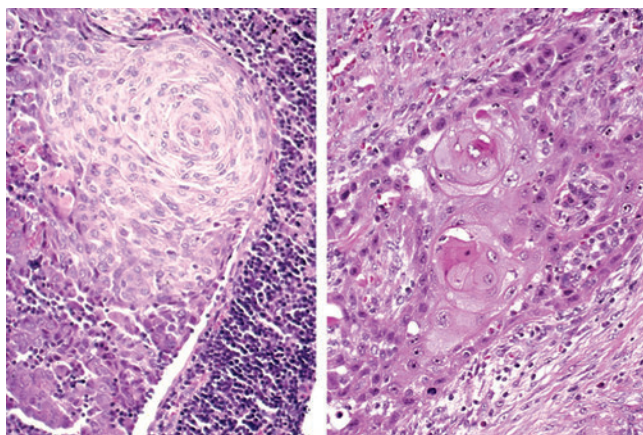


Fig. 28-91. Squamous metaplasia versus SCC.

Histologic features of squamous cell metaplasia (in the setting of chronic lymphocytic [Hashimoto] thyroiditis) versus thyroid squamous cell carcinoma. *Left*, Squamous metaplasia is characterized by bland cytomorphology composed of rounded nests without invasive growth lacking nuclear pleomorphism and mitotic activity. *Right*, Squamous carcinoma is infiltrative and composed of cells with prominent nuclear pleomorphism and dyskeratosis.

- Presence of abundant mucoid lakes, within which are clusters of tumor cells
- Tumor cells composed of large nuclei with prominent nucleoli
- Mucinous material positive for mucicarmine
- Immunohistochemistry
 - Lesional cells are immunoreactive for thyroglobulin, TTF-1 (nuclear), cytokeratin (low molecular weight), and MUC3
 - Negative for carcinoembryonic antigen, calcitonin, and high-molecular-weight cytokeratin
 - Increased proliferation index by Ki67 (MIB1) staining (>10%)
 - p53 overexpression
- Must be differentiated from:
 - Other thyroid neoplasms with mucin production that may include:
 - Papillary carcinoma
 - Follicular carcinoma
 - Follicular adenoma
 - Medullary carcinoma
 - Mucoepidermoid carcinoma
 - Metastatic mucinous carcinomas from other organs
- Appears to have aggressive behavior with death from disease in months to years following diagnosis

Adenosquamous Carcinoma of Thyroid Gland (Fig. 28-92)

- Extraordinarily rare thyroid tumor
- Too few cases in literature to suggest any correlation to low-grade mucoepidermoid carcinoma.
- Spectrum of histologic types seen in the salivary glands (low-grade, intermediate-grade, and high-grade) not seen in the thyroid gland
- Histologically, these tumors include squamous cell carcinoma with glandular foci as well as mucocytes.
- Neoplastic infiltrate characterized by cells with obvious squamous differentiation (keratinization, intercellular bridges), pleomorphism, increased mitotic activity, and invasive growth
- Intracytoplasmic and intraluminal mucin-positive material may be identified.
- Foci of undifferentiated carcinoma can occur, such that this tumor has been considered as variant of an undifferentiated (anaplastic) thyroid carcinoma.
- High-grade malignancy with treatment and biologic behavior similar to that for undifferentiated (anaplastic) thyroid carcinoma
- In presence of adenosquamous carcinoma of thyroid gland, primary tumor originating in adjacent organ (larynx or trachea) should be excluded.

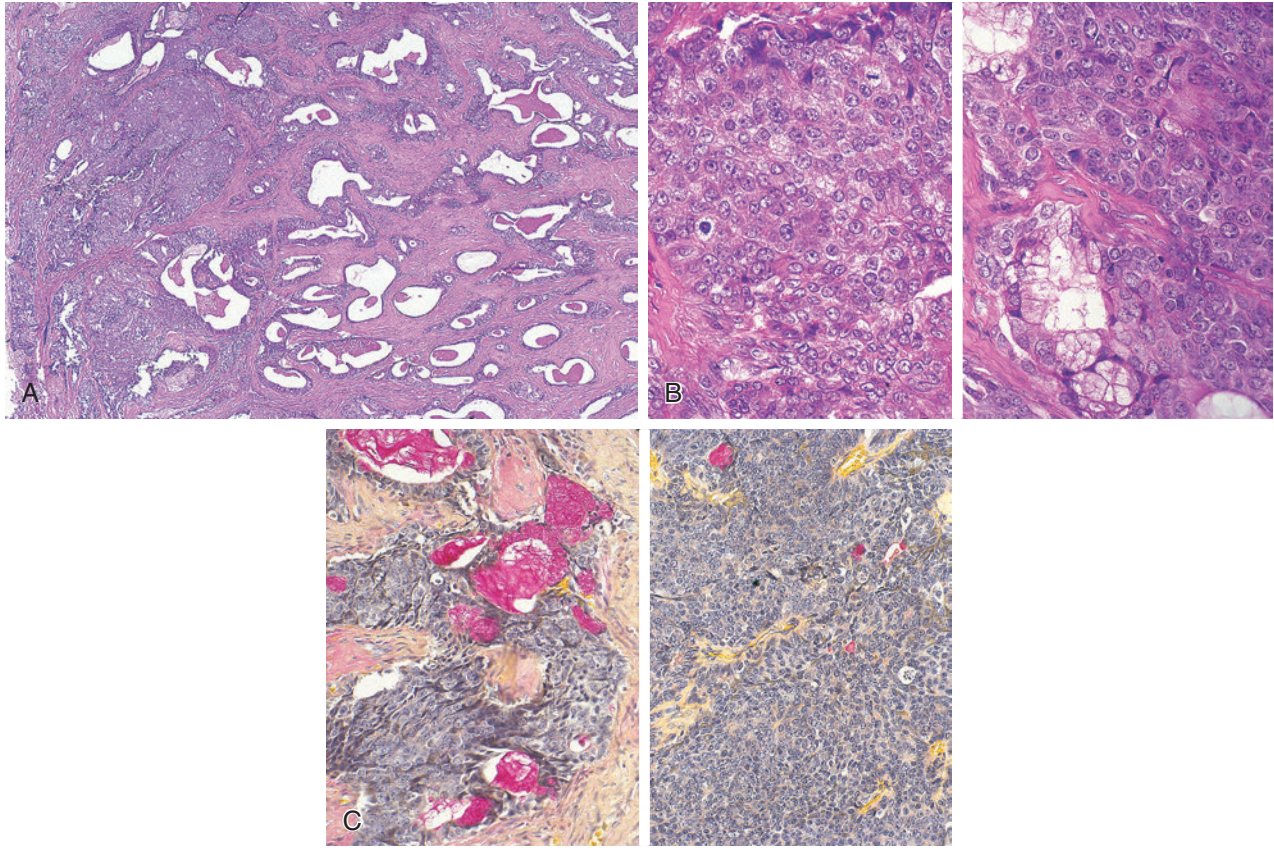


Fig. 28-92. Thyroid adenosquamous carcinoma.

A, The tumor is infiltrative and composed of solid nests (*upper left*) and glandular proliferation. **B**, *Left*, Undifferentiated carcinoma; *right*, glands and mucocytes; **C**, mucicarmine staining including (*left*) readily apparent intracytoplasmic and intraluminal mucin-positive material to (*right*) scattered mucin-positive cells.

NEUROENDOCRINE NEOPLASMS

- Thyroid neuroendocrine lesions/neoplasms include:
 - C-cell-related lesions:
 - C-cell hyperplasia
 - Medullary thyroid carcinoma
 - Mixed medullary and follicular cell neoplasms
 - Neuroendocrine carcinomas
 - Thyroid paraganglioma

C-CELL-RELATED LESIONS (C-CELL HYPERPLASIA AND THYROID MEDULLARY CARCINOMA)

See Chapters 26 and 27 for discussion of thyroid C-cells (parafollicular cells) and solid cell nests, respectively.

- C-cell-derived thyroid lesions include:
 - C-cell hyperplasia
 - Medullary thyroid carcinoma

C-Cell Hyperplasia (CCH)

(Figs. 28-93 through 28-95)

Definition: Multifocal quantitative increase in thyroid C-cells with replacement of thyroid follicles and follicular epithelial cells (see [Histology](#) below for further definitions).

- May more accurately be considered:
 - Pre-malignant proliferation or earliest phase in evolution of medullary thyroid carcinoma rather than non-neoplastic hyperplastic process
- Divided into reactive (“physiologic”) type and neoplastic type
- Reactive or “physiologic” CCH
 - Uncommon diffuse C-cell hyperplasia that may be difficult to identify by light microscopy
 - May occur in association with other diseases, including:
 - Hypercalcemia due to hyperparathyroidism
 - Hypercalcemia due to nonparathyroid causes

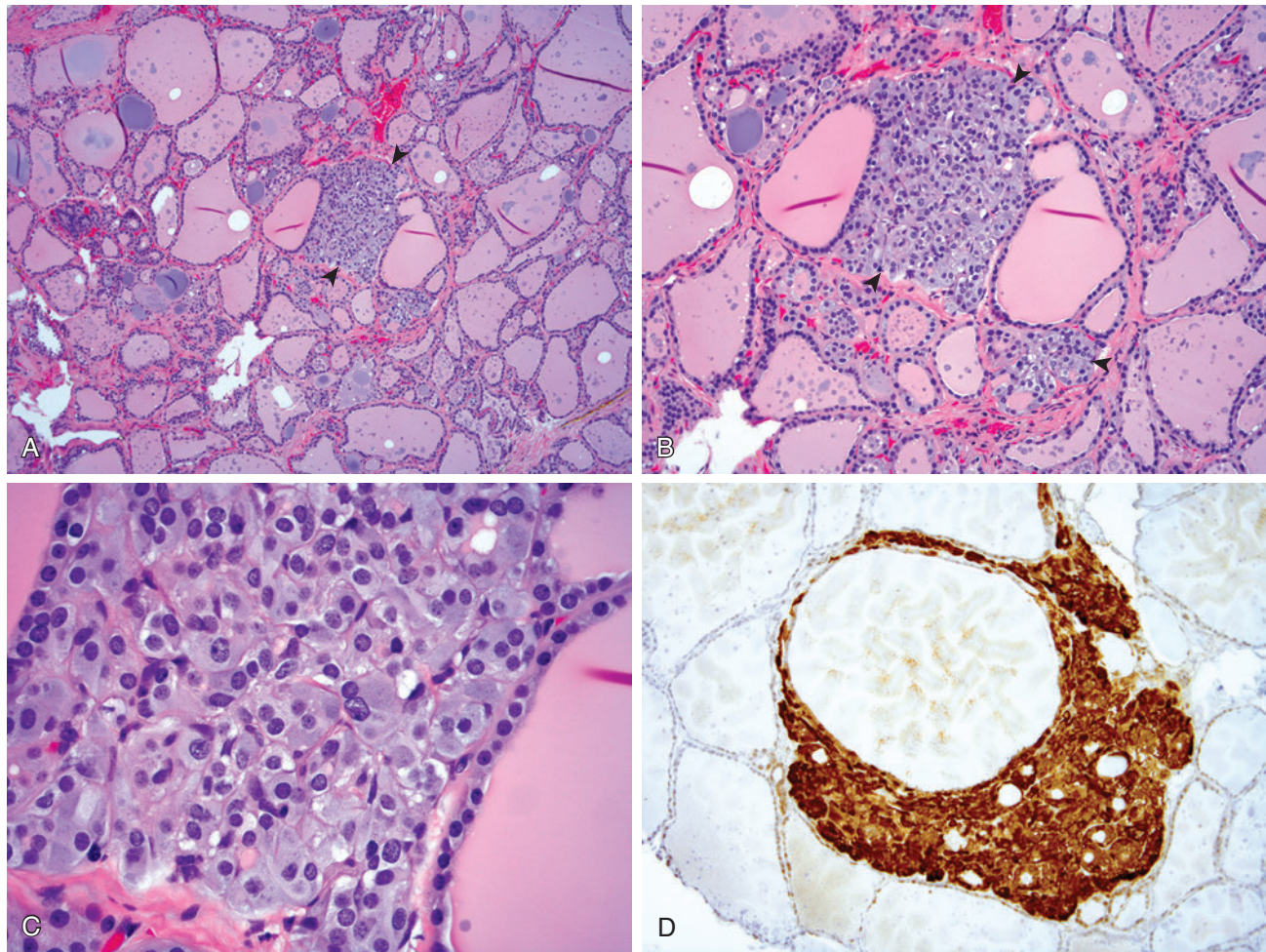


Fig. 28-93. Reactive C-cell hyperplasia.

A and B, At low magnification non-mass-forming nodular foci of C-cell hyperplasia seen around colloid-filled follicles (parafollicular) and appearing as smaller, darker nuclei devoid of colloid formation (*arrowheads*). **C,** C-cells are composed of round to oval nuclei with stippled chromatin and basophilic-appearing cytoplasm lacking significant nuclear atypia. **D,** C-cells show strong calcitonin immunoreactivity.

- Hypergastrinemia (Zollinger-Ellison syndrome)
- Adjacent to nonmedullary thyroid lesions (e.g., lymphocytic thyroiditis) and neoplasms (e.g., follicular adenoma, follicular carcinoma, papillary carcinoma)
- Neoplastic CCH
 - Appears as nodular foci associated with:
 - Hereditary medullary carcinoma, including:
 - Multiple endocrine neoplasia (MEN) syndromes (MEN-2A and MEN-2B)
 - Familial medullary carcinoma
- CCH may also be seen in association with phosphatase and tensin homolog deleted on chromosome ten (*PTEN*)-hamartoma tumor syndrome (PHTS):
 - Complex disorder caused by germline inactivating mutations of *PTEN* tumor suppressor gene
 - PHTS includes:
 - Cowden syndrome (CS)
 - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
 - Proteus-like syndromes
 - Affected individuals develop benign and malignant tumors in a variety of tissues, including thyroid gland.
 - Thyroid pathology in PHTS includes:
 - Multiple adenomatous nodules in background of lymphocytic thyroiditis (75%)
 - Papillary thyroid carcinoma (60%), including:
 - Papillary microcarcinoma, follicular variant, classical type
 - C-cell hyperplasia (55%):
 - Nodular or diffuse
 - Lymphocytic thyroiditis alone (55%)

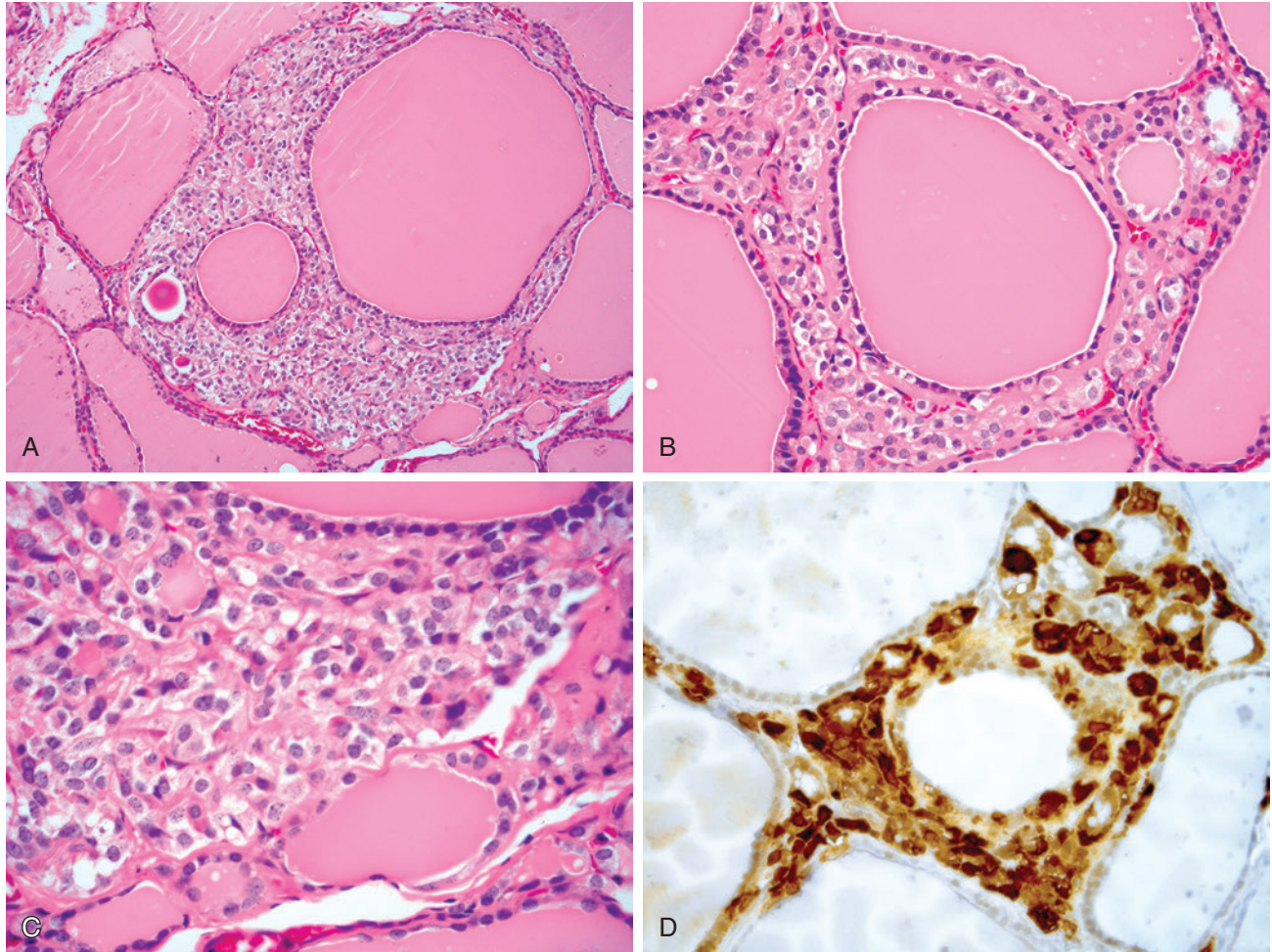


Fig. 28-94. Reactive C-cell hyperplasia.

A and B, In this example there is circumferential localization of C-cells around or encircling follicles (parafollicular).

C, C-cells are composed of round to oval nuclei with stippled chromatin lacking significant nuclear atypia. **D,** C-cells show strong calcitonin immunoreactivity.

- Follicular carcinoma (45%)
- Follicular adenoma (25%)
- Histologic criteria for CCH:
 - Based on cell count with no consensus
 - Various criteria include:
 - Clusters of more than 20 C-cells
 - More than 50 C-cells in one low-power field at a magnification of 100×
 - Increase in size and number of C-cells compared with age- and gender-matched controls (control groups normally having less than 10 C-cells per low-power field)
 - Above-cited criteria can be found in:
 - Normal thyroid glands, which may contain foci of up to 50 C-cells in a single low-power field
 - Nodules of C-cells may be seen in thyroid glands of older patients.
 - Around solid cell nests
 - Near to nonmedullary thyroid tumors
 - In association with chronic lymphocytic (Hashimoto) thyroiditis
- No specific criteria and/or markers assisting in differentiating reactive (physiologic) from neoplastic CCH, except perhaps for presence of nodular foci of CCH identifiable by light microscopy and confirmed by immunohistochemical staining, which support neoplastic proliferation

Reactive or “Physiologic” CCH

Clinical

- No specific demographics associated with reactive or physiologic CCH
- May or may not be associated with elevated serum calcium or calcitonin levels
 - Most patients with CCH do not have elevated basal levels of serum calcitonin but do have an

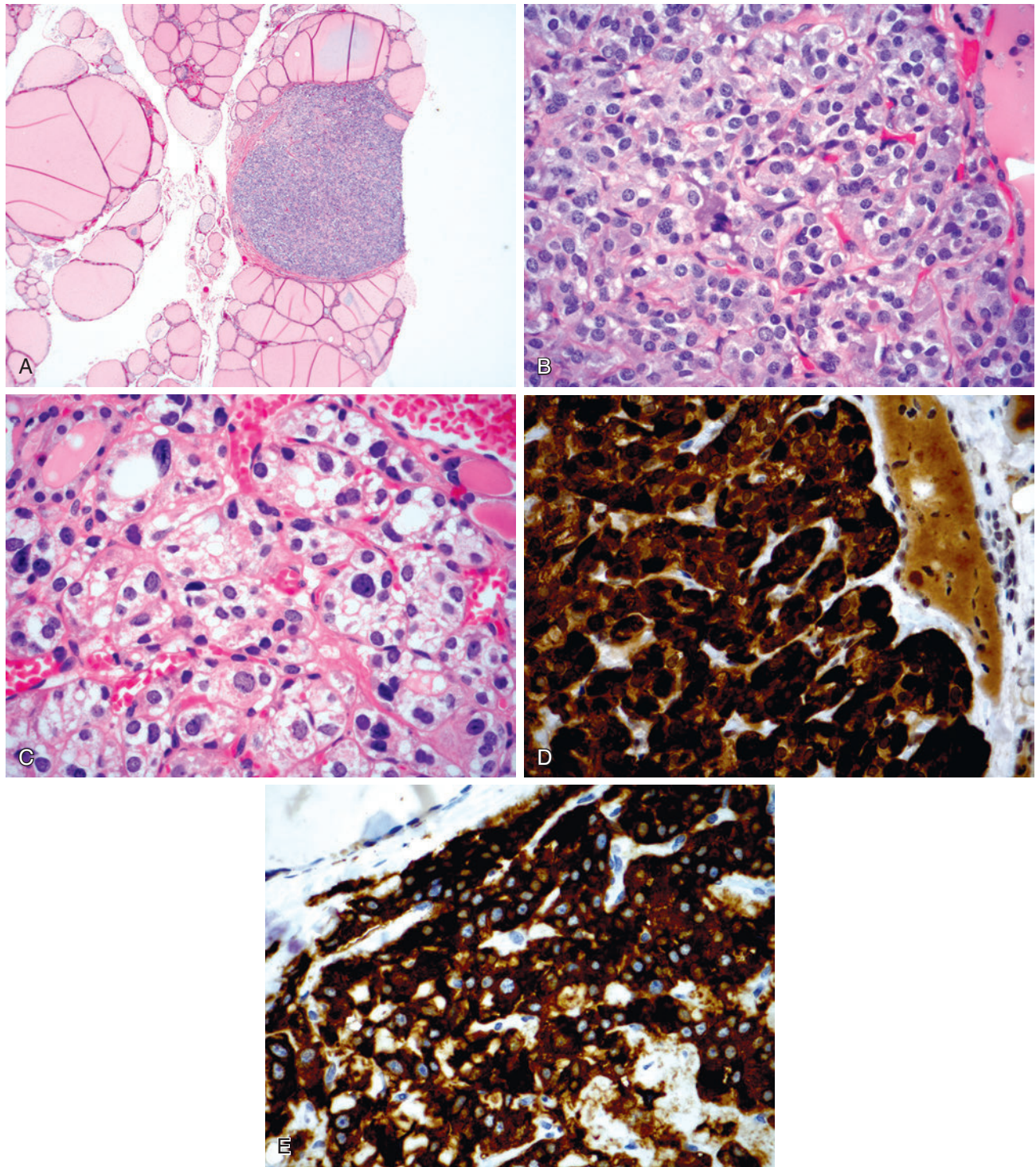


Fig. 28-95. Neoplastic C-cell hyperplasia (CCH).

A, Enlarged nodular focus readily identified at low magnification. **B**, Lesional cells composed of relatively uniform round to oval nuclei with stippled chromatin. **C**, Areas showing marked nuclear pleomorphism. Lesional cells are immunoreactive for **(D)** calcitonin and **(E)** synaptophysin. There are no established criteria assisting in differentiating nodular foci of neoplastic CCH from microscopic foci of medullary thyroid carcinoma (MTC); the images shown here could be interpreted as microscopic MTC but the absence of infiltrative growth, associated stromal sclerosis, and amyloid stroma even in the presence of nuclear pleomorphism support neoplastic CCH rather than microscopic MTC.

abnormal increase in serum calcitonin following provocative testing (calcium and/or pentagastrin stimulation testing)

- Patients with elevated basal calcitonin levels but whose values do not rise further following provocative testing should be retested after 3 months.
- Elevated levels of serum carcinoembryonic antigen (CEA) may be present.
- Exact mechanism for CCH identified adjacent to some thyroid follicular neoplasms is not known but may represent a reaction to chronic stimulation of gland by thyroid-stimulating hormone or a compensatory mechanism in response to destruction of gland by follicular tumor:
 - In support of these hypotheses is the fact that, in those cases with available tissue for study, CCH was limited to one lobe rather than multifocal and bilateral involvement as seen in MEN syndromes.

Pathology

Gross

- No specific macroscopic findings:
 - Without demonstrable mass

Histology

- Usually cannot be identified by light microscopy but requires immunohistochemical staining for identification, including:
 - Calcitonin
 - Synaptophysin or chromogranin
- Diffuse or focal proliferation, including:
 - Usually unilateral
 - Intrafollicular localization forming clusters within basement membrane of follicles surrounded by identifiable follicle
 - Circumferential localization around or encircling follicles:
 - Segmental within follicles
- Cytomorphologic features include:
 - Round to oval nuclei with stippled chromatin and basophilic-appearing cytoplasm
 - Not enlarged and lack (significant) nuclear pleomorphism or atypia

Differential Diagnosis

- Neoplastic CCH
 - *RET* protooncogene germline mutation:
 - Differentiates neoplastic (present) versus reactive/physiologic (absent) CCH
 - Evaluation of serum calcitonin levels does not differentiate patients with reactive (physiologic) from neoplastic C-cell hyperplasia.
- Solid cell nests
- Squamous metaplasia

- Intrathyroidal parathyroid tissue
- Intrathyroidal thymic tissue
- Palpation thyroiditis

Treatment and Prognosis

- Diagnosis of reactive (“physiologic”) C-cell hyperplasia generally can be treated medically with biochemical control.
- Excellent prognosis

Neoplastic CCH

Clinical

- Strongly associated with hereditary medullary thyroid carcinoma:
 - Usually present in association with MEN-2A, MEN-2B, and familial MTC alone
 - Usually absent in association with sporadic MTC
- May or may not be associated with elevated serum calcium or calcitonin levels:
 - Most patients do not have elevated basal levels of serum calcitonin but do have an abnormal increase in serum calcitonin following provocative testing with secretagogues for calcitonin, calcium, and pentagastrin.
 - Elevated levels of serum carcinoembryonic antigen (CEA) may be present.
- Patients with elevated basal calcitonin levels but whose values do not rise further following provocative testing should be retested after 3 months.

Pathology

Gross

- Generally, nondescript without a demonstrable mass lesion(s)

Histology

- Present diagnostic criteria for neoplastic CCH include:
 - Nodular or diffuse foci readily identifiable by light microscopy
 - Usually bilateral
 - Complete replacement/obliteration of follicle(s) with solid intrafollicular aggregates
- Cytomorphologic features include:
 - Enlarged cells with round to oval nuclei, stippled nuclear chromatin, and ample clear to pale-appearing cytoplasm
 - Mild to moderate nuclear pleomorphism or atypia
- Immunohistochemistry:
 - Calcitonin positive
 - Synaptophysin and chromogranin positive
 - Cytokeratin and CEA may be present.

- Thyroglobulin negative (except for those instances where the C-cell hyperplasia has not completely obliterated the follicular epithelial cells and thyroglobulin is seen within remnants of the follicular epithelium)
- Cytogenetics and molecular genetics:
 - Preferred diagnostic modality for hereditary form of medullary thyroid carcinoma rather than identifying C-cell hyperplasia and/or elevated serum calcitonin levels includes presence of:
 - *RET* protooncogene germline mutation:
 - Present in all cells of body
 - Present in tumor cells
 - Presence of *RET* mutation should prompt screening of family members as well as evaluation for other components of MEN syndrome (see Section 10).
 - Identification of C-cell hyperplasia in a patient whose thyroid has been removed for other reasons should initiate molecular testing for *RET* mutation.
 - Evaluation of serum calcitonin levels does not differentiate patients with reactive from neoplastic C-cell hyperplasia.

Differential Diagnosis

- Reactive (physiologic) CCH:
 - *RET* protooncogene germline mutation:
 - Differentiates neoplastic (*RET* present) versus reactive/physiologic (*RET* absent) CCH
 - Evaluation of serum calcitonin levels does not differentiate patients with reactive (physiologic) from neoplastic C-cell hyperplasia.
- Medullary thyroid carcinoma (MTC)—in particular, medullary microcarcinoma (microscopic MTC):
 - No established criteria assisting in differentiating nodular foci of neoplastic CCH from microscopic foci of MTC
 - Features supporting medullary microcarcinoma include:
 - Presence of nuclear pleomorphism
 - Presence of associated stromal sclerosis
 - Presence of amyloid stroma
 - Invasive growth
- Solid cell nests
- Squamous metaplasia
- Intrathyroidal parathyroid tissue
- Intrathyroidal thymic tissue
- Palpation thyroiditis

Treatment and Prognosis

- Neoplastic C-cell hyperplasia with *RET* germline mutation generally necessitates total thyroidectomy:
 - Thyroidectomy performed even in young patients (<10 years of age)

- Medullary thyroid carcinoma can be found in a large percentage of cases (>60%).
- Lymph node metastasis may be identified in small percentage of cases, and there may be a need for lymph node dissection (even in the young patient).
- Increased morbidity and mortality occur in MEN syndromes due to non-thyroid neoplasms or to medullary thyroid carcinoma but not as a result of CCH.

Medullary Thyroid Carcinoma (MTC) (Figs. 28-96 through 28-102)

Definition: Malignant thyroid neuroendocrine tumor with C-cell (parafollicular) differentiation.

Synonyms: C-cell carcinoma; solid carcinoma; solid amyloidotic carcinoma; neuroendocrine carcinoma of thyroid gland

Clinical

- Represents up to 5% to 10% of all thyroid neoplasms
- Occurs in two forms (Table 28-11):
 - Sporadic or nonfamilial MTC:
 - Represents approximately 70% to 80% of all cases
 - Unassociated with multiple endocrine neoplastic (MEN) syndrome
 - Hereditary MTC:
 - Represents approximately 20% to 30% of all cases
 - Associated with one of three clinical MEN syndromes, including:
 - MEN-2A
 - MEN-2B
 - Familial MTC
- All patients with diagnosis of MTC should be suspected of having genetic form of disease until proven otherwise.
- Sporadic MTC:
 - Most common form (70% to 80% of all cases)
 - Slightly more common in women than in men; primarily occur in older individuals (as compared to the familial form) with a mean age at diagnosis in the fifth to sixth decades of life
 - Clinical presentation
 - Unilateral palpable painless thyroid mass:
 - Bilaterality may occur in up to a third of patients.
 - Signs and symptoms may include:
 - Hoarseness, dysphagia, stridor
 - Incidence of cervical lymphadenopathy at presentation is high (40% to 50%).
 - Distant metastasis (lung, liver, bone) uncommon (approximately 12%)

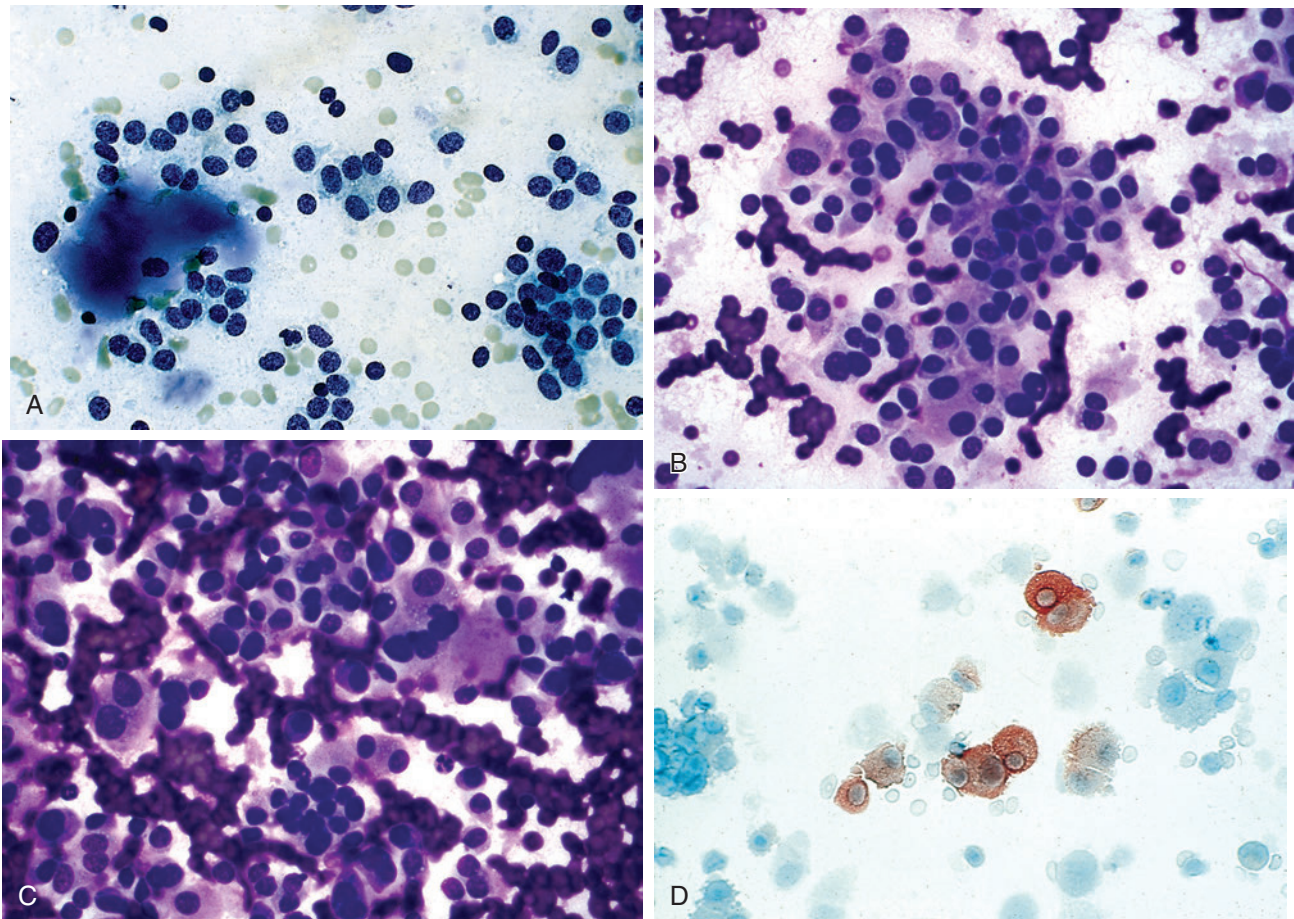


Fig. 28-96. Medullary thyroid carcinoma, fine-needle aspiration biopsy.

A, Increased cellularity with single cells or small cell clusters including round to oval cells and a fragment of amyloid (*left*). **B** and **C**, Tumor cells are round to oval, polygonal, and/or plasmacytoid with round to oval, often eccentrically located, nuclei with stippled or coarse chromatin pattern and abundant granular eosinophilic cytoplasm with some showing metachromatic red (azurophilic) cytoplasmic granules (Diff-Quik). **D**, Calcitonin immunoreactivity confirms the diagnosis. The FNAB diagnosis would be "malignant; poorly differentiated carcinoma consistent with undifferentiated (anaplastic) thyroid carcinoma (Bethesda VI)."



Fig. 28-97. Medullary thyroid carcinoma.

Medullary thyroid carcinoma appearing as a solitary, circumscribed but focally infiltrative (*upper right*) tan-white and nodular thyroid mass.

- Patients with clinically evident MTC:
 - Almost always have elevated serum levels of calcitonin in basal state or following intravenous administration of secretagogues calcium or pentagastrin
 - Occasionally, serum calcitonin (and carcinoembryonic antigen) may not be elevated (non-secretory MTCs).
- Absence of germline mutation of *RET* protooncogene:
 - MTCs with somatic *RET* mutations (found only in tumor cells) present in one third to two thirds of cases of which:
 - 75% to 95% have replacement of methionine by threonine at codon 918
 - MTCs with *RET* somatic mutation as compared to those without mutation:

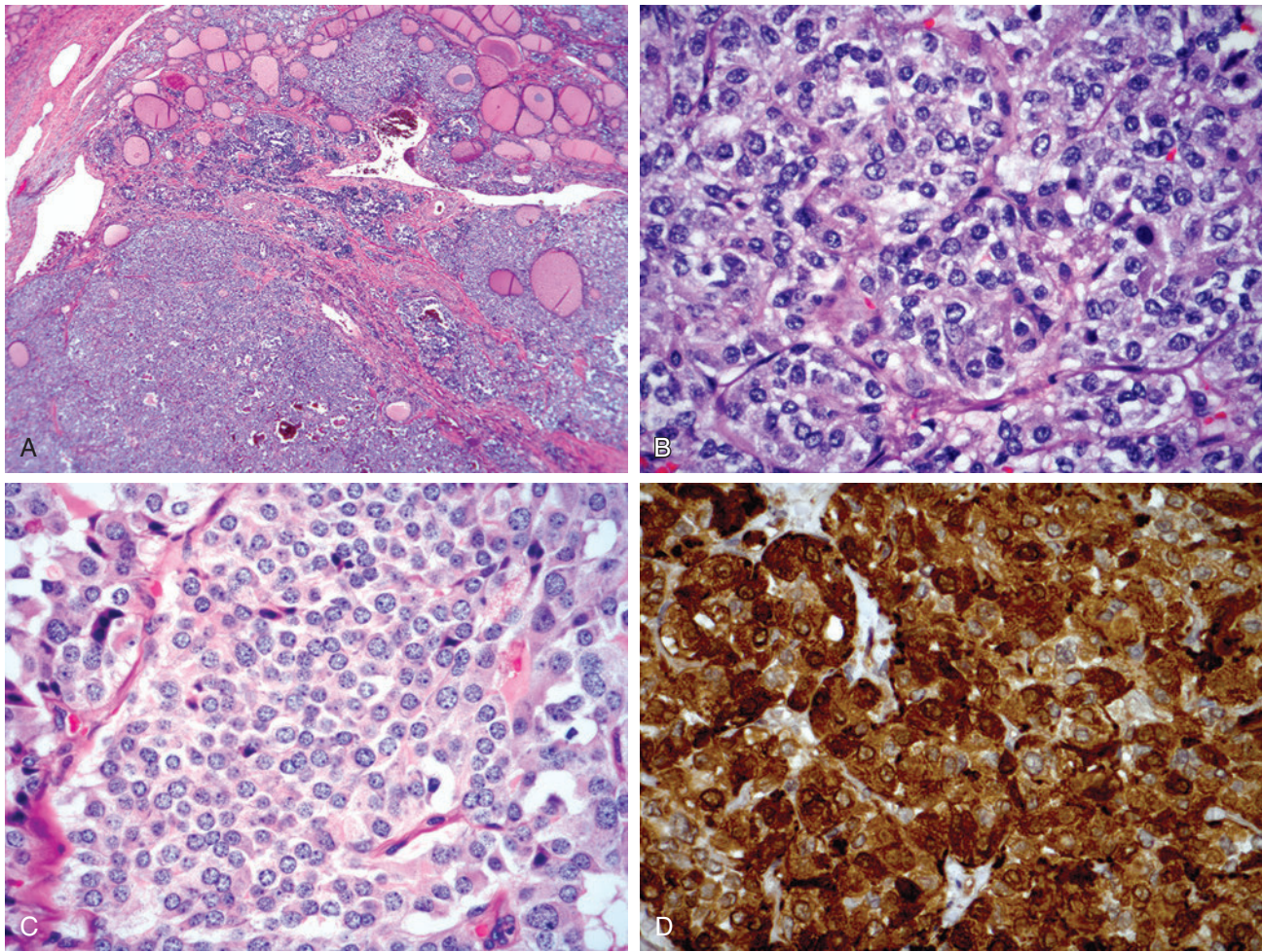


Fig. 28-98. Medullary thyroid carcinoma.

A, Infiltrative tumor including lesional cells invading into adjacent thyroid parenchyma; **(B)** lobular/organoid and **(C)** solid growth. Lesional cells include round to oval cells with round to oval and variably pleomorphic nuclei with coarse or stippled nuclear chromatin and basophilic to eosinophilic granular cytoplasm; **(D)** diffuse calcitonin reactivity. Additional immunoreactivity includes synaptophysin, chromogranin, and carcinoembryonic antigen (not shown).

- Higher frequency of regional lymph node and distant metastasis
- Tend to have worse prognosis:
 - Tumors with codon 918 appear to be more aggressive compared to other somatic *RET* mutations
- Presence of somatic *RAS* mutations:
 - Present in significant percentage of sporadic MTCs (>50%)
 - Only found in *RET*-negative sporadic MTCs
- Hereditary MTC:
 - Less common than sporadic MTC, representing 20% to 30% of all cases
 - Clinical presentation may correlate with pathologic features in other organs involved by MEN syndrome, including:
 - Adrenal gland, parathyroid, pituitary gland, gastrointestinal tract, pancreas
 - Germline mutation of *RET* protooncogenes present in 85% of families with hereditary MTC
 - Occurs in association with
 - MEN-2A
 - MEN-2B
 - Familial MTC
- MTC in association with MEN-2A (multiple endocrine adenomatosis 2 [MEA2]; Sipple syndrome):
 - Most common of three subtypes, accounting for 75% to 90% of familial cases
 - Characterized by presence of:
 - MTC
 - Pheochromocytoma (approximately 50%)

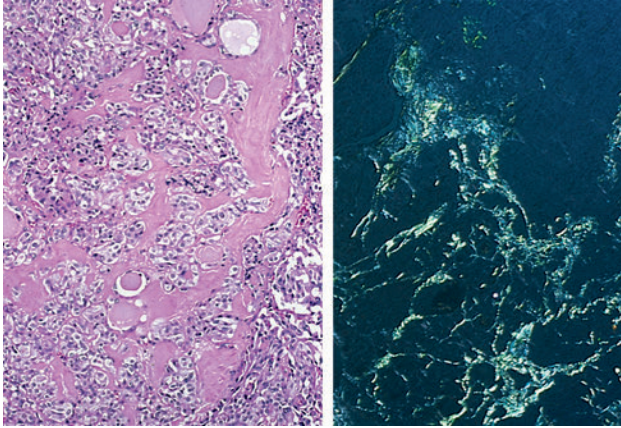


Fig. 28-99. Amyloid in MTC.

Left, Medullary thyroid carcinoma with associated amyloid deposition appearing on hematoxylin and eosin stain sections as acellular, eosinophilic-appearing material. *Right*, Congo red stain demonstrating classic apple-green birefringence of the amyloid as seen under polarization.

- Primary parathyroid hyperplasia (20% to 30%)
 - Rare cases associated with Hirschsprung disease and cutaneous lichen amyloidosis
- Autosomal dominant pattern of inheritance
- Slightly more common in women than in men; mean age at diagnosis is in the third to fourth decades of life
- MTC usual first manifestation of syndrome
- Clinical presentation:
 - Slow-growing, painless thyroid mass
 - Multicentric and bilateral in more than 90% of cases
 - Incidence of cervical lymphadenopathy at presentation is low (<15%).
 - Distant metastasis (lung, liver, bone) is rare (<3%).
- Germline mutation of *RET* protooncogene
 - Usually involve exon 10 and 11
 - Most common genetic abnormality found in 95% of families with MEN-2A
 - Genetic testing for *RET* protooncogene has largely replaced serum calcitonin measurement for diagnosis of hereditary MTC.
- MTC in association with MEN-2B (MEN-2B, MEN-3, Wagenmann-Froboese syndrome):
 - Least common of three subtypes, accounting for approximately 5% of familial cases
 - Characterized by presence of:
 - MTC
 - Pheochromocytoma (approximately 50%)
 - Mucosal neuroma and gastrointestinal ganglioneuromatosis (100%)
 - Marfanoid appearance (100%)
 - Rarely associated with parathyroid hyperplasia
 - Autosomal dominant pattern of inheritance
 - Slightly more common in women than in men; mean age at diagnosis is in second decade of life:
 - Usually presents in patients <10 years of age
 - May even occur in neonatal period
 - Clinical presentation:
 - Painless thyroid mass
 - In addition, these patients have:
 - Mucosal neuromas (oral mucosa, lips, tongue, eyelids)
 - Ganglioneuromatosis of the gastrointestinal tract
 - Children with MEN-2B may present with clinical picture identical to Hirschsprung disease: rectal biopsy reveals proliferation rather than absence of ganglia.
 - Skeletal deformities including Marfan-like habitus, pes cavus
 - Multicentric and bilateral in more than 90% of cases
 - Incidence of cervical lymphadenopathy at presentation is approximately 38%.
 - Development of distant metastasis (lung, liver, bone) in approximately 20%
- Germline mutation of *RET* protooncogene:
 - Point mutation at exon 16:
 - Replacement of methionine by threonine at codon 918
 - Identified in 95% of cases with MEN-2B
- Genetic testing for *RET* protooncogene has largely replaced serum calcitonin measurement for diagnosis of hereditary MTC.
- Familial MTC (MTC alone):
 - Second most common of three subtypes, accounting for approximately 15% of familial cases
 - Not associated with lesions of other organs (hence designation as MTC alone)
 - Autosomal dominant pattern of inheritance
 - Slightly more common in women than in men; mean age at diagnosis is in fifth to sixth decades of life
 - Clinical presentation:
 - Painless thyroid mass
 - Multicentric and bilateral in more than 90% of cases
 - Incidence of cervical lymphadenopathy at presentation is 10% to 20%
 - Distant metastasis (lung, liver, bone) rarely, if ever, occurs.

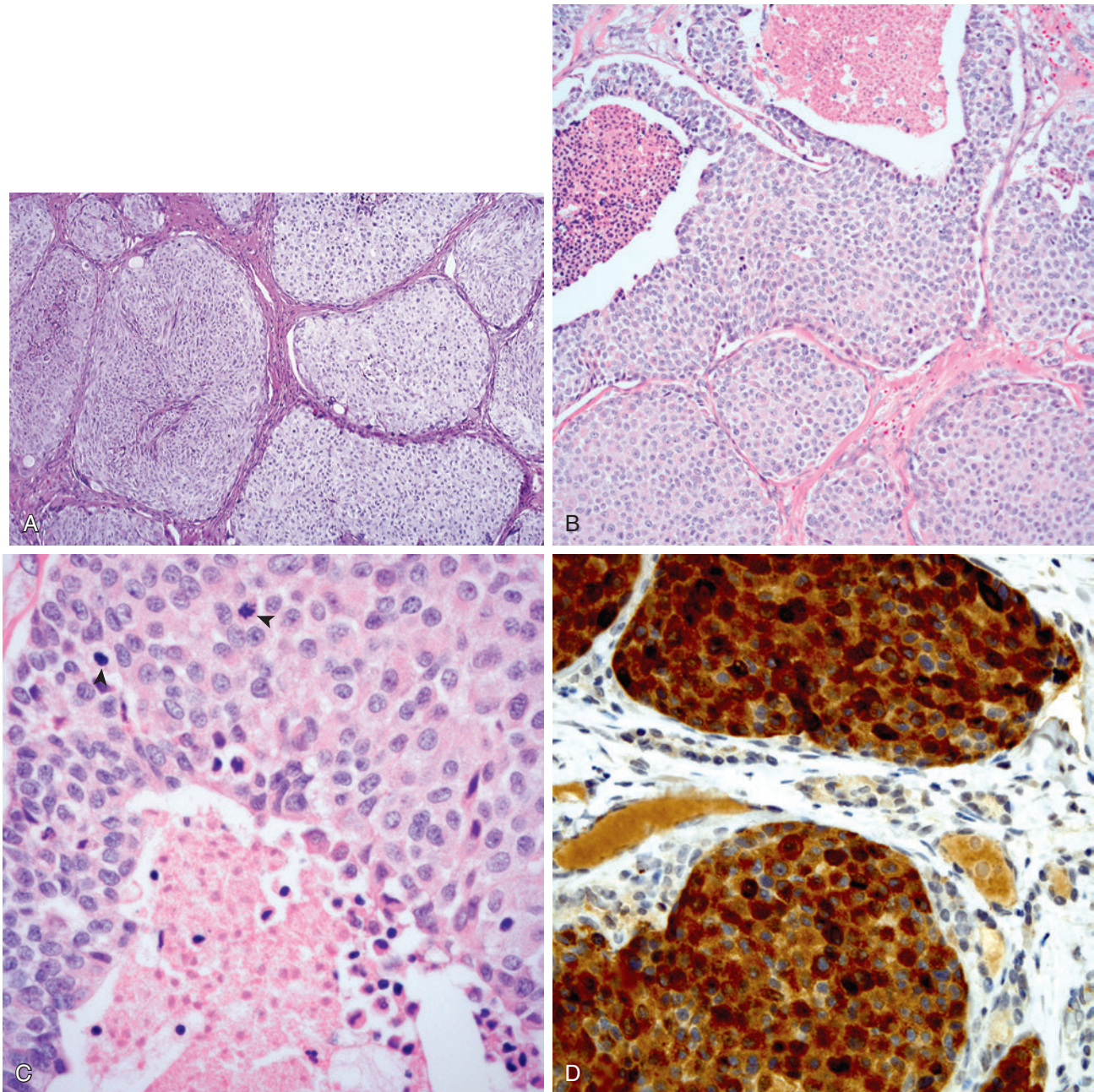


Fig. 28-100. Medullary thyroid carcinoma.

Medullary thyroid carcinoma may show **(A)** lobular or insular growth; **(B)** foci of confluent necrosis and **(C)** increased mitotic activity (*arrowheads*). Such features might suggest a diagnosis of a poorly differentiated thyroid carcinoma but the presence of **(D)** calcitonin reactivity as well as synaptophysin and chromogranin (not shown) coupled with absence of thyroglobulin and TTF-1 (not shown) would be diagnostic for medullary thyroid carcinoma.

- Germline mutation of *RET* protooncogene:
 - 85% of families show mutations in codons of exons 10 and 11.
 - Mutations in codons 768, 790, 791, 804, 848, 883, 891, 904
- Genetic testing for *RET* protooncogene has largely replaced serum calcitonin measurement for diagnosis of hereditary MTC.
- Testing:
 - First-degree relatives of patients affected by a familial form of MTC should undergo genetic evaluation to determine if they also have genetic evidence (i.e., *RET* protooncogene mutations) indicative of familial TMC.
 - Genetic evidence of familial TMC guides therapy (see below).

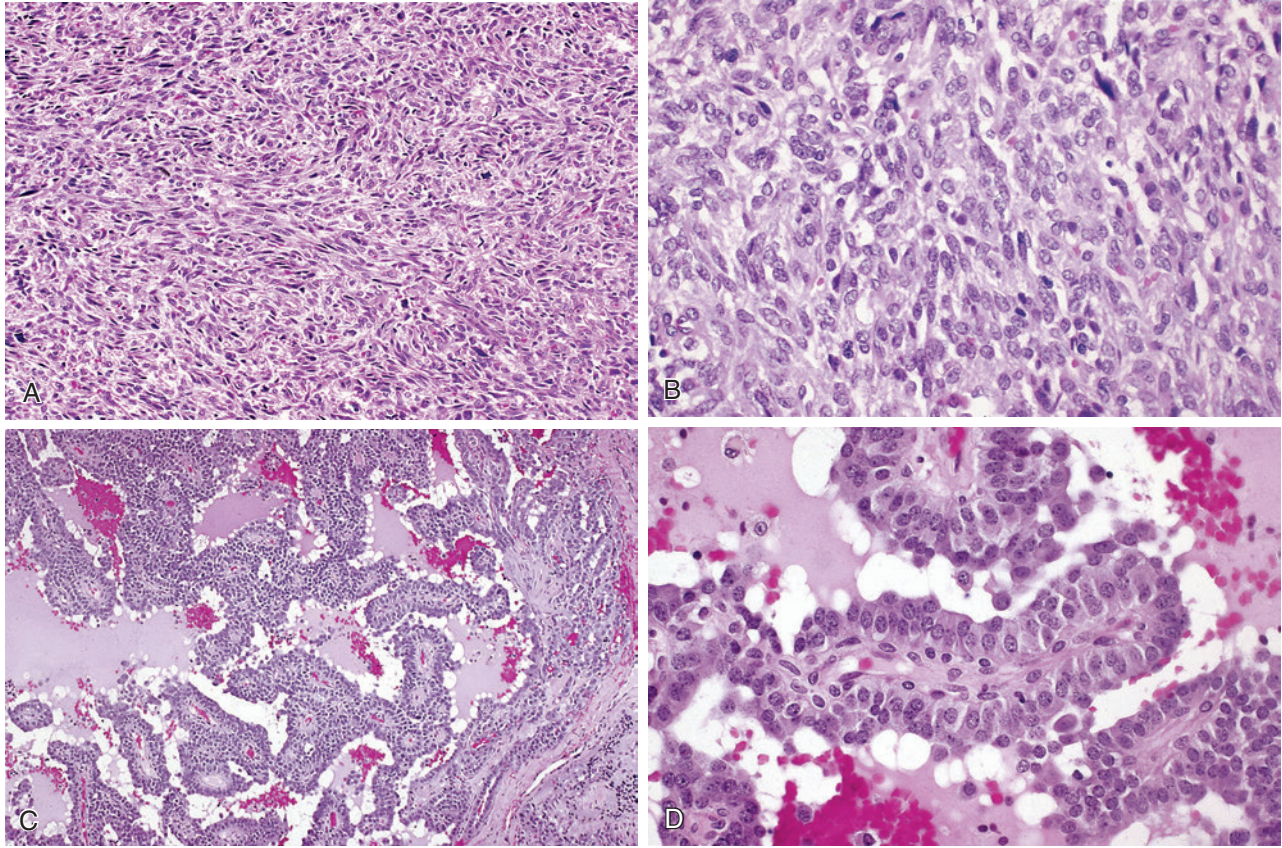


Fig. 28-101. Histologic variant of medullary thyroid carcinoma.

Histologic variants of medullary thyroid carcinoma may include **(A and B)** spindle cell and **(C and D)** papillary. These variants were confirmed by immunohistochemical staining for calcitonin and neuroendocrine markers and absence of thyroglobulin and TTF-1 (not shown).

- Once a family member has been diagnosed with MEN syndrome, all at-risk family members should be screened.
- Testing should be performed annually until age of 30, at which time more than 90% of all MEN gene carriers are detected by screening methods.
- Additional signs and symptoms may include:
 - Paraneoplastic syndromes owing to production of bioactive peptides and amines, including:
 - Severe watery diarrhea (10% to 30%)
 - Flushing, carcinoid syndrome
 - Renal stones, hypertension
 - Cushing disease owing to secretion of adrenocorticotrophic hormone (ACTH) may rarely occur in association with primary or metastatic MTC.
- Radiology
 - Radionuclide imaging:
 - Hypofunctioning (“cold”) nodule
 - Ultrasound:
 - Solid mass
 - MTC does not concentrate radioiodine.
- Imaging with ^{131}I metaiodobenzylguanidine (MIBG) useful tool in diagnosis
 - ^{131}I MIBG is guanethidine analog used in detection of neoplasms of neural crest origin
 - Many neural crest-derived tumors (including medullary thyroid carcinoma and pheochromocytoma) belong to dispersed neuroendocrine system (DNES), formerly known as the amine precursor uptake and decarboxylase (APUD) system, and sequester norepinephrine into intracellular granules.
 - MIBG is structurally similar to norepinephrine and competes with norepinephrine for uptake and storage in chromaffin granules within adrenergic cells.
 - Uptake of MIBG not dependent on ability of a tumor to actively synthesize and secrete catecholamines
- Plain film of the neck:
 - May reveal dense calcification considered a feature of this tumor

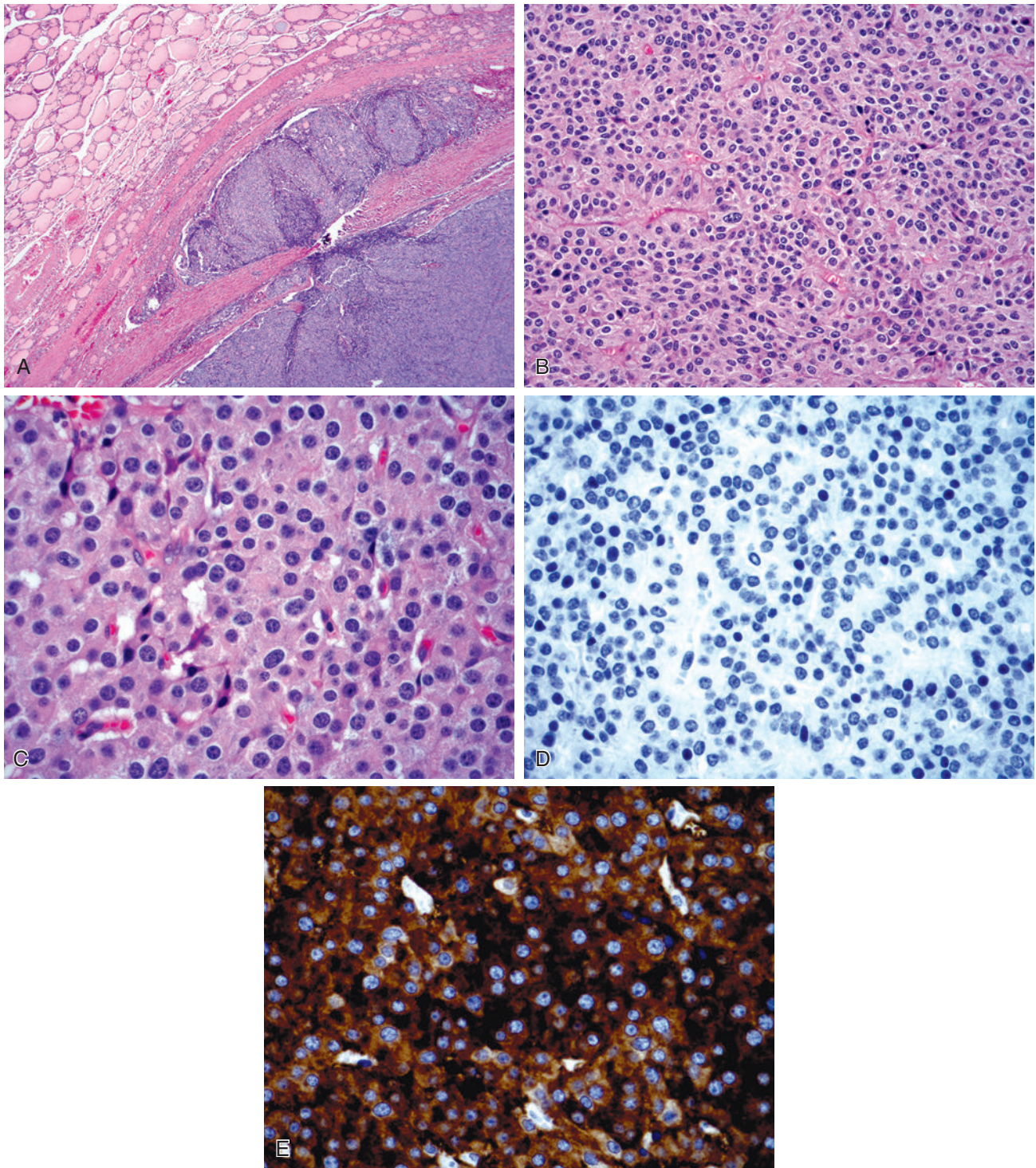


Fig. 28-102. Atypical or calcitonin-poor medullary thyroid carcinoma.

A, Cellular thyroid tumor with capsular invasion. **B**, Lobular and solid growth with fibrovascular stroma. **C**, Cytomorphologic features are similar to those seen in typical medullary thyroid carcinomas. Immunohistochemical staining shows **(D)** absence of calcitonin but **(E)** presence of synaptophysin. In addition, immunoreactivity is present for chromogranin, NSE, and CEA (not shown) with absence of thyroglobulin and TTF-1 reactivity (not shown).

TABLE 28-11 Forms of Medullary Thyroid Carcinoma

	Sporadic (Nonfamilial)	MEN-2A	MEN-2B	Familial MTC
Synonym(s)		Multiple endocrine adenomatosis 2 (MEA2); Sipple syndrome	MEN-3; Wagenmann- Froboese syndrome	MTC alone
Percentage of cases of MTC	80%	Approximately 75% to 90% of familial cases	Approximately 5% of familial cases	Approximately 15% of familial cases
Gender/age	F > M; 5th-6th decades	Slight F > M; 3rd-4th decades and younger	Slight F > M; infancy and early childhood (1st-2nd decades)	Slight F > M; 5th-6th decades of life
Inheritance	Noninherited	Autosomal dominant	Autosomal dominant	Autosomal dominant
Germline RET proto-oncogene mutation	Absent; somatic <i>RET</i> mutations (found only in tumor cells) present in $\frac{1}{3}$ to $\frac{2}{3}$ of cases 75% to 95% have replacement of methionine by threonine at codon 918	Present; usually involve exon 10 and 11; most common genetic abnormality found in 95% of families with MEN-2A	Present; point mutation at exon 16 (codon 918); identified in 95% of cases with MEN-2B	Present; 85% of families show mutations in codons of exons 10 and 11
Associated lesions	None; CCH usually absent but may be present near tumor	CCH; pheochromocytoma; primary hyperparathyroidism with parathyroid proliferative disease (adenoma; hyperplasia)	CCH; pheochromocytoma; oral mucosal neuromas; ganglioneuromatosis of intestines; marfanoid habitus; medullated corneal nerve fibers	CCH
Bilateral tumor	Usually unilateral; may be bilateral in up to 33% of patients	>90%	>90%	>90%
Treatment	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy
Metastasis	LN: 40% to 50% (at presentation) Distant: 12%	LN: <15% (at presentation) Distant: rare (<3%)	LN: 38% (at presentation) Distant: 20%	LN: 10% to 20% (at presentation) Distant: 0
Prognosis	Indolent course with: 5-year survival rates of 70% to 80% 10-year survival rates of 50% to 75% 15-year survival rates of 65%	Indolent course with much lower tumor-related mortality rates as compared to MEN-2B	More aggressive with early dissemination and increased tumor-related deaths	Least aggressive with no tumor- related deaths

CCH, C-cell hyperplasia; LN, lymph nodes; MTC, medullary thyroid carcinoma.

Pathology

Fine-Needle Aspiration Biopsy

- Cytologic variability from case to case, reflecting histologic variability
 - Increased cellularity with single cells or small (syncytial) cell clusters
 - Tumor cells vary and include:
 - Round to oval, spindle-shaped, polygonal, and/or plasmacytoid cells
 - Round to oval often eccentrically located nuclei with stippled or coarse chromatin pattern
 - Intranuclear inclusions occasionally present:
 - Nucleoli usually inconspicuous but may be prominent
 - Binucleate and multinucleate cells are common.
 - Mild to moderate nuclear pleomorphism
 - Nuclear grooves typically absent
 - No significant increase in mitotic activity
 - Abundant granular eosinophilic cytoplasm:
 - Distinct metachromatic red (azurophilic) cytoplasmic granules
 - Seen in air-dried preparations stained with Romanowsky method and not in Papanicolaou stained preparations

- Present in approximately 5% to 10% of cases
- Correspond to neurosecretory granules
- Extracellular homogeneous eosinophilic to pale orange, amorphous clumps, spheres, or rods can be seen and correspond to amyloid.
 - Congo red staining can confirm presence of amyloid.

Gross

- Sporadic tumors:
 - Typically unilateral, solitary lesions
- Hereditary tumors:
 - Usually multifocal and bilateral
- Usually identified in middle aspects of lateral lobe(s)
 - Represents areas of greatest concentration of C-cells
 - Isthmic involvement occurs secondarily from large tumor originating in lateral lobe(s).
- Variability in size, including:
 - Barely visible to large tumors occupying a part or entire affected lobe
- May be encapsulated:
 - Larger tumors tend to be well delineated or circumscribed but not encapsulated.
 - Some tumors have infiltrative growth.
- On sectioning, tan-white, yellow, gray, or pink varying in consistency from soft to rubbery to firm:
 - Hemorrhage and necrosis not usually present but calcifications can be appreciated

Histology

- Histologic features variable from case to case; however, irrespective of clinical setting in which MTC occurs (i.e., sporadic versus hereditary), histology is similar.
- Vary from circumscribed to encapsulated to unencapsulated to infiltrative
 - Extension of the tumor into adjacent thyroid parenchyma is often present.
- Growth patterns include:
 - Organoid, lobular, trabecular, solid, insular, or sheet-like:
 - Cell nests separated by a highly (fibro)vascular stroma
 - Less often, may exhibit pseudopapillary, follicular, glandular, or cribriform growth patterns
- Cytomorphologic features include:
 - Round to oval to spindle-shaped to plasmacytoid cells
 - Round to oval nuclei with coarse or stippled chromatin
 - Nuclei may be eccentrically situated, resulting in plasmacytoid appearance but paranuclear

clear zone or “hof” typical of plasma cells is not present.

- Nucleoli usually inconspicuous
- Intranuclear pseudoinclusions can be seen.
- Binucleate and multinucleate cells common
- Ill-defined cytoplasm with basophilic to eosinophilic to amphophilic and granular
- Clear cell changes may be seen.
- Mild to moderate nuclear pleomorphism and mitotic figures can be seen but, in general, no significant pleomorphism or increase in mitotic rate.
- Necrosis and hemorrhage not characteristically present
- Calcification and psammoma bodies (with concentric laminations) may be identified.
- A prominent neutrophilic cell infiltrate may occasionally be present.
- Stromal amyloid:
 - Seen in up to 85% of cases
 - Appears as homogeneous, acellular, eosinophilic bands or nodules
 - May be focally present or may be diffuse, almost completely replacing tumor
 - Associated calcifications and foreign body giant cell reaction may be identified.
 - In some cases no associated amyloid deposition
 - Multinucleated giant cells may be present in association with amyloid, and amyloid can be seen within cytoplasm of multinucleated giant cells.
- Colloid-filled follicles can be seen within tumor:
 - Not an indication of dual C-cell and follicular differentiation
 - Represent remnants of follicular epithelium entrapped by MTC
- Invasive growth may be present and includes:
 - Extension into adjacent thyroid parenchyma
 - Angioinvasion
 - Extrathyroidal invasion into perithyroidal soft tissue and/or into adjacent organs (e.g., larynx, trachea, esophagus)
- C-cell hyperplasia in association with MTC:
 - Strongly associated with hereditary medullary thyroid carcinoma:
 - Usually present in association with MEN-2A, MEN-2B, and familial MTC alone
 - Typically present either adjacent to or separate from MTC
 - Usually absent in association with sporadic MTC
- Histologic variants of MTC (Box 28-7):
 - Irrespective of variant, nuclear features and immunohistochemical staining associated with typical MTC are present.
 - Generally no prognostic significance identified in association with MTC variants

BOX 28-7 Histologic Variants of Medullary Thyroid Carcinoma

- Classic or conventional type (organoid)
- Medullary microcarcinoma
- Spindle-shaped
- Oncocytic
- Papillary
- Glandular/tubular (follicular)
- Giant cell (anaplastic)
- Small cell (neuroblastoma-like)
- Carcinoid-like
- Hyalinizing trabecular adenoma-like
- Paraganglioma-like
- Angiosarcoma-like
- Squamous cell
- Clear cell
- Mucin producing
- Pigmented or melanin-producing
- Atypical (“calcitonin poor”)
- Mixed medullary-follicular carcinoma or medullary-papillary carcinoma

- Medullary microcarcinoma:
 - Measures <1 mm in greatest dimension
 - Common in thyroids prophylactically excised owing to presence of *RET* germline mutation but can be identified in sporadic MTCs
 - May be multifocal and bilateral
 - May be associated with elevated serum basal calcitonin levels
 - Histologic features similar to MTC:
 - May show features seen in other histologic variants (see below)
 - Characterized by complex microarchitectural pattern, desmoplastic stromal response, and (focal) amyloid deposition
 - May be associated with:
 - Extrathyroidal extension (approximately 8%)
 - Regional lymph node metastasis (20% to 30%) and may be related to size:
 - Medullary microcarcinomas measuring ≤5 mm associated with a probability of lymph node metastases of approximately 23%; probability increased in patients with tumors >5 mm
 - Distant metastasis (approximately 5%)
 - Rarely may present with distant (e.g., lung) metastasis
 - Overall 10-year survival rates for patients with localized, regional, and distant disease stages include 96%, 87%, and 50%, respectively
 - Extrathyroid extension and tumor size retain independent association with lymph node metastases.
- Differentiation from neoplastic CCH may be problematic:
 - No established criteria assisting in differentiating nodular foci of neoplastic CCH from microscopic foci of MTC
 - Features supporting medullary microcarcinoma include:
 - Presence of nuclear pleomorphism
 - Presence of associated stromal sclerosis
 - Presence of amyloid stroma
 - Invasive growth
- Spindle cell:
 - Dominated by and/or exclusively composed of spindle-shaped cells:
 - Spindle-shaped cells are commonly seen in usual MTC.
 - Dominant component in approximately 20% of cases
- Oncocytic:
 - Partly or entirely composed of cells with oncocytic cytoplasmic change
 - May resemble oncocytic (Hürthle cell) follicular epithelial cell neoplasms, including presence of prominent eosinophilic nucleoli
 - Histologic findings that may assist in differentiating oncocytic MTC from oncocytic follicular epithelial cell neoplasms include presence of:
 - Amphophilic rather than brightly eosinophilic cytoplasm
 - Tumor nests divided by sharply outlined fibrous stroma
 - Immunohistochemical findings (see below) allow for differentiation but histologic similarities to oncocytic follicular epithelial cell neoplasms may result in erroneous light microscopic diagnosis without consideration for performing immunohistochemical staining.
- Papillary or pseudopapillary:
 - Artifactual separation of lesional cells results in pseudopapillae.
 - Uncommonly, true papillary architecture may be present.
- Glandular (tubular) or follicular:
 - Rare variant
 - Characterized by presence of follicles that may appear empty or contain eosinophilic secretions
 - May also show solid and trabecular growth patterns
- Giant cell (anaplastic):
 - Presence of predominant population of large cells with marked pleomorphism, bizarre-appearing nuclei, and nuclear pseudoinclusions:
 - May be multinucleated or multilobulated

- No significant increase in mitotic activity
- Foci of conventional MTC may be present.
- Small cell or neuroblastoma-like:
 - Characterized by presence of small cells with hyperchromatic nuclei and scant cytoplasm with sheet-like, trabecular, or nodular growth
 - Increased mitotic activity and necrosis may be present.
 - Foci of more typical MTC may be identified but may require extensive sampling.
 - Immunoreactive for calcitonin, synaptophysin, chromogranin, and cytokeratins:
 - Some cases reported to be calcitonin negative
- Carcinoid-like:
 - Presence of organoid, trabecular, or glandular growth separated by fibrovascular stroma simulate appearance of typical carcinoid
- Hyalinizing trabecular tumor-like:
 - Encapsulated MTC showing organoid and trabecular pattern with hyalinized stroma composed of polyhedral to spindled tumor cells with hyaline-appearing cytoplasm
- Paraganglioma-like:
 - Organoid or nested growth similar to paraganglioma
 - S100 protein positive peripherally situated sustentacular cells identified
- Angiosarcoma-like or pseudoangiosarcomatous
 - Presence of cellular dehiscence with associated hemorrhage may result in cleft-like or pseudo-vascular spaces simulating angiosarcoma.
 - Staining for endothelial markers (e.g., CD31, CD34, Factor VIII-related antigen, Fli1, ERG) negative
- Squamous cell:
 - Rarely, squamous differentiation reported
- Clear cell:
 - Rare variant
 - Focally or entirely composed of cells with clear-appearing cytoplasm
- Mucin-producing:
 - Also referred to as amphicrine-composite calcitonin producing
 - Presence of signet ring or goblet cells containing mucin
 - Ultrastructural findings include presence of neurosecretory granules and glandular feature.
- Pigmented or melanin-producing:
 - Rare cases show presence of intracytoplasmic melanin
- Atypical (“calcitonin poor”) medullary thyroid carcinoma:
 - Histologic features of typical MTC with immunoreactivity for neuroendocrine markers (i.e., synaptophysin and chromogranin), NSE and CEA but absent to very little calcitonin staining, absence of thyroglobulin, and TTF-1:
 - May be classified as nonmedullary neuroendocrine carcinoma of thyroid (see below)
- Histochemistry:
 - MTC cells:
 - Argyrophilic (Grimelius stain) but less often are argentaffinic (Fontana-Masson stain)
 - Intra- and extracellular periodic acid Schiff (PAS), alcian blue, and mucicarmine positive staining can be seen.
 - Melanin pigment may be found by argentaffin stains (Fontana-Masson).
 - Amyloid:
 - Congo red imparts an apple-green birefringence in polarized light.
 - Crystal violet imparts metachromatic appearance.
- Immunohistochemistry:
 - MTC cells:
 - Calcitonin most sensitive and specific marker:
 - Present in >95% of cases
 - May be negative representing either:
 - Atypical (“calcitonin poor”) medullary thyroid carcinoma
 - Nonmedullary neuroendocrine carcinoma of thyroid
 - Synaptophysin and chromogranin positive
 - Thyroid transcription factor-1 (TTF-1) reactivity (nuclear) variably present from case to case, including:
 - Focal and weak to diffuse and intense nuclear staining
 - Carcinoembryonic antigen reactivity:
 - Sensitive but not specific marker
 - Cytokeratins (AE1/AE3, CAM 5.2, CK7) present:
 - CK20 negative
 - Additional markers that may be positive (but generally unnecessary in diagnosis) include:
 - Neuron-specific enolase (NSE), calcitonin gene-related peptide (CGRP), somatostatin, ACTH, bombesin, Leu-enkephalin, serotonin, insulin, glucagon, gastrin, vasoactive intestinal peptide (VIP), substance P, human chorionic gonadotropin, and others
 - PAX8 (nuclear) may be positive.
 - S100 protein staining:
 - May show preferential peripheral sustentacular-like pattern:
 - Noted in association with familial MTC but not sporadic MTC
 - Thyroglobulin negative
 - Amyloid:
 - Positive reactivity with amyloid A (AA) antibody

- Electron microscopy:
 - Membrane-bound neurosecretory granules
 - Characteristic ultrastructural feature
 - Shown to contain calcitonin
 - Granules been divided into larger granules (type I) and smaller granules (type II), measuring on average 280 nm and 130 nm, respectively
- Cytogenetics and molecular genetics:
 - See [Clinical](#) section above.

Differential Diagnosis

- Hyalinizing trabecular tumor
- Follicular adenoma
- Follicular carcinoma
- Papillary thyroid carcinoma
- Paraganglioma (see below)
- Non-thyroid neuroendocrine carcinomas especially from larynx (i.e., moderately differentiated neuroendocrine carcinoma or atypical carcinoid):
 - Metastatic tumors to cervical lymph nodes may occur in absence of a known primary tumor.
 - Histologic and immunohistochemical features are typical for a neuroendocrine carcinoma, including immunoreactivity for calcitonin (>80%) as well as synaptophysin, chromogranin, cytokeratins, and CEA.
 - In this scenario, MTC is leading diagnosis but a neuroendocrine carcinoma from mucosal sites of head and neck especially from the (supraglottic) larynx may demonstrate identical histologic features and immunohistochemical staining pattern as MTC.
 - Differentiation based on serum calcitonin and/or TTF1 staining:
 - Most important diagnostic test is presence or absence of elevated serum calcitonin levels:
 - MTC almost invariably associated with elevated serum calcitonin levels
 - Upper aerodigestive tract (e.g., larynx) mucosal neuroendocrine tumors not associated with elevated serum calcitonin levels
 - Diffuse TTF-1 (nuclear) reactivity reported in MTC but absent in laryngeal moderately differentiated neuroendocrine carcinoma
- Amyloid goiter
- Malignant lymphoma
 - During surgery, parathyroid glands identified and, if enlarged, excised
- Prophylactic total thyroidectomy and neck dissection in MTC:
 - Recommended in patients with germline *RET* mutations including children under 3 years of age
 - Recommended for children with MEN-2B:
 - Total thyroidectomy and lymph node dissection performed in first month of life or as soon as phenotype identified:
 - Most cases of MEN-2B are de novo phenotype, most commonly identified in 3- to 10-year age period.
 - In such children surgical cure is uncommon.
 - Relative aggressiveness of MTC associated with specific *RET* mutations, including:
 - Presence of codon 918 mutation:
 - Indicative of aggressive disease phenotype whether mutation is hereditary (MEN-2B) or acquired as somatic mutation
 - Surgery performed in first month of life or as soon as phenotype identified
 - Presence of codon 634 *RET* mutation:
 - Aggressive phenotype accounting for approximately 80% of hereditary MTC
 - Surgery performed <5 years of age
 - Presence of mutations of codons 768, 790, 791, and 804:
 - In certain kindreds these mutations associated with metastasis and deaths
 - In other kindreds these mutations never associated with deaths
 - Consideration for surgery <5 years of age or delay in following criteria met:
 - ◻ Less aggressive family history
 - ◻ Normal serum calcitonin
 - ◻ Normal neck ultrasound
 - Prophylactic thyroidectomies in above situations may not show macroscopic tumor:
 - CCH and/or medullary microcarcinoma(s) may be seen by histologic evaluation aided by calcitonin immunohistochemical staining.
- Regional lymph node dissection in MTC
 - Metastatic disease to regional lymph nodes occurs early in disease course, warranting neck dissection, including:
 - Prophylactic central lymph node dissection indicated as part of the initial therapeutic management
 - Central lymph node dissection includes nodes from hyoid bone to innominate vein
 - Lateral neck dissection:
 - Patients with palpable thyroid tumors often have metastatic tumor to lateral cervical lymph nodes.

Treatment and Prognosis

- Preferred treatment for all forms of MTC may include:
 - Total thyroidectomy
 - Lymph node resection

- Modified or radical neck dissection reserved for those patients with jugular node metastasis (sampled intraoperatively) or disease that invades jugular veins or sternocleidomastoid muscles.
 - Metastatic disease may occur at an early age, including within first decade of life.
 - Metastatic disease (even at presentation) may occur even in presence of encapsulated MTC.
- Distant metastasis:
 - Less frequently, distant metastasis to liver, lungs, bone, and adrenal glands may occur.
- Local recurrence:
 - May occur in up to one third of patients following treatment
- Other therapeutic modalities may include:
 - Standard chemotherapy and radiation therapy (external, radioactive iodine)
 - Not been shown to be effective in treatment of MTC
 - Not radiosensitive tumor
 - Radiotherapy can be used for those patients with inoperable disease and whose tumor may be compressing and compromising vital structures (trachea, esophagus, large vessels).
 - No effective chemotherapeutic regimens for MTC
 - Radioactive iodine therapy does not play a role in management because neoplastic cells do not uptake iodine and therefore ablative therapy does not work.
 - Targeted drug therapies:
 - Promising and being examined in therapeutic clinical trials
 - Kinase inhibitor therapy:
 - Vandetanib or cabozantinib may be recommended for select patients with metastatic MTC.
- Postoperative management of MTC may include:
 - Monitoring of serum calcitonin and carcinoembryonic antigen (CEA) levels:
 - Serum calcitonin measurement:
 - Used to follow patients with residual or metastatic disease
 - Sequential measurements over extended periods useful for quantitating tumor mass:
 - Almost direct correlation between calcitonin measurements and tumor volume
 - Points regarding serum calcitonin measurement:
 - Secretion of calcitonin is episodic and affected by ambient plasma calcium concentration, exercise, eating (gastrin stimulation)
 - May normally vary by factor 2- to 3-fold, so direct comparison of any two measurements provides little useful information
 - Aggressive MTCs paradoxically lose ability to transcribe CT/CGRP gene such that falling calcitonin levels may be an indicator of poor prognosis.
 - Patients with serum calcitonin levels >5000 pg/ml (normal usually <10 pg/ml) following total thyroidectomy and lymph node dissection most commonly have metastatic disease outside neck region; in such patients presence of disease almost always detected by imaging (e.g., ultrasound, CT scan) of chest or abdomen; if radiologic imaging is negative, metastasis may be present in liver, a location where microscopic metastases may be difficult to detect.
 - CEA measurements:
 - Less short-term variability of plasma concentrations than for calcitonin
 - Useful for monitoring tumor mass
 - Insensitive and inaccurate marker for detecting early MTC owing to fact that:
 - May be elevated in cigarette smokers
 - May be elevated in association with other tumor types
 - Has broad range of normality
 - Stable CEA levels with or without changes in calcitonin levels suggests stable or slowly progressive disease
 - Rapidly rising CEA levels (with or without rapidly rising calcitonin levels):
 - Suggests emergence of more aggressive tumor
 - More aggressive behavior may be associated with persistently elevated CEA levels in association with decreasing calcitonin levels in serum and tissue.
- Prognosis (approximately):
 - 5-year survival rates are 70% to 80%.
 - 10-year survival rates are 50% to 78%.
 - 15-year survival rates are 65%.
- Prognostic factors:
 - Clinical stage (see [Table 28-6](#)):
 - Most important prognostic factor
 - Tumors confined to thyroid without evidence of metastatic disease have an excellent prognosis, with almost 100% cure rates following surgery.
 - Earlier detection (smaller tumor, lower stage), better survival:
 - Patients whose thyroid lesion or tumor is discovered in screening process for familial disease usually have C-cell hyperplasia or small neoplastic foci and have an excellent prognosis following surgery.

- Tumors larger than 1 cm have an unfavorable prognosis.
- Patients whose tumors are not totally excised or who have distant metastasis or who have elevated postoperative calcitonin or carcinoembryonic antigen (CEA) levels have a less favorable prognosis:
 - Even in this group there is variability in outcome, with some patients surviving for long periods of time, whereas others succumb to disease in relatively short time frames.
- 5-year observed and relative survival rates per stage include:
 - Stage I: 100% and 100%
 - Stage II: 88% and 98%
 - Stage III: 74% and 81%
 - Stage IV: 25% and 28%
- Age/gender:
 - Patients under 40 years of age have a better prognosis.
 - Patients older than sixth and seventh decades have a worse prognosis.
 - Women have better prognosis than men.
- Hereditary versus sporadic:
 - In decreasing order (best to worst) survival patterns of MTC are:
 - Familial (non-MEN) > sporadically or in association with MEN-2A > MEN-2B
 - MEN-2B-associated MTC are aggressive tumors with early dissemination and increase in tumor-related deaths.
- Calcitonin and CEA:
 - Calcitonin-rich tumors (>75% of cells) associated with better prognosis than calcitonin-poor tumors (<25% of cells):
 - Upon recurrence or relapse, calcitonin-rich tumors may become calcitonin poor.
 - Survival statistics do not necessarily apply for longer periods of time (beyond the 5-year range).
 - Biochemical cure defined as normal serum calcitonin levels is associated with good survival rates (10-year survival of 98%).
 - Inability to achieve a biochemical cure associated with worse survival rates (10-year survival of 70%)
 - Decreased calcitonin immunoreactivity coupled with increased CEA reactivity reported to be associated with worse prognosis
- Pathologic factors other than calcitonin and CEA immunoreactivity that may (but not consistently) correlate with prognosis include:
 - Tumor size:
 - Smaller tumor, better prognosis

- Encapsulation:
 - Encapsulated tumors have more favorable prognosis
- Extrathyroidal extension:
 - Invasion beyond thyroid gland equates to higher tumor stage and worse prognosis
- Histologic type:
 - Small cell type (if it exists) purportedly a more aggressive tumor
- Amyloid content:
 - More amyloid content associated with better prognosis further enhanced by presence of calcification
 - Amyloid free/poor tumors may behave more aggressively than amyloid.
- Pleomorphism, increased mitotic activity, and necrosis:
 - Associated with worse prognosis

MIXED MEDULLARY-FOLLICULAR CARCINOMA (FOLLICULAR-PARAFOLLICULAR CARCINOMA) AND MIXED MEDULLARY-PAPILLARY CARCINOMA

- Controversial tumor category
- Defined as:
 - Neoplasm in which there is an admixture of medullary thyroid carcinoma characterized by typical morphologic features and immunoreactivity for calcitonin with one of the following:
 - Thyroid follicular carcinoma characterized by an invasive carcinoma with colloid-filled follicles and immunoreactivity for thyroglobulin
 - Papillary thyroid carcinoma characterized by a neoplasm with characteristic nuclear features and immunoreactivity for thyroglobulin
- Although evidence supports existence of these tumor types, they are rare and a more common occurrence is not “dual” differentiation but either:
 - Presence of medullary thyroid carcinoma with entrapped non-neoplastic thyroid follicular epithelium with diffusion of thyroglobulin from surrounding thyroid tissue or
 - Collision tumor, including:
 - Separate and/or colliding foci within same gland of medullary thyroid carcinoma and:
 - Papillary thyroid carcinoma
 - Follicular carcinoma
- Evidence to support existence of a true mixed neoplasm includes:

- Some cases reported to be familial
- Immunoreactivity for calcitonin and thyroglobulin in MTC and follicular carcinoma components, respectively
- Ultrastructural findings include presence of neurosecretory granules and cells with follicular differentiation.
- Most compelling evidence to support existence of such a tumor type would be metastatic disease that includes foci of MTC and thyroid follicular cell-derived tumor (follicular carcinoma or papillary thyroid carcinoma) by light microscopic and immunohistochemical staining.
- Treatment and biologic behavior controversial given too few cases in literature but suggestion that treatment protocols follow those of MTC

THYROID NEUROENDOCRINE CARCINOMAS (OTHER THAN MTC) (see Fig. 28-102)

- Controversial category that may include atypical or calcitonin-poor medullary thyroid carcinoma or nonmedullary neuroendocrine carcinoma
- Atypical or calcitonin-poor medullary thyroid carcinoma (also referred to as C-cell derived calcitonin-free neuroendocrine carcinoma) characterized by tumor with:
 - Architectural and cytomorphology of neuroendocrine carcinoma
 - Chromogranin, synaptophysin, and neuron-specific enolase reactivity
 - Absence or near absence of calcitonin reactivity
 - Presence of calcitonin gene-related peptide (CGRP):
 - Supportive evidence of C-cell derivation
 - Absence of thyroglobulin
 - May be reactive for TTF-1, PAX8
 - Reactive for cytokeratins (AE1/AE3 and CK8/18),
 - One case in literature reported:
 - In situ hybridization lacked expression for calcitonin and thyroglobulin mRNA
 - Genetic analysis negative for *RET* mutation
- Nonmedullary neuroendocrine carcinoma of thyroid characterized by:
 - Architectural and cytomorphology of neuroendocrine carcinoma
 - Expression of thyroglobulin (and TTF-1), synaptophysin, and chromogranin
 - Absence of calcitonin staining
 - Expression of thyroglobulin and TTF-1 would support derivation from follicular epithelial cells rather than C-cells.
- In theory, spectrum of neuroendocrine carcinomas (NEC) seen in other organs may occur in thyroid, but in reality such tumor types occurring in thyroid gland are extremely rare.
 - Classification of NEC includes:
 - Carcinoid tumor (well-differentiated neuroendocrine carcinoma)
 - Atypical carcinoid (moderately differentiated neuroendocrine carcinoma)
 - Small or large cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma)
 - Of above thyroid small cell neuroendocrine carcinoma reported:
 - Rare tumor type
 - Histologically similar to small cell neuroendocrine carcinoma of more common sites (i.e., lung)
 - Immunohistochemistry:
 - Cytokeratin, chromogranin, synaptophysin, TTF-1 positive
 - Calcitonin negative
 - Presence of calcitonin confers a diagnosis of small cell variant of MTC
 - Very aggressive-behaving tumor
- Prior to a diagnosis of a primary thyroid neuroendocrine carcinoma, a metastasis to thyroid gland from a neuroendocrine carcinoma of another organ (metastatic to or directly invading thyroid gland) site should be excluded.

THYROID PARAGANGLIOMA (Fig. 28-103)

Definition: Benign tumor originating from neural crest-derived paraganglia of autonomic nervous system identified in thyroid gland.

Clinical (Limited to the Thyroid Gland)

- Rare primary thyroid neoplasm
- More common in women than in men; occurs in adults
- Patients present with an asymptomatic thyroid mass; systemic symptoms are not present.
- Patients are euthyroid.
- Serum calcitonin levels not elevated
- Radioisotope scan shows presence of a hypofunctioning (“cold”) solitary mass
- Histogenesis:
 - Presence of intrathyroidal paraganglia has not been definitively identified.
 - Paraganglia, derived from inferior laryngeal paraganglial tissue, may be found in thyroid capsule,

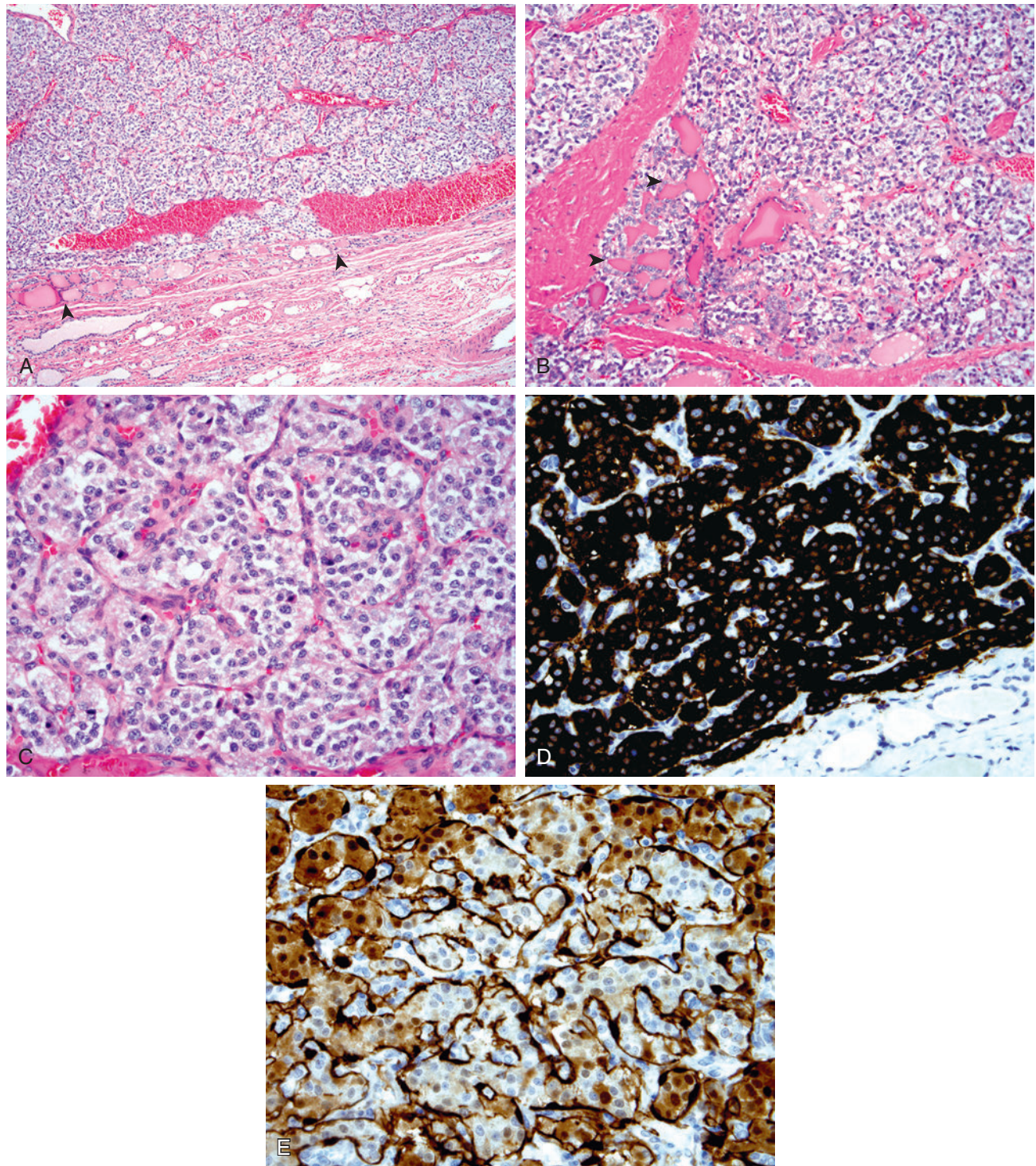


Fig. 28-103. Thyroid paraganglioma.

A, Circumscribed tumor separated from thyroid parenchyma (*arrowheads*). **B**, Colloid-filled follicles (*arrowheads*) enveloped by tumor. **C**, Characteristic cell nest or organoid growth (Zellballen) separated by fibrovascular stroma and composed of cells with uniform nuclei and stippled-appearing nuclear chromatin. **D**, Lesional cells are diffusely and strongly reactive for synaptophysin. **E**, S100 protein preferentially is reactive in the peripherally located sustentacular cells although scattered tumor (chief) cells are also S100 protein positive.

perhaps migrating to this site during embryogenesis.

Pathology

Gross

- Encapsulated, firm lesions with a nodular appearance, tan-brown, and measuring up to 3.5 cm in greatest dimension.

Histology

- Histologic features include the presence of a cell nest or organoid growth (Zellballen) with a fibrovascular stroma that surrounds and separates tumor nests.
- Composed predominantly of chief cells, which are round or oval with uniform nuclei, dispersed chromatin pattern, and abundant eosinophilic, granular, or vacuolated cytoplasm:
 - Spindling of the chief cells may be present.
- Sustentacular cells represent other cellular component of tumor, which is difficult to appreciate by light microscopy:
 - These cells represent modified Schwann cells and are seen at the periphery of the cell nests as spindle-shaped, basophilic-appearing cells.
- No evidence of follicular differentiation or colloid formation within neoplasm
- Cellular pleomorphism may be seen; mitoses and necrosis are infrequently identified.
- Amyloid stroma not seen
- Histochemistry:
 - Tumor cells are argyrophilic (Churukian-Schenck).

- Reticulin staining delineates the cell nests.
- Argentaffin (Fontana-Masson), mucin, and periodic acid Schiff stains are negative.
- Immunohistochemistry:
 - Chief cells:
 - Reactivity for synaptophysin, chromogranin; S100 protein may be positive
 - Nonreactive for calcitonin, calcitonin gene-related protein (CGRP), CEA, thyroglobulin, TTF-1, cytokeratins
 - Sustentacular cells:
 - Reactivity for S100 protein, SOX10
- Electron microscopy:
 - Membrane-bound neurosecretory granules of varying sizes can be seen.
- Cytogenetics and molecular biology:
 - Mutations of PGL1 and SDH (succinate dehydrogenase) loci identified

Differential Diagnosis

- Hyalinizing trabecular tumor
- Medullary thyroid carcinoma
- Carotid body paraganglioma with extension into thyroid
- Papillary thyroid carcinoma

Treatment and Prognosis

- Conservative surgical excision (lobectomy) is curative.
- These tumors are benign:
 - Malignant behavior, as seen by locoregional invasion, is extraordinarily uncommon.
- Concomitant carotid body tumors may be present.

LYMPHOPROLIFERATIVE DISEASES OF THE THYROID GLAND

BENIGN LYMPHOPROLIFERATIVE DISORDERS

Langerhans Cell Histiocytosis (LCH) (Fig. 28-104)

Definition: Rare involvement of thyroid gland by Langerhans cell histiocytes.

Clinical and Pathology (Limited to Thyroid Involvement)

- For more complete discussion see Section 7, Ear and Temporal Bone.
- Thyroid involvement by LCH is rare and may occur:
 - Part of systemic disease with secondary thyroid involvement is more common:

- Patients present with thyroid nodule(s).
- Identified at autopsy
- As incidental microscopic foci identified in thyroid gland resected for other reasons (e.g., adenomatoid nodules, papillary thyroid carcinoma, lymphocytic thyroiditis, other) is less common
- No gender predilection; occurs over a wide age range from 2 months to 55 years, with a median age of 37 years
- Fine-needle aspiration biopsy:
 - Smears show isolated, loose aggregates and histiocyte-like cells with grooved or contorted nuclei mixed in varying proportions with many mature eosinophils, scattered and small lymphocytes, multinucleated giant cells, and foamy histiocytes.

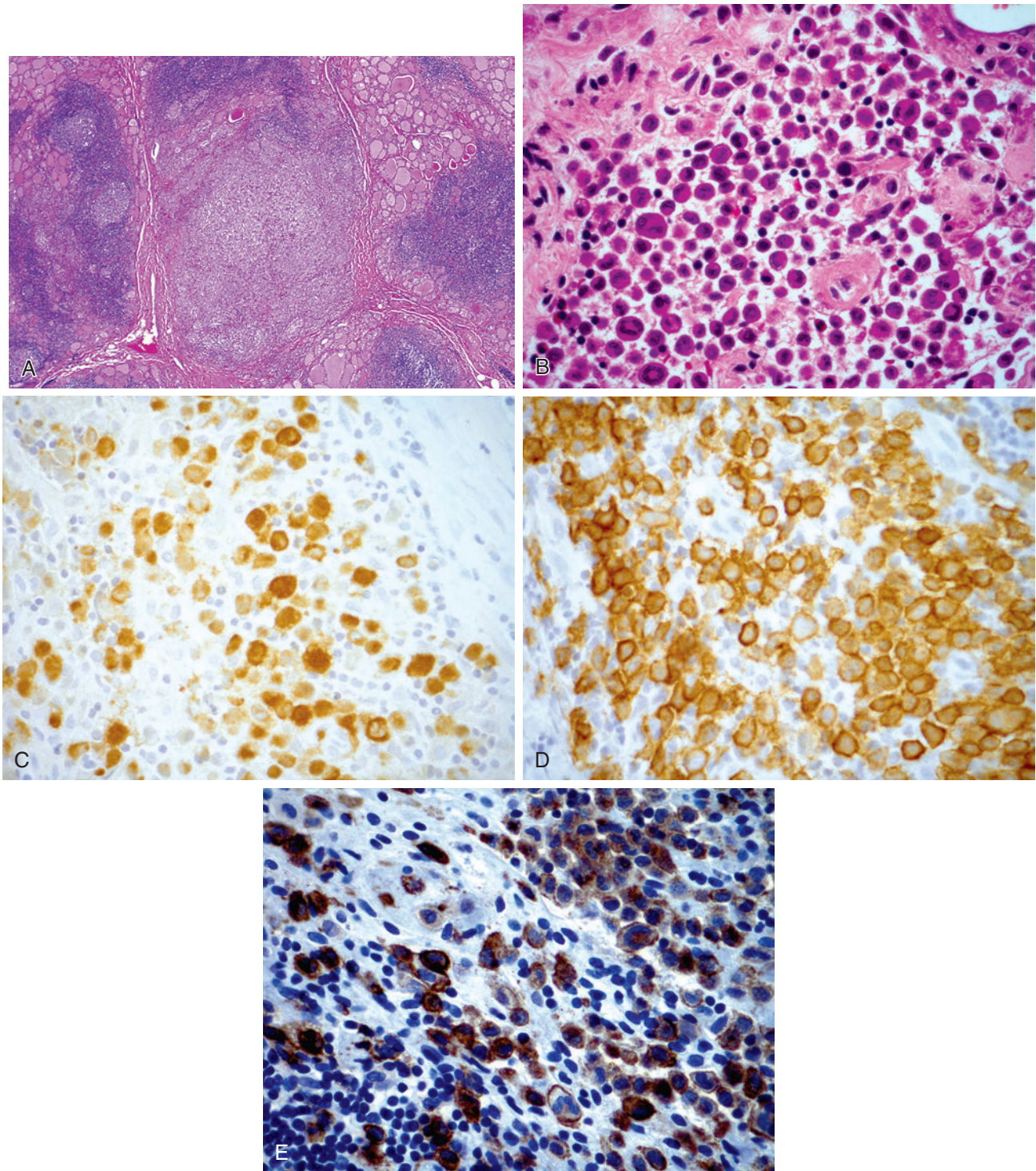


Fig. 28-104. Langerhans cell histiocytosis of the thyroid.

A, Low magnification shows an incidentally identified small nodular-appearing focus in a background showing changes of chronic lymphocytic (Hashimoto) thyroiditis. **B**, At higher magnification, the cellular focus includes Langerhans cells characterized by vesicular nuclei with indented, notched, grooved, vesicular or “coffee-bean” shape and scattered eosinophils. Langerhans cells are immunoreactive for **(C)** S100 protein, **(D)** CD1a, and **(E)** Langerin.

- Histologically:
 - Thyroid involvement by LCH may be:
 - Focal (more common)
 - Diffuse
 - Langerhans histiocytes characterized by enlarged cells with vesicular nuclei and indented, notched, grooved, vesicular, or “coffee-bean”-shaped appearance, one or two nucleoli, and pale to eosinophilic finely vacuolated cytoplasm:
 - Intracytoplasmic phagocytosed cellular debris can be found.
 - Variable amount of eosinophils can be seen intermingled with the Langerhans cell histiocytes and tend to be more concentrated near areas of necrosis.
 - Histiocytic foci may infiltrate thyroid parenchyma, causing effacement of follicular architecture with destruction of thyroid follicles.
 - Reactive changes of follicular epithelium, including enlargement of cell size, can be seen.
 - Lymphocytic thyroiditis in the thyroid tissue not involved by LCH commonly found
 - Histiocytic cell proliferation may extend beyond the confines of the capsule, resulting in thyroid gland adhering to surrounding soft tissue or muscle.
 - Involvement of adjacent parathyroid gland(s) may occur.
- Immunohistochemistry:
 - Langerhans cells are reactive for:
 - S-100 protein, CD1a, Langerin
 - Lysozyme and CD68 also positive
 - No reactivity for thyroglobulin, TTF-1, cytokeratins
- Electron microscopy:
 - Intracytoplasmic rod-shaped granules (Birbeck granules) can be identified.

Treatment and Prognosis

- Localized disease treated by surgical resection
- Patients with isolated disease to thyroid, prognosis is favorable:
 - These patients do not subsequently develop systemic involvement.
- Systemic disease treated by combination chemotherapy
- Those patients with thyroid involvement associated with systemic disease have an aggressive clinical course with a poor prognosis.
 - Death due to disease-related complications generally occur in short periods of time (within 1 year).
- Given disparity in clinical outcome between localized (isolated) LCH versus systemic involvement, imperative to exclude systemic disease in those patients who may initially present with thyroid involvement

Extranodal Sinus Histiocytosis with Massive Lymphadenopathy (ESHML)

Definition: Idiopathic, predominantly nodal-based histiocytic proliferative disorder associated with an indolent biologic course with spontaneous resolution.

- Extranodal involvement may occur as part of a generalized process involving lymph nodes or may involve extranodal sites independent of lymph node status.

Synonyms: Rosai-Dorfman disease; Destombes-Rosai-Dorfman syndrome

Clinical and Pathology (Limited to Thyroid Involvement)

- For more complete discussion including images, see Section 1, Sinonasal Tract.
- Thyroid involvement by SHML is rare and may represent secondary extension from perithyroidal lymph nodes or may occur independent of nodal involvement.
- Clinically, SHML of thyroid may simulate subacute thyroiditis presenting with subclinical hypothyroidism and painful goitrous thyroid.
- Histology (cytopathology):
 - Histiocytic cells (so-called SHML cells), characterized by round to oval, vesicular to hyperchromatic nuclei, with an abundant amphophilic to eosinophilic, granular to foamy to clear-appearing cytoplasm; nucleoli may be prominent and eosinophilic or may be inconspicuous
 - Characteristically, SHML cells demonstrate emperipolesis:
 - Phagocytized cells most often lymphocytes but plasma cells, erythrocytes, and polymorphonuclear leukocytes can also be seen engulfed within the histiocytic cell cytoplasm.
 - Emperipolesis readily identifiable in nodal-based disease but extranodal sites may be more difficult feature to identify, although it can usually be found.
 - Can be diagnosed by fine-needle aspiration biopsy
- Immunohistochemistry:
 - SHML cells:
 - Most striking feature is presence of diffuse S100 protein reactivity but negative for CD1a and Langerin
 - Also demonstrate consistent immunoreactivity with vimentin, alpha-1-antichymotrypsin (ACT), CD68, lysozyme, and MAC-387
 - Less frequently, SHML cells may show immunoreactivity with Ki-1 and alpha-1-antitrypsin (AAT).

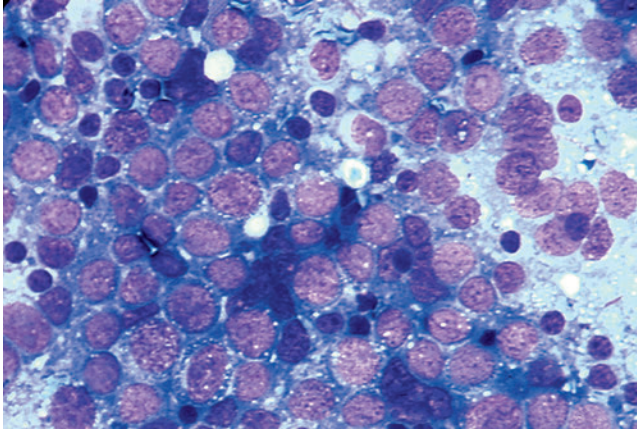


Fig. 28-105. DLBCL.

Diffuse large B-cell lymphoma of the thyroid gland, fine-needle aspiration biopsy. Cellular smear mostly composed of large lymphoid cells with nuclei over three times the size of admixed smaller lymphocytes (Diff-Quik).

- Negative for thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers (e.g., synaptophysin, chromogranin)
- Too few cases of thyroid involvement to make any definitive comments on therapy and prognosis:
 - In all likelihood, treatment and behavior are similar to vast majority of patients with ESHML, who have an excellent prognosis, often with spontaneous resolution of their disease, without any specific therapy.

MALIGNANT LYMPHOPROLIFERATIVE NEOPLASM

Non-Hodgkin Malignant Lymphoma (NHML)

(Figs. 28-105 through 28-109)

Definition: Primary involvement of thyroid gland by malignant tumor composed of lymphoid cells usually of B-cells:

- Secondary involvement of thyroid gland by lymphoma more frequent than primary disease
- Approximately 20% of patients with disseminated lymphoma have thyroid involvement.
- For more complete discussion see Section 3, Pharynx.

Clinical

- Primary non-Hodgkin malignant lymphomas make up approximately 5% of all thyroid malignant

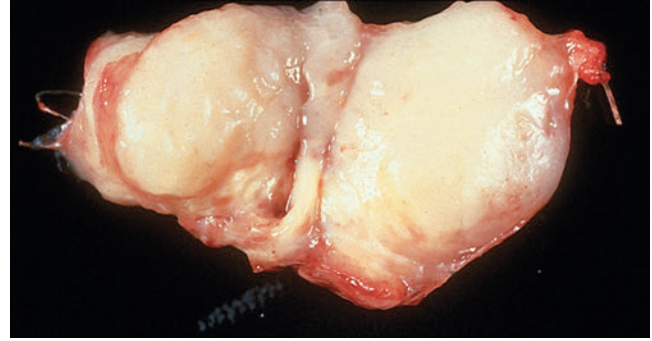


Fig. 28-106. DLBCL.

Primary thyroid malignant lymphoma with near complete replacement of the thyroid gland by a tan-white to yellow “fish flesh”-appearing lesion that on cut section has a bulging surface. Thyroid lymphomas tend to be poorly demarcated from the surrounding thyroid parenchyma and typically (completely) replace the involved thyroid tissue.

neoplasms and 2% to 3% of extranodal lymphomas.

- Much more common in women than in men; predominantly but not exclusively disease of older individuals in sixth to seventh decades of life
- Clinical presentation:
 - Usually rapidly enlarging, firm, and nontender thyroid gland:
 - Enlargement often occurs over a short period of time (weeks to months).
 - In general, only other thyroid neoplasm that presents as a rapidly enlarging thyroid mass is undifferentiated (anaplastic) thyroid carcinoma, which also tends to occur in the same age population as thyroid malignant lymphoma.
 - Other complaints may include:
 - Pain, hoarseness, dysphonia, vocal cord paralysis, dysphagia, dyspnea, and stridor
 - More uncommonly, superior vena cava obstruction may occur.
 - Not all thyroid lymphomas present as a rapidly enlarging mass; some may present as:
 - Gradual diffuse enlargement
 - Slowly growing nodule(s)
 - Development in patient with long-standing chronic lymphocytic (Hashimoto) thyroiditis
 - Incidental finding in thyroidectomy specimen:
 - Usually represents extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, MALT type
- On palpation, thyroid gland is:
 - Usually asymmetric, hard, bulky mass often multinodular but may be uninodular

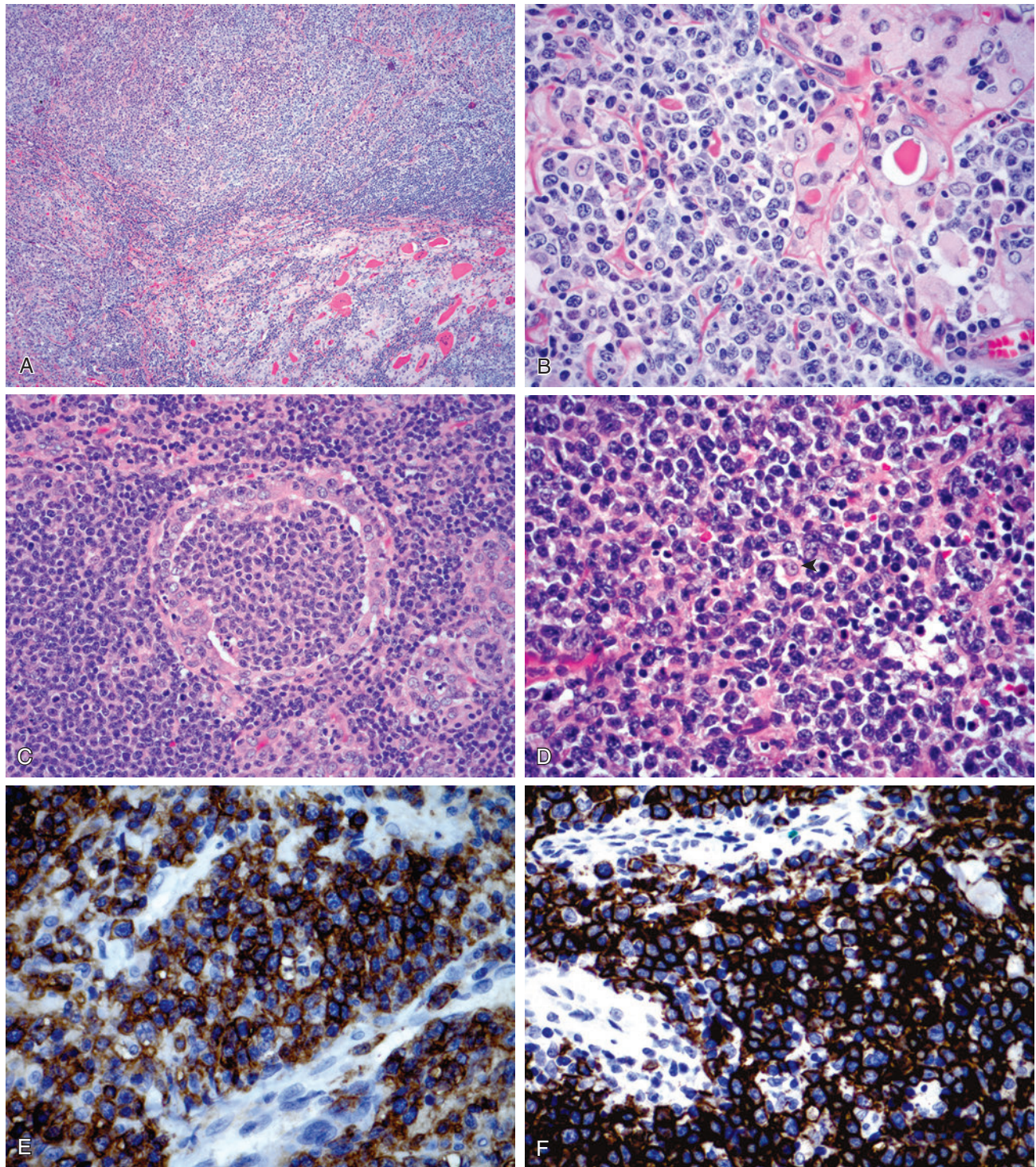


Fig. 28-107. Diffuse large B-cell lymphoma of the thyroid.

A, Cellular infiltrate with diffuse growth pattern and effacement of the thyroid parenchyma; residual adjacent thyroid parenchyma with changes of chronic lymphocytic (Hashimoto) thyroiditis is present (*lower right*). **B,** Sheets of large neoplastic cells infiltrate around residual thyroid follicles. **C,** Neoplastic cells colonize (pack or stuff) thyroid follicles creating lymphoepithelial lesions. **D,** Neoplastic lesional cells are round to oval nuclei with prominent eosinophilic nucleoli slightly larger than identifiable histiocytic nuclei (*arrowhead*) and at least twice the size of scattered small lymphocytes. The neoplastic cells are immunoreactive for **(E)** CD45 and **(F)** CD20.

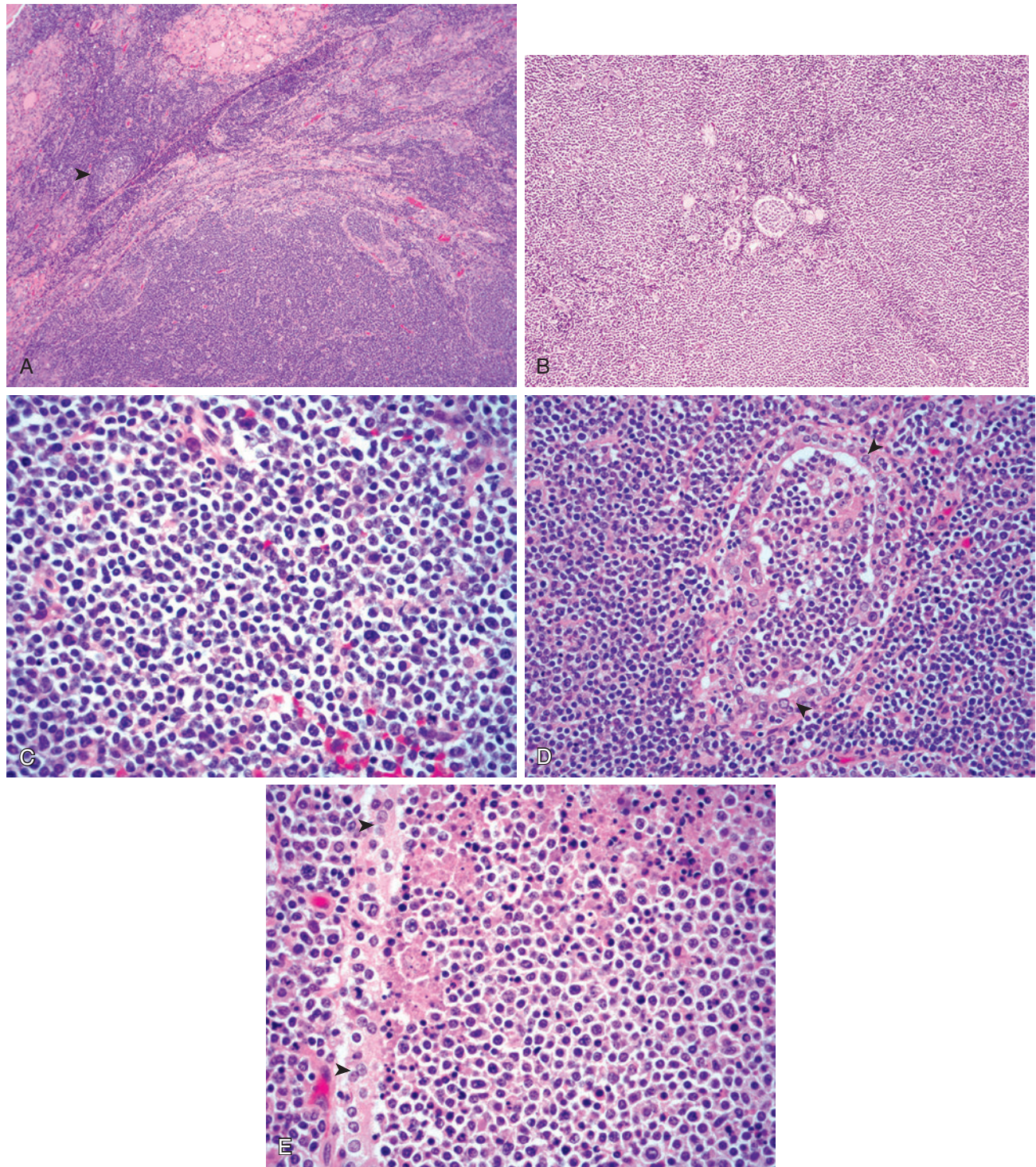


Fig. 28-108. Extranodal marginal zone B-cell lymphoma of the MALT type of the thyroid gland.

A, In the lower portion of the illustration there is a diffuse cellular infiltrate with effacement of thyroid architecture and absence of identifiable germinal centers seen adjacent to residual thyroid parenchyma with changes of chronic lymphocytic (Hashimoto) thyroiditis (*upper left*), including an identifiable germinal center (*arrowhead*). **B**, In areas there is a vaguely nodular (follicular) pattern. **C**, Neoplastic infiltrate includes cells with dark staining and folded nuclei with scanty pale-appearing cytoplasm (centrocyte-like appearance). **D**, Lymphoepithelial cells characterized by neoplastic cells colonizing (packing or stuffing) thyroid follicles identified by the presence of residual follicular epithelial cells (*arrowheads*). **E**, Another example of a lymphoepithelial lesion in MALT lymphoma of the thyroid, including foci of necrosis and residual identifiable follicular epithelial cells (*arrowheads*).

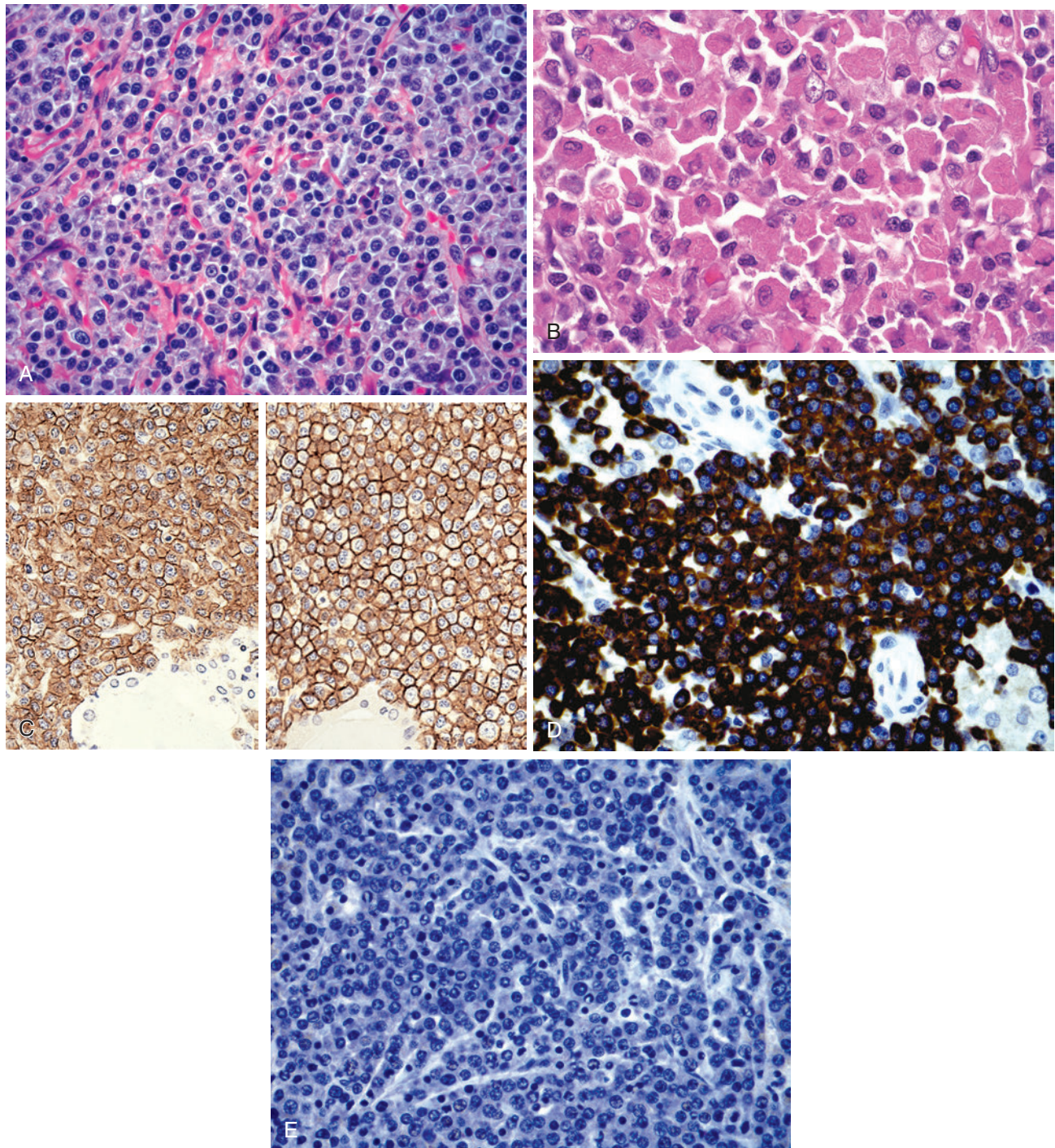


Fig. 28-109. Extranodal marginal zone B-cell lymphoma of the MALT type of the thyroid gland.

A, Cells with plasmacytoid differentiation may be seen and may predominate in any given tumor, simulating a plasmacytoma. **B**, Crystalloid immunoglobulin deposits can be seen in the plasmacytoid cells. **C**, Neoplastic cells are immunoreactive for (*left*) CD45 and (*right*) CD20 that contrast to the findings seen in plasmacytomas that are CD45 negative and usually CD20 negative (as well as CD138 positive, not shown); in situ hybridization for immunoglobulin light chains show (**D**) kappa light chain restriction with (**E**) absence of lambda light chain.

- Cervical adenopathy (uni- or bilateral) may be present and includes varying degrees of nodal fixation.
 - Most patients are euthyroid.
 - Minority of patients may be hypothyroid probably caused by a pre-existing chronic lymphocytic (Hashimoto) thyroiditis rather than to lymphomatous infiltrate:
 - In setting of chronic lymphocytic (Hashimoto) thyroiditis, antithyroid antibodies (antithyroglobulin and antimicrosomal) may be present on laboratory analysis.
 - Rarely, hyperthyroidism may occur perhaps due to rapid destruction of thyroid follicular epithelium with release of colloid and thyroid hormone into circulation.
 - Radiology:
 - Appear as hypofunctioning “cold” nodules on thyroid scan:
 - Lymphomatous infiltrates do not concentrate radioiodine.
 - CT scans may show:
 - Nodularity
 - Extension or invasion within gland or into perithyroidal soft tissue
 - Necrosis and calcification
 - On ultrasound, thyroid lymphomas may appear as extremely hypoechoic masses.
 - Often this is in setting of a gland with decreased echogenicity due to presence of chronic lymphocytic (Hashimoto) thyroiditis.
 - Magnetic resonance imaging:
 - Shows an intensity similar to that of chronic lymphocytic (Hashimoto) thyroiditis
 - T2-weighted images show homogeneous areas of high intensity.
 - Etiology:
 - Chronic lymphocytic (Hashimoto) thyroiditis:
 - Thyroid lymphoma almost always associated with chronic lymphocytic (Hashimoto) thyroiditis:
 - Patients with chronic lymphocytic (Hashimoto) thyroiditis have an estimated 67 times greater risk than normal individuals of developing malignant lymphoma.
 - Factors supporting this relationship include:
 - Immunologically mediated (autoimmune) disease that may lead to development of malignant clone following persistent chronic antigenic stimulation of lymphocytes, thereby increasing susceptibility to neoplastic transformation
 - Transitional areas of reactive lymphoid hyperplasia to areas of unequivocal lymphoma can be seen.
 - Morphologic continuum exists between chronic lymphocytic (Hashimoto) thyroiditis and low-grade B-cell lymphoma and high-grade lymphoma.
 - Clonal rearrangements of immunoglobulin genes on rare occasion may be present in chronic lymphocytic (Hashimoto) thyroiditis.
 - Radiation:
 - Prior irradiation to head and neck region may represent another possible etiologic factor in development of thyroid malignant lymphoma.
 - Microorganisms:
 - Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) are associated with various infectious pathogens
 - *Chlamydia psittaci* found in:
 - Nongastrointestinal MALT lymphomas, including thyroid MALT lymphoma
 - Autoimmune precursor lesions including but not limited to chronic lymphocytic (Hashimoto) thyroiditis by polymerase chain reaction amplification and direct sequencing
 - Suggests possible involvement of *C. psittaci*-induced antigenic-driven MALT lymphomagenesis
- Thyroid lymphomas share many features with lymphomas of salivary gland origin, including:
 - Both are associated with an immunologically mediated, extranodal lymphoid infiltrate:
 - Chronic lymphocytic thyroiditis for thyroid and lymphoepithelial sialadenitis (LESA) for salivary glands
 - Both show presence of lymphoepithelial lesions.
 - Both may present with lymphoma limited to particular site without concomitant or subsequent involvement of other sites.
 - Concomitant or metachronous involvement of other sites such as gastrointestinal tract may occur in thyroid and salivary gland lymphomas.

Pathology

- Virtually every type of non-Hodgkin malignant lymphoma occurs in thyroid gland:
 - Most are of B-cell immunophenotype.
 - Uncommonly, lymphomas with T-cell immunophenotype may occur.
- Nearly all thyroid lymphomas are either:
 - Diffuse large B-cell lymphoma (DLBCL): most common (>70%):
 - May arise de novo or via transformation of extranodal marginal zone B-cell lymphoma, MALT type
 - Extranodal marginal zone B-cell lymphoma (MALT lymphoma)

Fine-Needle Aspiration Biopsy

- DLBCL:
 - Cytologic diagnosis generally straightforward and not as problematic as diagnosis of MALT lymphoma
 - Cellular smear composed of monotonous and dis-cohesive population of large cells with round to oval, vesicular nuclei, prominent nucleoli, and moderate to abundant basophilic cytoplasm:
 - Twice as large as small mature lymphocytes
 - Numerous nuclei stripped of cytoplasm (“naked nuclei”)
 - Necrotic debris in the background
 - Lymphoglandular bodies (Söderström bodies, hyaline bodies, or lymphoid globules) may be identified:
 - Represent round (detached) cytoplasmic fragments of lymphoma cells with diameter between 2 and 7 μm
 - Appear pale basophilic in Romanowsky stained preparation
- MALT lymphoma:
 - Variable cellularity but usually cellular of lymphoid cells in isolation and in clusters
 - Heterogeneous cell population with admixture of small cells and intermediate sized (1.5 to 2 times as large as small mature lymphocytes) cells with slightly vesicular nuclei, pale chromatin, small nucleoli, and moderate amount of cytoplasm
 - Small cells may be admixed with larger cells with eccentric nuclei, coarse chromatin, and prominent nucleoli.
 - Plasmacytoid cells may predominate.
 - Numerous plasma cells may be present.
 - May be impossible to distinguish from Hashimoto thyroiditis

Gross

- Range in size from as small as 1 cm to >15 cm.
- On cut section, homogeneous, tan-white, “fish flesh” appearance, rubbery to hard consistency
 - Bulging surface
 - Necrosis may or may not be present.
- Poor demarcation from surrounding thyroid parenchyma may be present and complete replacement of thyroid gland may occur:
 - May involve one or both lobes
- Often extension beyond thyroid capsule into adjacent soft tissues:
 - Thyroid may be adherent to surrounding structures.
 - Hemorrhage and necrosis are usually not present.
- Non-neoplastic thyroid may be nodular or lobular in appearance with associated fibrosis.

- Suggest presence of chronic lymphocytic (Hashimoto) thyroiditis

Histology

General Features

- Following morphologic features seen in both DLBCL and MALT lymphoma:
 - Effacement of thyroid architecture
 - Neoplastic cellular infiltrate permeating between non-neoplastic follicles
 - Presence of lymphoepithelial lesions characterized by neoplastic cells “packing” or “stuffing” thyroid follicles:
 - In association with MALT lymphoma referred to as MALT balls
 - Absence of germinal centers within neoplastic infiltrate:
 - In lymphoma with a follicular growth pattern, follicles are composed of the neoplastic cellular infiltrate and do not demonstrate spectrum of differentiation normally seen in normal germinal center, including tingible body macrophages.
 - Extension of neoplastic infiltrate beyond thyroid capsule into perithyroidal soft tissues:
 - May result in thyroid being adherent to surrounding structures
 - Vascular invasion may be identified.

Diffuse Large B-Cell Lymphoma

(For more detailed discussion see Section 3, Pharynx.)

- Diffuse infiltrate comprised of sheets of large neoplastic cells with round to oval nuclei, vesicular chromatin, prominent eosinophilic nucleoli, and moderate amount of amphophilic cytoplasm:
 - Nuclear size \geq size of histiocyte nucleus and 2 \times size of small lymphocyte
- Immunohistochemistry (for more detailed discussion see Section, Pharynx):
 - CD45 positive
 - Reactivity for B-cell markers, including:
 - CD20, CD79a, PAX5
 - Cytokeratins, thyroglobulin, TTF-1, PAX8, calcitonin, and neuroendocrine markers negative:
 - Residual follicular epithelial cells reactive for cytokeratins, thyroglobulin, TTF-1, PAX8
- Cytogenetics and molecular genetics:
 - Occasional cases with:
 - t(8;14) involving *MYC* and immunoglobulin heavy chain (*IGH*)
 - Translocation of *BCL6* locus at chromosome 3q27
 - Thyroid carcinoma-associated genetic mutations reported, including:
 - *BRAF*, *NRAS*

Extranodal Marginal Zone B-Cell Lymphoma of the MALT Type

(For more detailed discussion, see Section 3, Pharynx.)

- Neoplastic cells:
 - Dark staining and folded nuclei with scanty pale-appearing cytoplasm (centrocyte-like appearance)
 - May colonize lymphoid follicles
 - Follicular colonization may be prominent, creating a follicular architecture simulating follicular lymphoma.
- Plasma cells commonly seen intermingled with neoplastic cells and may include:
 - Dutcher bodies
 - Cytoplasmic immunoglobulin invaginating into the nucleus creating the appearance of an intranuclear inclusion
 - Mott cells: Cytoplasmic immunoglobulin inclusion or crystals
- Plasmacytic differentiation may be seen and may predominate in any given tumor simulating a plasmacytoma:
 - In this setting, immunohistochemical stains are helpful in differentiating malignant lymphoma with plasmacytic differentiation from a plasmacytoma:
 - Malignant lymphoma with plasmacytic differentiation: CD45, CD20 positive
 - Plasmacytoma: CD45 negative; usually CD20 negative and CD138 positive
 - Monotypic immunoglobulin light chain restriction for either kappa or lambda light chain (by immunohistochemistry or in situ hybridization) may be present in approximately one third of cases.
- Large cell transformation of neoplastic cells may be present in areas adjacent to low-grade component and/or in follicles.
- Immunohistochemistry (for more detailed discussion see Section 3, Pharynx):
 - CD45, CD20, CD79a positive
 - CD5, CD10, CD23, BCL6 negative
 - Cytokeratins, thyroglobulin, TTF-1, PAX8, calcitonin, and neuroendocrine markers negative:
 - Residual follicular epithelial cells are reactive for cytokeratins, thyroglobulin, TTF-1, and PAX8.
- Cytogenetics and molecular genetics:
 - Clonal rearrangement of immunoglobulin heavy chain (*IGH*)
 - Chromosomal rearrangement t(3;14)(p14.1;q32) with *FOXP1/IGH* fusion found in approximately 50% of cases

Differential Diagnosis

- Chronic lymphocytic (Hashimoto) thyroiditis (Table 28-12)

- Undifferentiated (anaplastic) carcinoma
- Thyroid carcinoma with insular growth
- Medullary thyroid carcinoma

Treatment and Prognosis

- Prior to initiation of any therapy, clinical staging is essential for planning of treatment:
 - Clinical staging includes:
 - Radiologic assessment of neck, mediastinum, retroperitoneum, abdomen, and pelvis
 - Complete blood count
 - Bone marrow biopsy
 - Performed to exclude more widespread disease
- MALT lymphoma:
 - Almost always localized (stage I or II)
 - Early stage (stage IE) intrathyroidal MALT lymphomas typically have an indolent course and may be treated with single-modality surgery, radiotherapy, or a combination of both.
 - 62% 5-year survival for MALT lymphoma
 - Tumors with plasmacytic differentiation reported to have prognosis approaching 100% 5-year survival
- DLBCL:
 - More aggressive
 - More apt to have stage IIIIE or IVE disease
 - Survival outcomes highest with multimodal therapy incorporating monoclonal antibodies, chemotherapy, and radiotherapy
 - 45% 5-year survival rates for DLBCL
- Prognosis:
 - Prognosis in presence of extrathyroidal extension and/or higher-stage (widespread) disease significantly worse than low-stage disease:
 - With extrathyroidal extension 5-year survival is 35% to 40%.
 - With disseminated disease, 5-year survival is 5%.
- Need for thyroidectomy remains controversial:
 - Some surgeons advocate surgical resection of gland in patients with low-stage disease as it allows for removal of entire tumor.
 - Some surgeons advocate surgical excision of a sufficient amount of tissue for diagnostic purposes only, followed by initiation of radiotherapy and/or chemotherapy.
 - Surgical intervention justified for debulking of large tumors or decompression of tumors compromising vital structures
- Factors that affect prognosis include:
 - Stage:
 - Lower the stage, better the prognosis
 - Higher stage (with disseminated disease) 5% 5-year survival

TABLE 28-12 Thyroid Malignant Lymphoma versus Chronic Lymphocytic (Hashimoto) Thyroiditis

Features	Malignant Lymphoma	Chronic Lymphocytic (Hashimoto) Thyroiditis
Thyroid architecture and follicular epithelium	Effaced; destruction of follicular epithelium; lymphoepithelial lesions ("packing" or "stuffing" of the follicles with neoplastic cells)	Preserved; no destruction of follicular epithelium; oncocyctic cytoplasmic changes and nuclear enlargement; prominent nucleoli often seen; lymphoepithelial lesions not identified
Germinal centers	Absent in lymphomatous areas; follicles may be present but are composed of malignant cells without tingible body macrophages	May be rescent; heterogeneous cell population; tingible body macrophages in lymphoid follicles
Cellular components	DLBCL: Diffuse infiltrate comprised of sheets of large neoplastic cells with round to oval nuclei, vesicular chromatin, prominent eosinophilic nucleoli and moderate amount of amphophilic cytoplasm; MALT lymphoma: have dark staining and folded nuclei with scanty pale-appearing cytoplasm (centrocyte-like appearance) may colonize lymphoid follicles. Monotypic plasma cells may be intermingled with neoplastic cells.	Polymorphous composed of mature lymphocytes, histiocytes, and plasma cells
Extrathyroidal extension	Malignant cellular infiltrate often "spills out" into perithyroidal soft tissues; thyroid may be adherent to surrounding structures	Sharp outline between benign lymphocytic cell infiltrate and perithyroidal soft tissue; thyroid not adherent to surrounding structures
Immunohistochemistry	B-cell lineage specificity; show kappa or lambda light chain restriction	No lineage specificity or light chain restriction; both B-cells and T-cells are present in the benign cellular infiltrate; light chain restriction is not present
Associated parenchymal changes	Chronic lymphocytic thyroiditis	Squamous metaplasia; fibrosis; lymphoepithelial cysts

DLBCL, Diffuse large B-cell lymphoma; *MALT*, mucosa-associated lymphoid tissue.

- Extrathyroidal extension:
 - With extrathyroidal extension, 35% to 40% 5-year survival rate
 - For intrathyroidal tumors (without with extrathyroidal extension) >80% 5-year survival
- Cervical or mediastinal lymph node involvement associated with worse prognosis
- Age:
 - Patients over 65 years of age at diagnosis have worse prognosis.
- Tumor recurrence portends adverse prognosis.
- Other findings:
 - Large tumor size (>10 cm), presence of necrosis, and angioinvasion associated with worse prognosis

Other Thyroid Malignant Lymphoproliferative Neoplasms

- Thyroid involvement by other malignant lymphomas can occur but generally are uncommon and may include:
 - Follicular lymphoma:

- Rare
- Histologic features similar to follicular lymphoma of other sites
- May be associated with lymphoepithelial lesions
- Most cases associated with chronic lymphocytic (Hashimoto) thyroiditis
- Two groups based on clinical and pathologic findings:
 - First group (share features with nodal follicular lymphomas):
 - Histologic low-grade (grade 1-2/3)
 - Usually express CD10, BCL2 and/or have t(14;18)/IGH/BCL2 translocation
 - High clinical stage (III, IV)
 - Disease usually spread beyond thyroid involving lymph nodes and sometimes bone marrow
 - Achieve partial or complete remission after treatment
 - Second group:
 - Histologic high grade (grade 3/3)
 - Lack CD10, BCL2, and/or have t(14;18)/IGH/BCL2 translocation

- Low clinical stage (I)
 - Complete remission after treatment
- Plasmacytoma:
 - Rare
 - May be part of systemic multiorgan involvement (multiple myeloma) or occurs as an isolated phenomenon (extramedullary plasmacytoma)
 - Must be differentiated from extranodal marginal zone B-cell lymphoma of the MALT type with marked plasmacytic differentiation
 - For more complete discussion see Section 5, Larynx.
- Hodgkin lymphoma:
 - Rare in thyroid
 - Most often occurs secondary to cervical or mediastinal nodal disease
 - Rarely, may be primary in thyroid gland
 - Most common type is nodular sclerosing
- Rare thyroid lymphomas may include:
 - Burkitt lymphoma
 - Peripheral T-cell lymphoma, including anaplastic large cell lymphoma and some expressing $\gamma\delta$ T-cell receptor
 - Mantle cell lymphoma
 - Intravascular large B-cell lymphoma

NONEPITHELIAL NEOPLASMS OF THE THYROID EXCLUDING LYMPHOPROLIFERATIVE DISEASES

MESENCHYMAL TUMORS OF THE THYROID GLAND

Benign Mesenchymal Tumors

- Rare group of tumors that may occur in the thyroid gland
- May present as a solitary thyroid nodule or mass; may also be identified in thyroid gland removed for another lesion such as an adenomatoid nodule or a neoplasm (e.g., follicular adenoma)
- Neoplasms may include:
 - Vascular:
 - Hemangioma:
 - CD31, CD34, Factor VIII-related antigen reactivity
 - Lymphangioma
 - D2-40 (podoplanin) reactivity
 - Neural:
 - Benign peripheral nerve sheath tumor (benign Schwannoma)
 - Histology identical to soft tissue and other sites
 - Diffuse S100 protein and Sox10 (nuclear) reactivity
 - Negative for thyroglobulin, TTF-1, cytokeratins, calcitonin, neuroendocrine markers
 - Granular cell tumor:
 - Extraordinarily rare thyroid tumor
 - Histology identical to mucosal sites
 - Diffuse S100 protein reactivity as well as GFAP, CD68
 - Negative for thyroglobulin, TTF-1, cytokeratins, calcitonin, neuroendocrine markers
 - Muscle:
 - Leiomyoma (Fig. 28-110):
 - Encapsulated
 - Benign spindle cell proliferation lacking cytologic atypia, mitotic activity, or necrosis
 - Actin (muscle specific and smooth muscle actin) reactivity
 - Adipose tissue:
 - Lipoma and adenolipoma:
 - May in fact represent follicular epithelial cell neoplasm with associated mature fat rather than a true lipomatous neoplasm
 - Solitary fibrous tumor (SFT) (Fig. 28-111):
 - Rare thyroid tumor indistinguishable from pleural based on other extrapleural solitary fibrous tumors
 - Predominantly occurs in women; tumor of adult ages
 - Present as a slow-growing neck mass:
 - May occur in association with intrathoracic thyroid glands/goiters
 - Patients are euthyroid.
 - Grossly, well-circumscribed to encapsulated, solid, gray-white mass measuring from 2 to 8 cm; cystic foci may be seen
 - Morphologically identical to pleural and extrapleural counterparts, including:
 - Alternating hypercellular and hypocellular areas
 - Haphazardly arranged uniform, bland-appearing spindle- to stellate-shaped cellular proliferation with scanty cytoplasm and admixed collagen bundles (so-called ropey collagen)

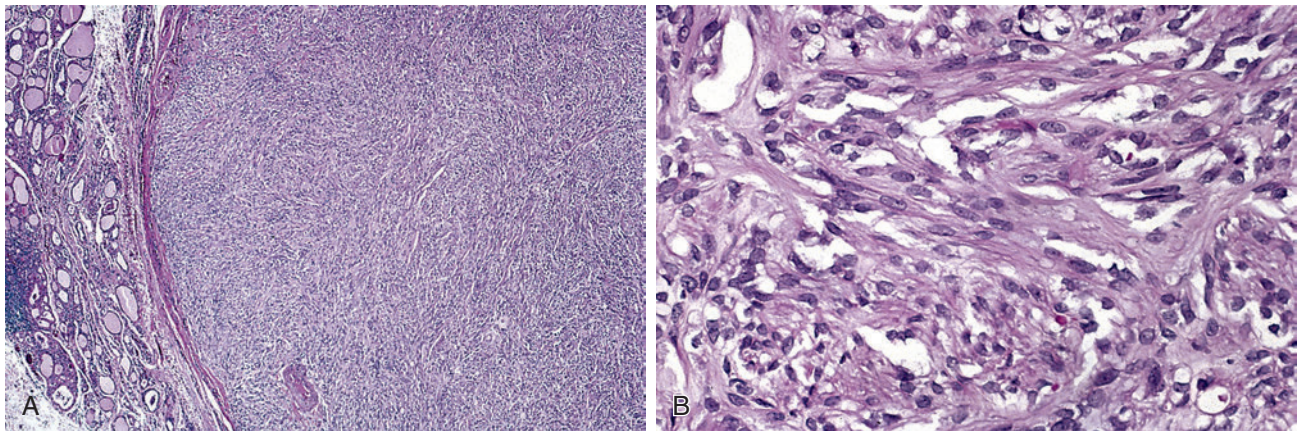


Fig. 28-110. Intrathyroidal leiomyoma.

A, Intrathyroidal leiomyoma. Thinly encapsulated spindle cell tumor separated from adjacent thyroid parenchyma (*upper left*). **B**, At higher magnification the tumor is composed of bland cells with elongated, cigar-shaped nuclei. Immunoreactivity was present for smooth muscle actin (not shown).

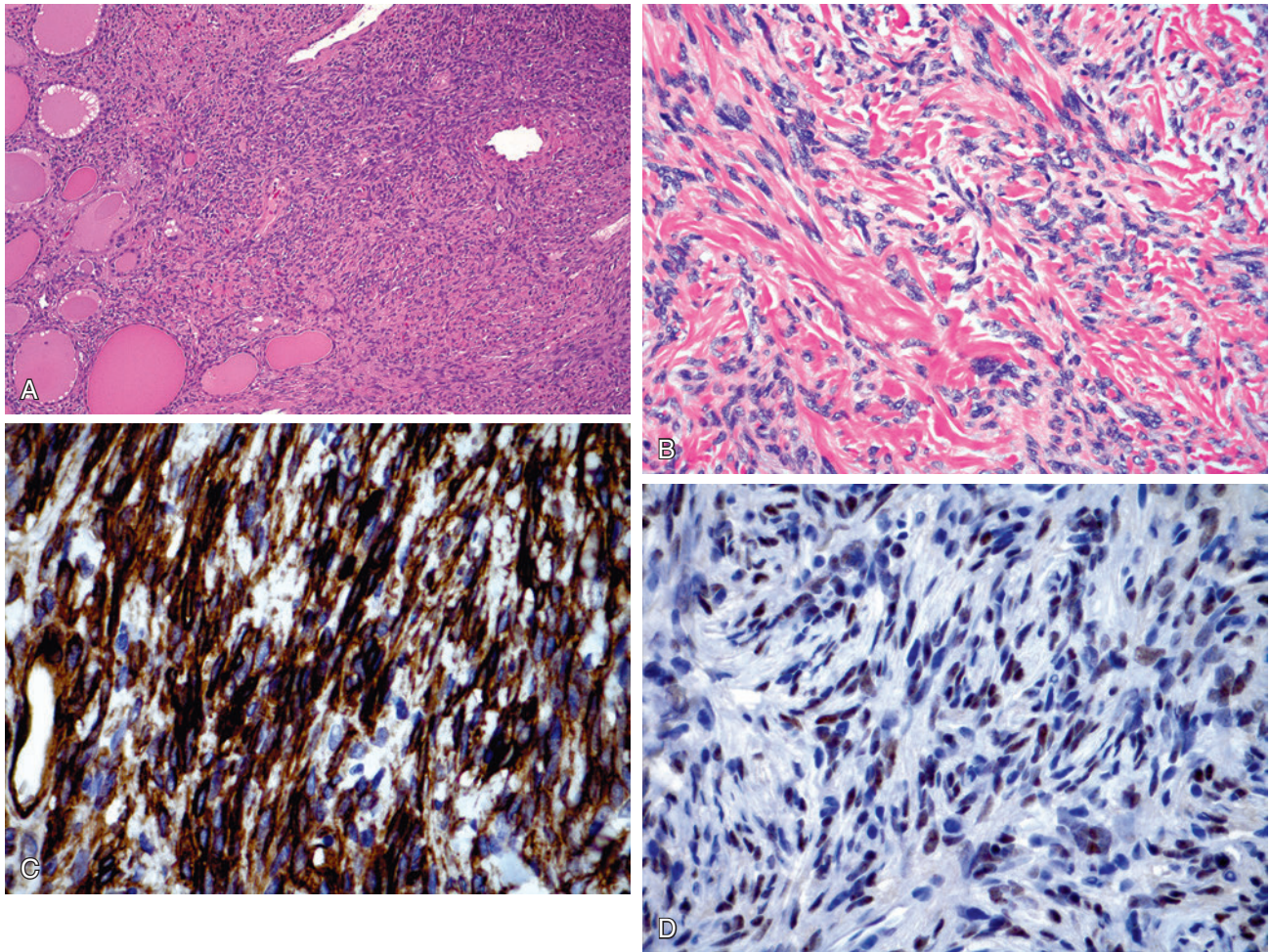


Fig. 28-111. Solitary fibrous tumor of the thyroid gland.

A, Spindle cell proliferation merging with and enveloping thyroid follicles (*left*). **B**, Bland spindle- to stellate-shaped cells with indistinct cytoplasmic borders and stromal collagenization; lesional cells are immunoreactive for **(C)** CD34 and **(D)** STAT6 (nuclear).

- Absence of pleomorphism, mitotic activity, or necrosis
- Tend to have circumscribed borders but thyroid follicles may be entrapped at the periphery of the lesion
- Immunoreactivity present for:
 - CD34, STAT6 (nuclear), vimentin, bcl-2, and CD99
 - No immunoreactivity for cytokeratins, thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers, S100 protein, SMA, desmin, CD5, and CD117
- Majority are benign but rare thyroid malignant SFTs reported characterized by:
 - Marked nuclear pleomorphism and increased mitotic activity
 - Local recurrence and pulmonary metastasis
- Surgical excision usually curative for thyroid benign mesenchymal neoplasms

Malignant Mesenchymal Tumors (Sarcomas)

General Considerations

- Primary sarcomas of thyroid gland are rare:
 - Prior to invoking a diagnosis of a primary thyroid sarcoma, involvement of thyroid secondary to a primary cervical neck or mediastinal sarcoma, or metastasis to thyroid from a remote site should be excluded.
- Thyroid sarcomas may include:
 - Angiosarcoma (see below)
 - Malignant peripheral nerve sheath tumor (malignant schwannoma)
 - Leiomyosarcoma (Fig. 28-112)
 - Liposarcoma
 - Fibrosarcoma
 - Osteosarcoma

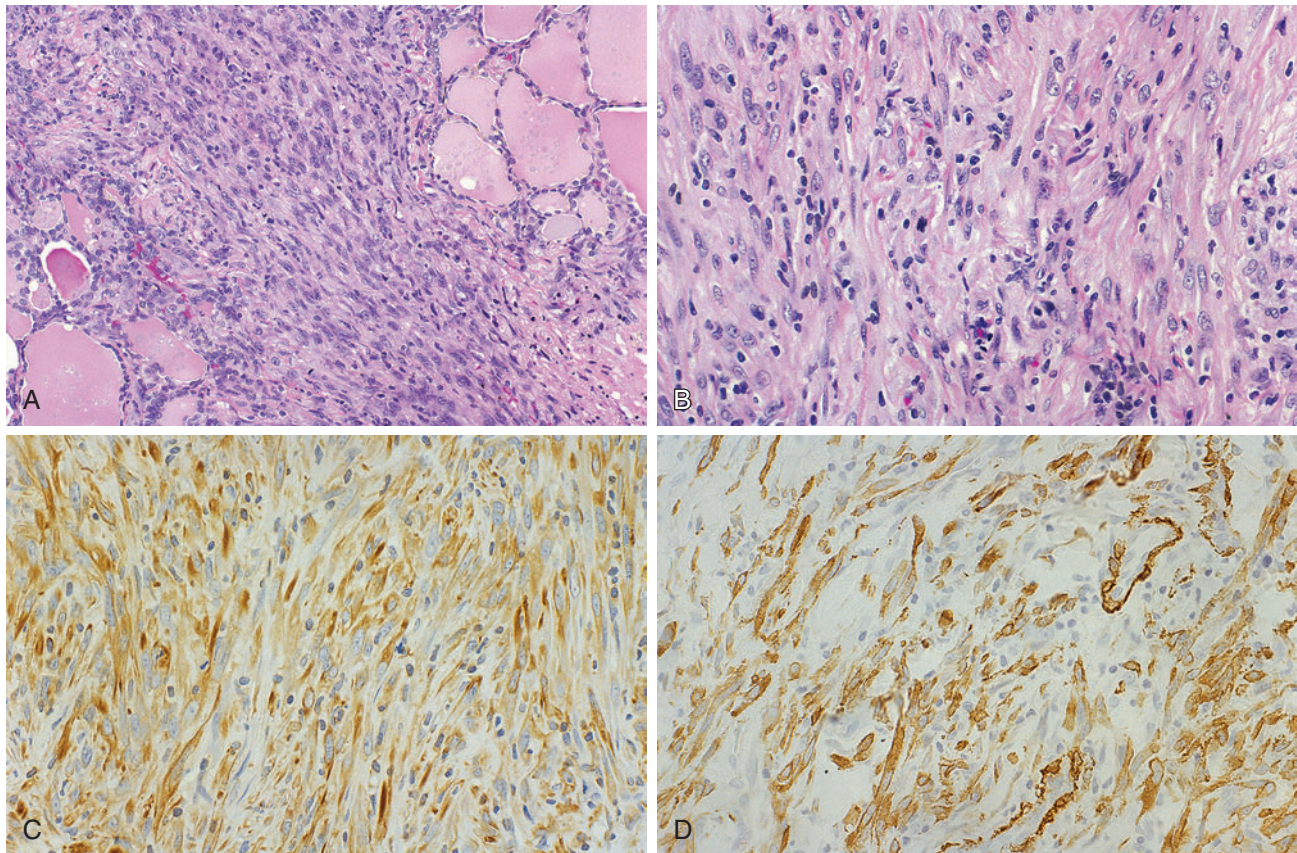


Fig. 28-112. Thyroid leiomyosarcoma.

A, The tumor is unencapsulated and infiltrative comprised of spindle-shaped cells with fascicular growth. **B**, Neoplastic cells are pleomorphic with identifiable mitotic figures. Immunohistochemical confirmation of a leiomyosarcoma includes reactivity for **(C)** vimentin and **(D)** smooth muscle actin.

- Extrasosseous Ewing sarcoma family of tumors
 - Chondrosarcoma
 - Follicular dendritic cell tumor sarcoma (see Section 3, Pharynx, for more discussion)
- Whether these tumors are true sarcomas rather than undifferentiated (anaplastic) carcinomas with sarcomatoid features remains controversial issue:
 - Academic argument as treatment and prognosis generally follow that of an undifferentiated (anaplastic) thyroid carcinoma

Angiosarcoma (Figs. 28-113 and 28-114)

Definition: Malignant neoplasm with endothelial differentiation.

Synonyms: Epithelioid angiosarcoma; malignant hemangioendothelioma

- Controversial diagnosis:
 - Contention of those who do not believe thyroid angiosarcoma exists is that these are undifferentiated (anaplastic) thyroid carcinoma (UTC) with angiosarcomatous features.
 - Specific designation as angiosarcoma or as UTC with angiosarcomatous features appears moot because these are high-grade malignant neoplasms similarly treated and sharing same poor prognosis and outcome.

Clinical

- Extremely rare
- Demographics and clinical presentation similar to those of undifferentiated (anaplastic) thyroid carcinoma:
 - Tendency to occur in older individuals
 - More common in women than in men

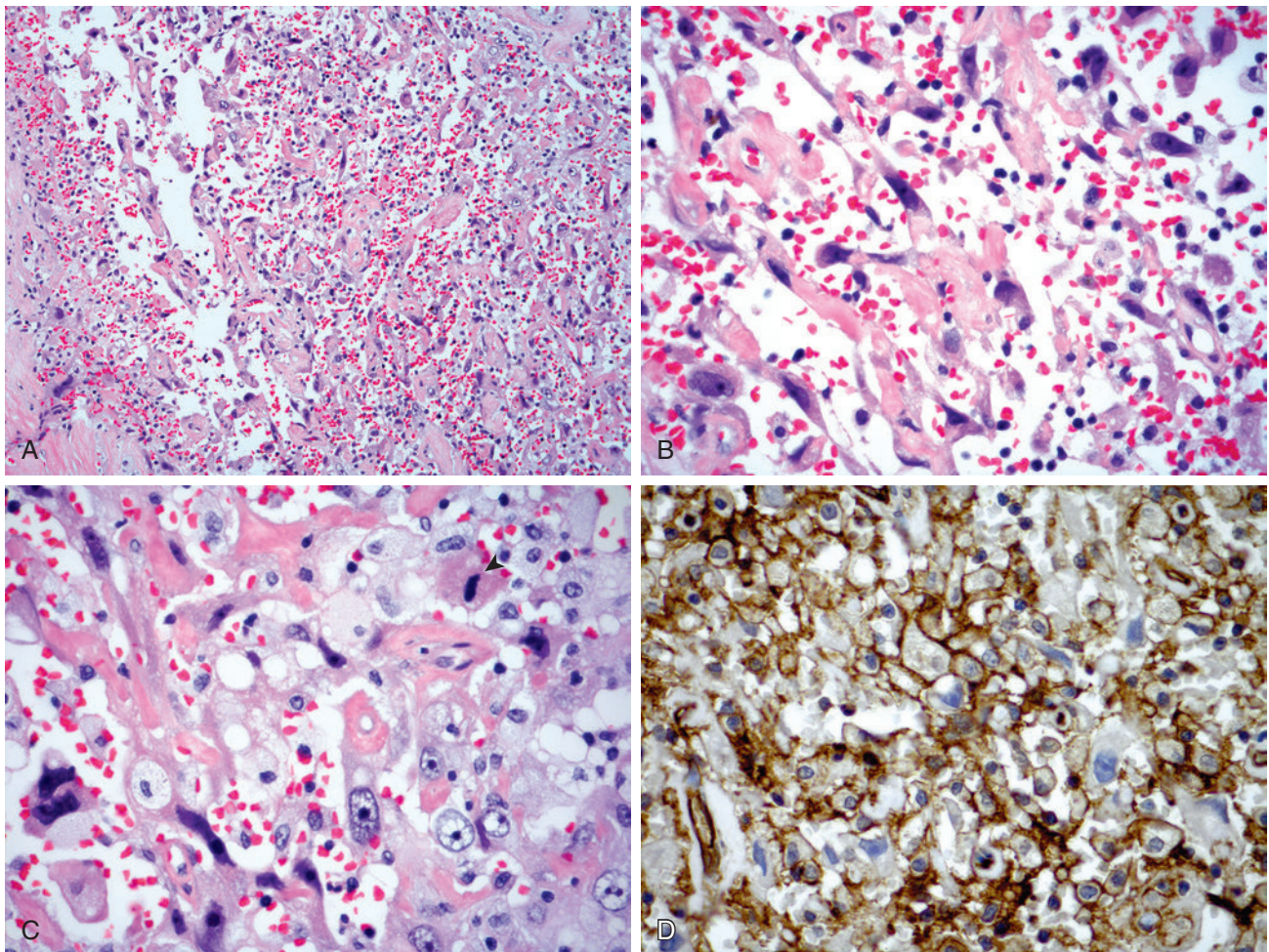


Fig. 28-113. Thyroid angiosarcoma.

A, The tumor is composed of dilated, ramifying, and intercommunicating vascular spaces lined by malignant cells. **B,** Malignant cells lining the vascular-appearing channel include pleomorphic spindle-shaped nuclei with variably enlarged eosinophilic nucleoli. **C,** Rounded (epithelioid)-appearing nuclei with associated foamy histiocytes and a mitotic figure (arrow). **D,** Lesional cells are CD31 immunoreactive.

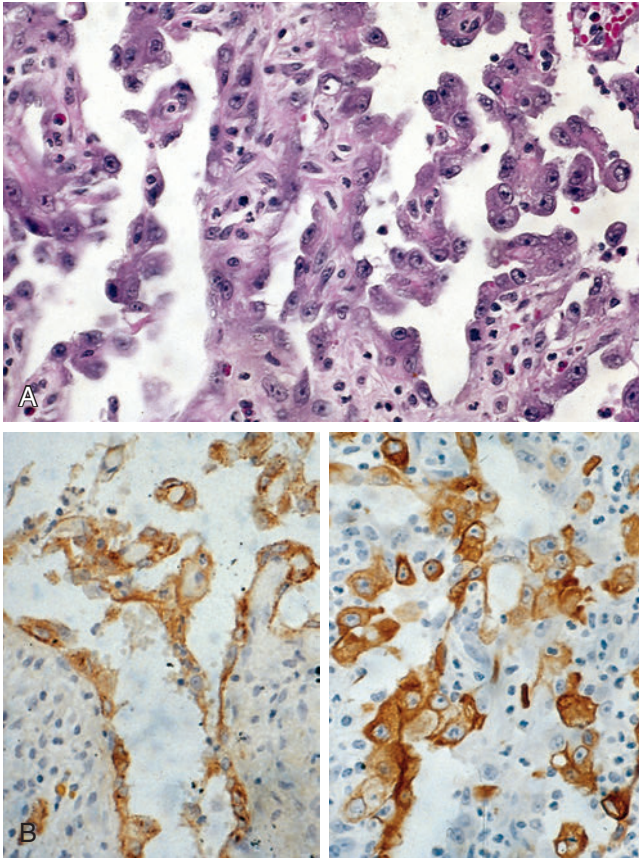


Fig. 28-114. Epithelioid angiosarcoma.

A, Malignant epithelioid neoplasm. **B**, Malignant cells are reactive for (left) cytokeratin (AE1/AE3) and (right) Factor VIII-related antigen. No immunoreactivity was present for thyroglobulin and TTF-1 (not shown).

- Clinical presentation:
 - Sudden enlargement of a long-standing goitrous thyroid with or without pain
 - May be associated with dyspnea and dysphagia
 - Chest pain and massive hemothorax may be present due to early metastatic tumor to the lung and pleura.
- Predilection for (but not exclusive to) mountainous or high-altitude regions of Europe (alpine regions):
 - Often iodine-deficient areas resulting in goitrous thyroids (endemic goiters)
 - Angiosarcomas often develop in long-standing goitrous glands.

Pathology

Fine-Needle Aspiration Biopsy

- Cellular smear composed of single cells and small clusters of neoplastic round to oval cells with eccentrically located nuclei, coarse nuclear chromatin, irregular nuclear membranes, single prominent

nucleoli vacuolated cytoplasm, and indistinct cell borders

- Features suggesting intracytoplasmic lumens may be identified.

Gross

- Typically large, invasive with associated necrosis and hemorrhage
 - Single nodule may be present.
 - Less commonly, may appear delineated or circumscribed nodular lesion

Histology

- Similar to high-grade (poorly differentiated) angiosarcomas of soft tissues characterized by:
 - Presence of dilated, ramifying, and anastomosing endothelial-lined vascular spaces
 - Presence of anastomosing vascular channels may only be focally present or obscured by solid cellular proliferation.
 - Endothelial cells are atypical or overtly malignant composed of spindle-shaped and epithelioid cells with large, pleomorphic, and vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm
 - Increased mitotic activity including atypical forms, hemorrhage, and necrosis consistently identified
 - Additional findings may include:
 - Vascular tufting
 - Intracytoplasmic vacuoles representing early attempts at lumina formation
 - Erythrocytes may or may not be present within these vacuoles
 - Multinucleated giant cells and bizarre cells can be seen.
- Invasive growth including destruction of thyroid follicular epithelium, as well as extrathyroidal extension often present
- Immunohistochemistry:
 - Endothelial markers including:
 - CD31, CD34, Factor VIII-related protein, Fli1 (nuclear), ERG (nuclear)
 - Vimentin positive
 - Cytokeratin usually negative:
 - May be positive (diffuse and strong intensity) especially in epithelioid angiosarcoma
 - Thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers negative
- Electron microscopy:
 - Weibel-Palade bodies appearing as intracytoplasmic rod-shaped membrane-bound structures are specific for endothelial cells representing the storage site for Factor VIII-related protein; however, these are best identified in well-differentiated malignant vascular tumors and are very difficult

to identify in poorly differentiated vascular tumors.

- Other ultrastructural features that can be seen in endothelial neoplasms but that are not specific for endothelial neoplasms include pinocytic vesicles, basal lamina, cytoplasmic filaments, and intracytoplasmic vacuoles.

Differential Diagnosis

- Undifferentiated (anaplastic) thyroid carcinoma with angiosarcomatous features
- Carcinosarcoma or true malignant mixed tumors of thyroid gland:
 - Most probably represent undifferentiated (anaplastic) thyroid carcinoma with sarcomatoid differentiation rather than differentiation of a malignant tumor along epithelial and mesenchymal cell lines
- Post-fine-needle aspiration biopsy-induced changes in central portions of adenomatoid nodule that may include:
 - Dilated vascular channels with thrombosis and organization including interanastomosing channels
 - Papillary endothelial hyperplasia:
 - May occur spontaneously in association with other lesions (e.g., adenomatoid nodules) in absence of prior traumatic event such as a fine-needle aspiration biopsy

Treatment and Prognosis

- Combination surgery, radiotherapy, and chemotherapy
- Prognosis is dismal with median survival of less than 4 months from diagnosis.
- Highly aggressive with widespread local invasive growth and early dissemination to lungs, pleura, lymph nodes, bone, and adrenal glands
- Small tumors confined to thyroid gland without extrathyroidal extension may be associated with a more favorable prognosis.

Teratoma

Definition: True neoplasm composed of tissue types representing all three germ layers, including ectoderm, endoderm, and mesoderm, occurring in areas in which these tissues are not natively identified.

- Classification predicated on admixture of cell types and includes:
 - Mature teratoma
 - Immature teratoma
 - Malignant teratoma
- Histologic grading:
 - Determined on basis of extent of neuroectodermal tissue and includes:

- Grade 0 = completely mature (benign):
 - Immature tissue and/or neuroectodermal tissue absent
- Grade 1 = predominantly mature (benign):
 - Immature neuroectodermal tissue limited to rare foci not >1 low-power field per slide
- Grade 2 = predominantly mature (benign):
 - Immature neuroectodermal tissue common not >3 low-power field per slide
- Grade 3 = mostly immature (malignant):
 - Immature neuroectodermal tissue prominent >4 low-power field per slide
- Most common locations in head and neck include:
 - Neck and nasopharynx
 - Other less commonly involved sites include oral cavity (tonsil, tongue, palate), sinonasal cavity, external and middle ear and temporal bone, mandible and maxilla, and thyroid gland.

Thyroid Teratoma (Figs. 28-115 through 28-117)

- For teratoma of cervical neck to be considered of thyroid origin:
 - It must occupy a portion of the thyroid.
 - It must be in direct continuity or close anatomic relationship with the thyroid.
 - Is accompanied by total absence of thyroid gland
- Little clinical import ascribed to thyroid involvement by cervical teratoma in both adults and children; similarly, little clinical import relative to histogenesis (thyroid vs. nonthyroid) in those cervical teratomas that have anatomic relationship with thyroid gland

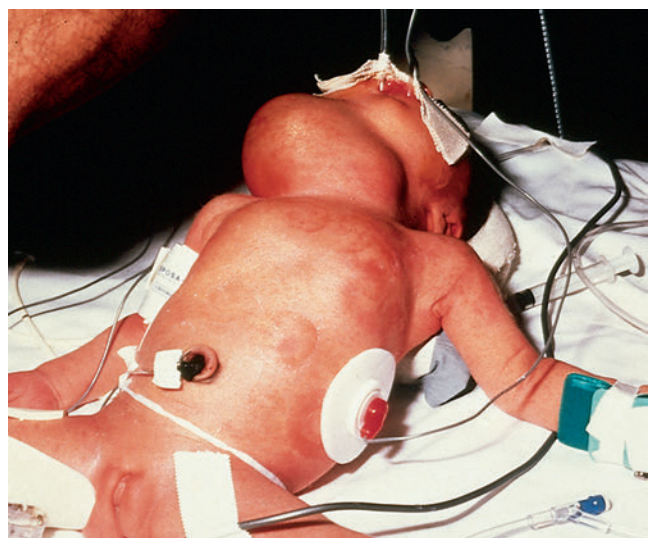


Fig. 28-115. Cervical/thyroid teratoma.

Infant with a massive midline and lateral teratoma that involved the thyroid gland.

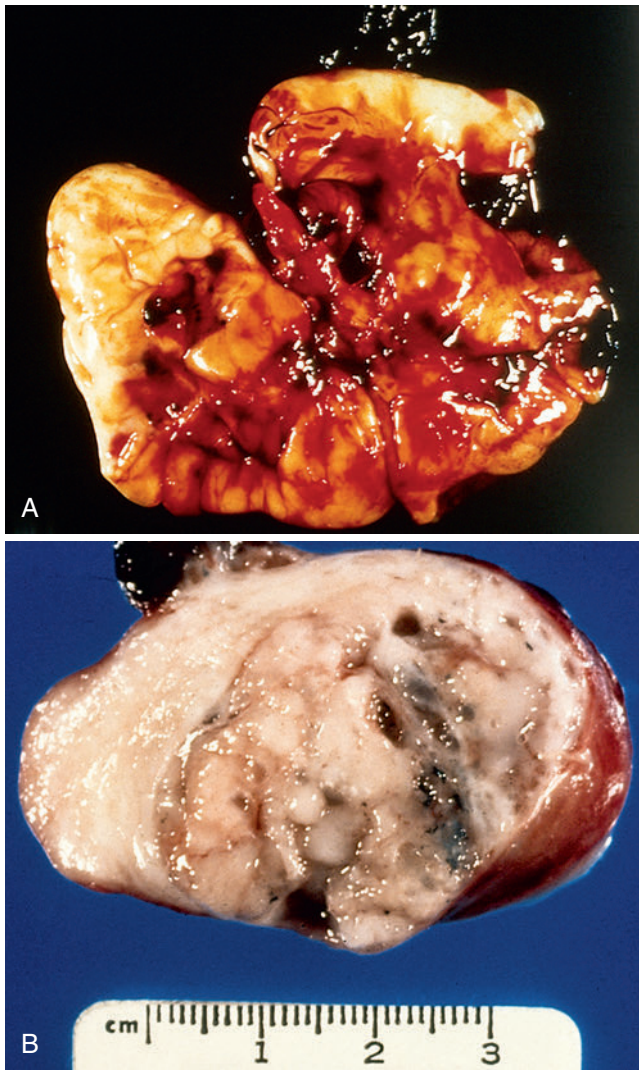


Fig. 28-116. Cervical/thyroid teratoma.

Gross appearance of cervical/thyroid teratomas may include **(A)** solid and cystic with associated hemorrhage and **(B)** predominantly solid and focally cystic with a white appearance.

- Most thyroid teratomas occur in neonates and infants (pediatric teratomas).

Pediatric Thyroid Teratomas

- Most occur in stillborns, neonates, or infants <1 year old
- Present as large midline or lateral neck mass with or without airway compression and compromise
- Large, often measuring >10 cm in greatest dimension:
 - On cut section are solid to cystic in appearance
- Histologically, admixture of all three germ layers, including:

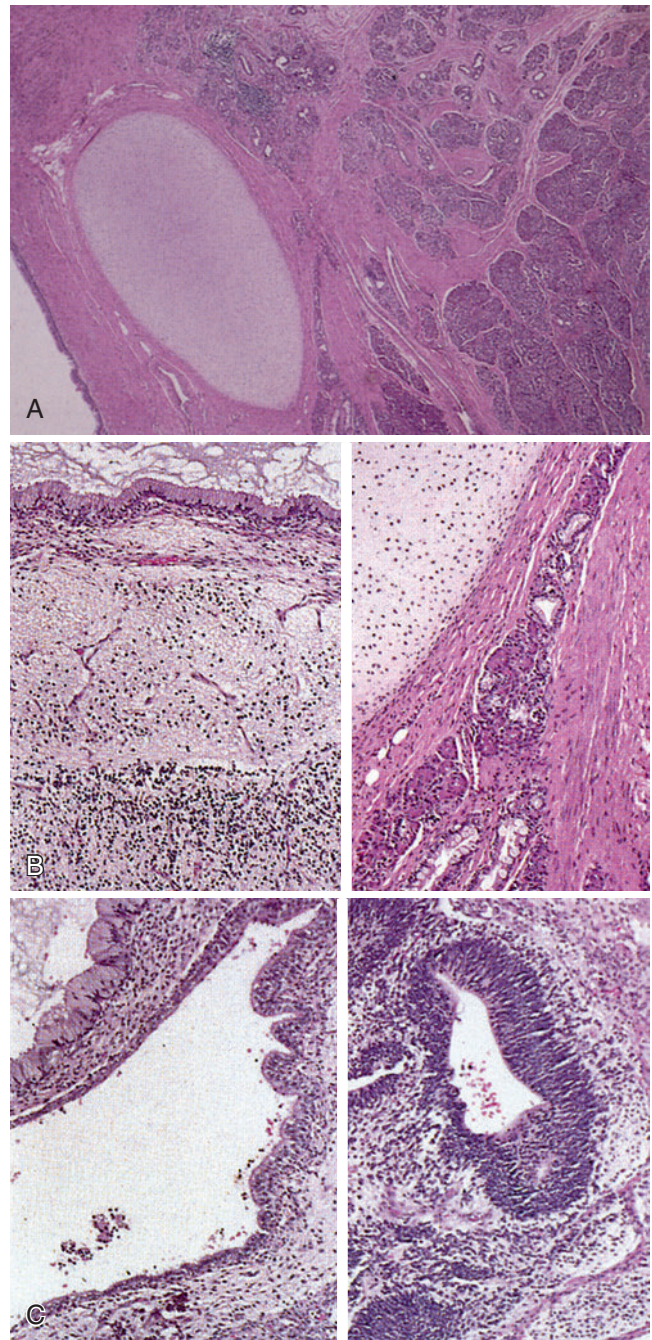


Fig. 28-117. Teratoma.

A, Intrathyroidal teratoma consisting of a respiratory epithelium (*lower left*), pancreatic tissue (*right*), and mature cartilage (*left of center*). **B**, *Left*, Intestinal-type mucin-producing epithelium (*top*) overlying neuroectodermal tissue including neurofibrillary matrix; *right*, mature cartilage and seromucous glands. **C**, Other example showing (*left*) ciliated respiratory and mucin-producing epithelium (*upper left*) and (*right*) primitive neuroectodermal tissue.

- Epithelial:
 - Keratinizing squamous, columnar, ciliated respiratory, or gastrointestinal-type epithelium, cutaneous adnexae, minor salivary glands
 - Thyroid follicular epithelium may be present (and should be confirmed as arising in thyroid) but may be extremely limited or absent.
- Neuroectodermal and central nervous system tissue that may include:
 - Mature glial tissue, neurofibrillary matrix, neural rosettes, choroid plexus, and/or pigmented retinal anlage
 - Immature neuroblastomal elements:
 - Diffuse or sheet-like growth
 - Small cells with hyperchromatic nuclei, increased nuclear-to-cytoplasmic ratio, increased mitotic activity, necrosis
 - Neural-type rosettes
 - Immunoreactivity may include NSE, GFAP, S100 protein, neurofilament protein
- Mesenchymal:
 - Cartilage, bone, fat, and muscle (smooth and skeletal)
- Surgical resection is preferred treatment.
- Most are benign with excellent prognosis:
 - Rarely, malignant teratomas occur in pediatric ages.
 - Thyroidectomy revealed no associated teratoma or other germ cell tumor.
 - Numerous bilateral pulmonary nodules present but no evidence of mediastinal mass
 - Favorable response to bleomycin, etoposide, and cisplatin chemotherapy
- Mixed germ cell tumor, including:
 - Embryonal carcinoma and choriocarcinoma
 - Occurred in 35-year-old man
 - Associated with high serum concentration of beta-HCG
 - Orchiectomy negative for tumor.

THYROID LESIONS WITH THYMIC DIFFERENTIATION

Spindle Epithelial Tumor with Thymus-Like Differentiation (SETTLE) (Figs. 28-118 and 28-119)

Definition: Low-grade malignant thyroid tumor characterized by lobulated architecture and presence of spindle-shaped epithelial cells and glandular-appearing structures.

Synonyms: Intrathyroid spindle cell tumor with mucous cysts; thyroid thymoma

Clinical

- Rare thyroid tumor
- Slight male predominance; may occur over a wide age range (first to eighth decades) but tends to occur most often in first and second decades of life with a mean age at diagnosis of 13½ years
- Clinical presentation usually that of asymptomatic (painless) thyroid or neck mass:
 - Less often patients may present with tenderness, tracheal compression, enlarging neck mass, or diffuse enlargement of thyroid gland.
 - Infrequently, regional nodal metastasis may be identified at presentation.
- Patients are euthyroid.
- Radiologic imaging:
 - “Cold” thyroid nodule
- Histogenesis:
 - Possible origin from remnants of branchial pouch
 - No definitive evidence to support thymic derivation

Pathology

Gross

- Vary from encapsulated to partially encapsulated to circumscribed to infiltrative
- Solid, tan-white, and firm, measuring from 1.8 to 5 cm in greatest dimension

Adult Thyroid Teratomas

- More common in women than in men; occurs over a wide age range, including children and young adults
- Often malignant akin to immature teratomas of gonads
- Histology:
 - Usually grade 3 (malignant):
 - Prominent neuroectodermal component (immature neuroblastomal elements)
 - May include yolk sac or embryonal components
- Treatment includes surgery, radiation, and chemotherapy.
- Most are malignant with aggressive behavior:
 - Invasive growth into adjacent structures
 - Tend to recur and metastasize (regional lymph nodes, distant)
 - Usually fatal over short time periods irrespective of attempts at controlling disease, including total thyroidectomy, radiation, chemotherapy
- Rare cases of primary thyroid extragonadal:
 - Yolk sac tumor:
 - Occurred in 10-year-old girl
 - Associated with marked elevation of serum α -fetoprotein levels

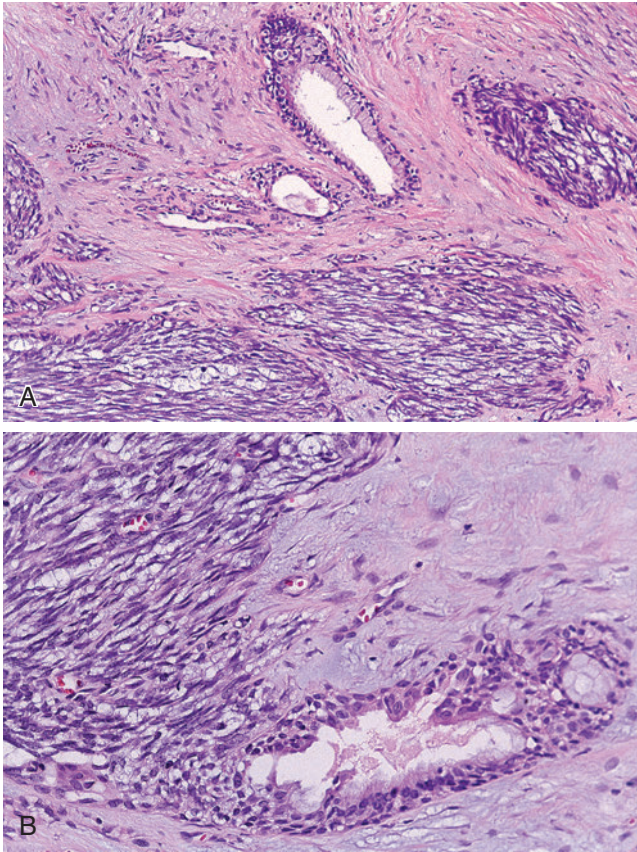


Fig. 28-118. SETTLE.

Spindle cell tumor with thymus-like differentiation (SETTLE). **A**, Sclerotic stroma divides tumor into incomplete lobules composed of a biphasic tumor, including spindle-shaped cells with reticulated pattern and glandular structures, the latter including mucinous cells. **B**, Spindle-shaped cells are characterized elongated hyperchromatic nuclei with little cytoplasm and minimal nuclear pleomorphism merging with a glandular structure lined by respiratory and mucin-producing epithelium.

- Vague whorled appearance and cysts may be present.

Histology

- Cellular neoplasm composed of spindle-shaped cells blending imperceptibly with epithelial structures (biphasic pattern):
 - Presence of sclerotic stroma dividing tumor into incomplete lobules
 - Spindled zones blend imperceptibly into areas showing epithelial differentiation.
 - Spindle-shaped cells:
 - Fascicular, reticular, and hyalinized growth patterns
 - Sharp interface with stroma
 - Elongated nuclei with delicate chromatin and inconspicuous nucleoli and little cytoplasm

- Minimal pleomorphism and mitotic activity
- Epithelial structures:
 - Appear in form of tubules, papillae, cords, glomeruloid glandular structures, Sertoli-like tubules, small glands, epithelial lined cystic spaces, and small islands
 - Lined by cuboidal to columnar cells with round or plump-appearing cells with round to oval, bland nuclei and moderate amount of cytoplasm
 - Branching or cystic glands lined by mucinous or respiratory epithelium containing abundant intracytoplasmic mucin may focally be present.
 - Squamous metaplasia may rarely be present.
- Entrapped thyroid follicles can be seen.
- An inflammatory cell component is typically scanty.
- Other uncommon findings:
 - Monophasic variant exclusively composed of either spindle-shaped cells or glandular structures may occasionally occur.
 - Mitoses and necrosis are typically absent, but an occasional case may have increased mitotic activity and necrosis.
 - Invasive growth including vascular space invasion can be identified.
- Histochemistry:
 - Mucin-positive material can be found along the luminal surface of the glandular spaces.
- Immunohistochemistry (all lesional cells):
 - Cytokeratins:
 - Extensive expression of AE1/AE3, CAM 5.2
 - Widespread CK7 expression
 - Limited expression of low-molecular-weight cytokeratins and EMA
 - CK20 negative
 - Vimentin, CD99, bcl-2, CD117, and INI-1 seen in majority of cases
 - p63 (nuclear) appears to be restricted to spindle-shaped cells, whereas glandular structures are nonreactive
 - TLE1 expression in rare cases
 - Thyroglobulin, TTF-1, PAX8, calcitonin, CEA, synaptophysin, chromogranin, S100 protein, and CD5 negative
- Electron microscopy:
 - Spindle cells show tonofilaments, desmosomes, and basal lamina.
- Cytogenetics and molecular genetics:
 - Absence of *SYT/SSX* translocation

Differential Diagnosis

- Synovial sarcoma:
 - Presence of t(X;18) translocation with *SYT/SSX* gene fusion may assist in the differential diagnosis from SETTLE.

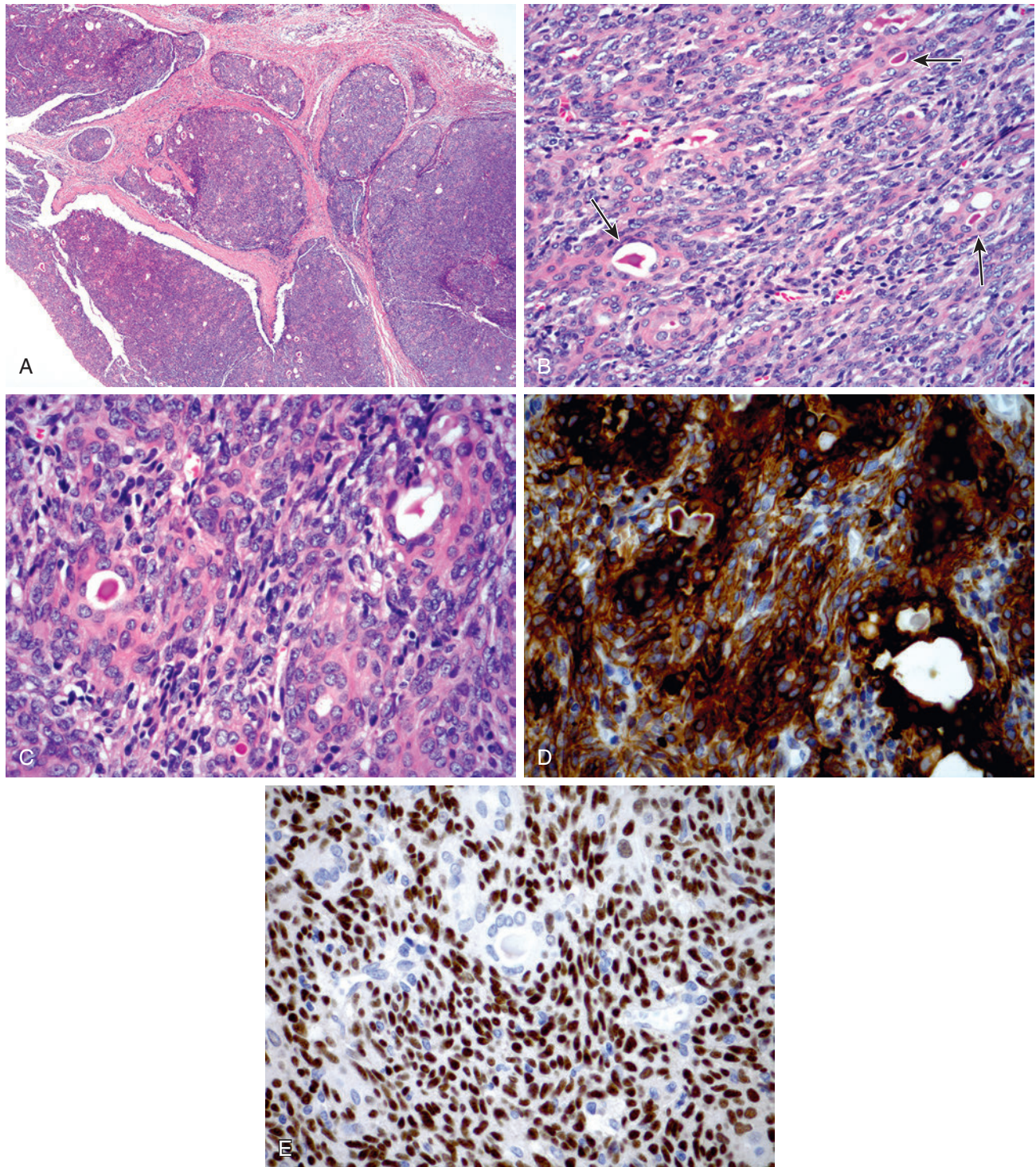


Fig. 28-119. SETTLE.

Another example of spindle cell tumor with thymus-like differentiation (SETTLE). **A**, Variably sized cellular nodules separated by sclerotic stroma. **B**, Biphasic tumor including spindle-shaped cells with fascicular growth pattern blending imperceptibly with glandular structures (*arrows*). **C**, The spindle-shaped cells include elongated nuclei with hyperchromatic to vesicular nuclei and minimal nuclear pleomorphism merging while the glandular structures form tubules and are lined by cuboidal to plump-appearing cells with round to oval, bland nuclei. **D**, Both glandular structures and spindle cells are cytokeratin (CAM 5.2) reactive. **E**, p63 (nuclear) expression preferentially marks spindle-shaped cells but not glandular structures.

- Ectopic thymoma:
 - Only rarely occurs in thyroid gland
 - Strong female predilection; most occur in middle age
 - Noninvasive
 - Histologically identical to mediastinal thymoma:
 - Encapsulated to circumscribed with jigsaw puzzle–like configuration
 - Admixture of epithelial cells (polygonal to spindle-shaped) and small lymphocytes
 - Prominent T-cell-rich infiltrate (TdT-positive)
- Thyroid (immature) teratoma
- Undifferentiated (anaplastic) thyroid carcinoma
- Spindle cell (sarcomatoid) squamous cell carcinoma

Treatment and Prognosis

- Surgical excision is preferred treatment:
 - May include lobectomy, subtotal thyroidectomy, or total thyroidectomy
- Variable and unpredictable behavior that includes:
 - Benign course
 - Protracted clinical course with development of delayed distant metastasis to (in descending order):
 - Lungs, cervical lymph nodes, mediastinum, kidney, and soft tissues
 - Overall metastatic rate of 71% with more than 5 years of follow-up
 - Despite metastatic disease clinical course may be protracted prior to death due to disease
 - 90% 5-year survival rate

Carcinoma Showing Thymus-Like Differentiation (CASTLE) (Fig. 28-120)

Definition: Thyroid gland carcinoma with features of thymic epithelial tumors.

Synonyms: Intrathyroidal epithelial thymoma; primary thyroid thymoma; lymphoepithelioma of thyroid gland; lymphoepithelioma-like carcinoma of thyroid

Clinical

- Rare tumor
- More common in women than in men; occurs over a wide age range with a mean age of 48½ years at diagnosis
- Clinical presentation usually that of asymptomatic thyroid or neck mass:
 - Most occur in thyroid gland (lower poles)
 - May arise in perithyroidal soft tissues
 - May be invasive at presentation with extension into adjacent soft tissue structures or fixation to or invasion of the trachea, resulting in symptoms related to tracheal compression or even hoarseness

- Patients are euthyroid.
- Radiologic imaging:
 - “Cold” thyroid nodule
- Histogenesis:
 - Probably originates from intrathyroidal thymic remnants
 - Origin from solid cell nests suggested may arise from branchial pouch remnants, the thyroid SCNs.

Pathology

Gross

- Vary from encapsulated to circumscribed to invasive
- Firm to hard in consistency, gray to pink, measuring from 3.5 to 5.8 cm in greatest dimension

Histology

- Architecture resemblance to lobulated appearance seen in thymic tumors (thymoma or thymic carcinoma), including:
 - Solid nests or lobules with an expansile or infiltrative growth into thyroid tissue in broad fronts
 - Dense fibrous bands and/or delicate fibrovascular stroma separate lobules and create lobulated or septated appearance
 - Limited to dense inflammatory component including lymphocytes and plasma cells identified
- Cellular composition includes epithelioid cells with large, pleomorphic nuclei with vesicular chromatin, small distinct nucleoli, and abundant eosinophilic cytoplasm with indistinct cell borders:
 - Squamous differentiation may be present, including:
 - Keratinization and intercellular bridges
 - Foci of abrupt keratinization resembling Hassall corpuscle may be present
 - Spindle-shaped tumor cells may be present.
- Mitotic activity can be seen:
 - 1 to 2 mitoses per 10 high-power fields
- Scanty to heavy inflammatory cell infiltrate may be seen in association with the epithelial cells.
- Ectopic thymic tissue may be identified in vicinity of tumor.
- Immunohistochemistry:
 - Tumor cells:
 - Cytokeratins and p63 positive
 - CD5 and CD117 almost always positive
 - Thyroglobulin, TTF-1, PAX8, calcitonin, and neuroendocrine markers negative:
 - Rarely, synaptophysin and chromogranin reactivity reported
 - EBV (by immunohistochemistry and in situ hybridization [EBER]) negative
 - p16 negative

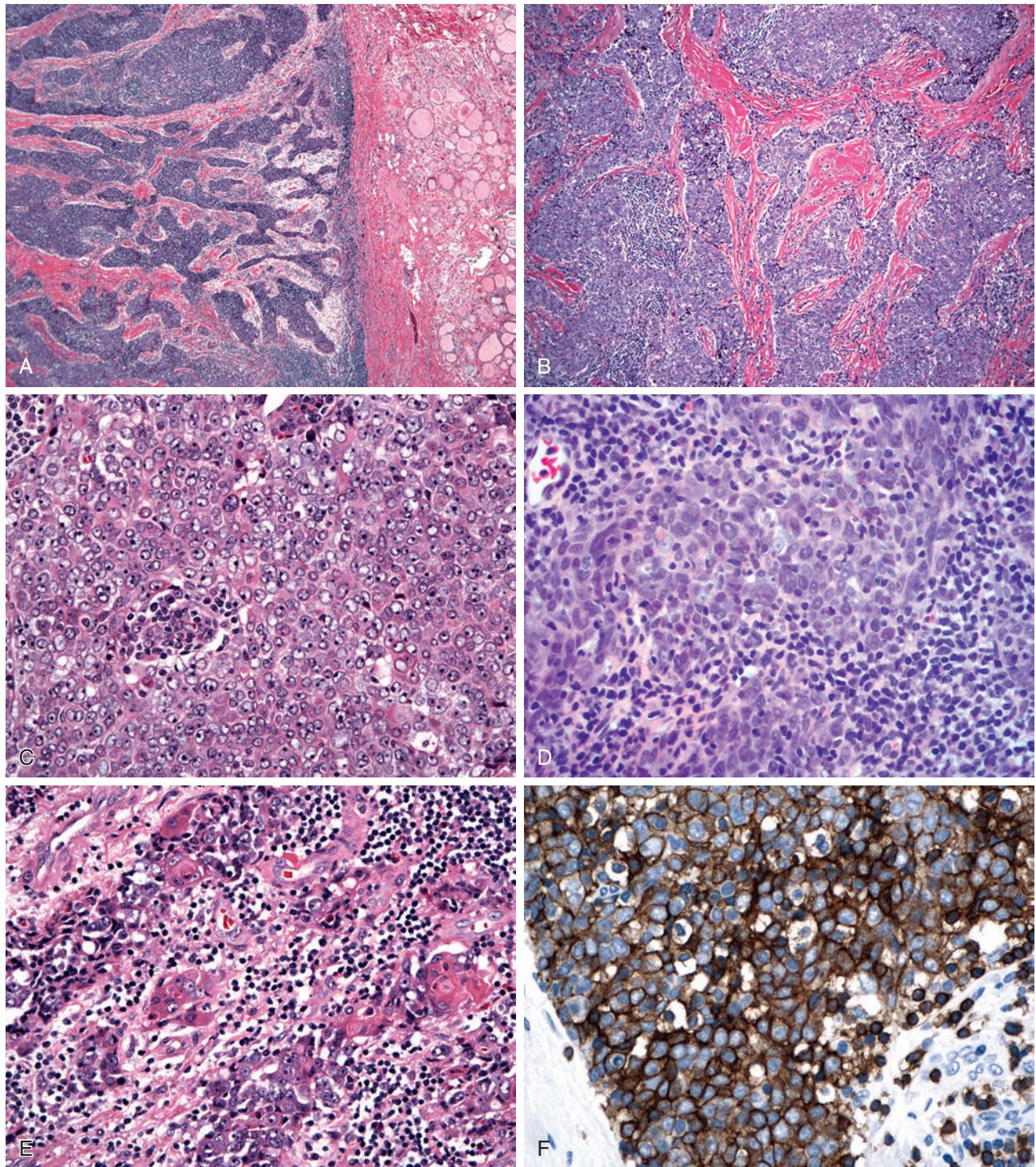
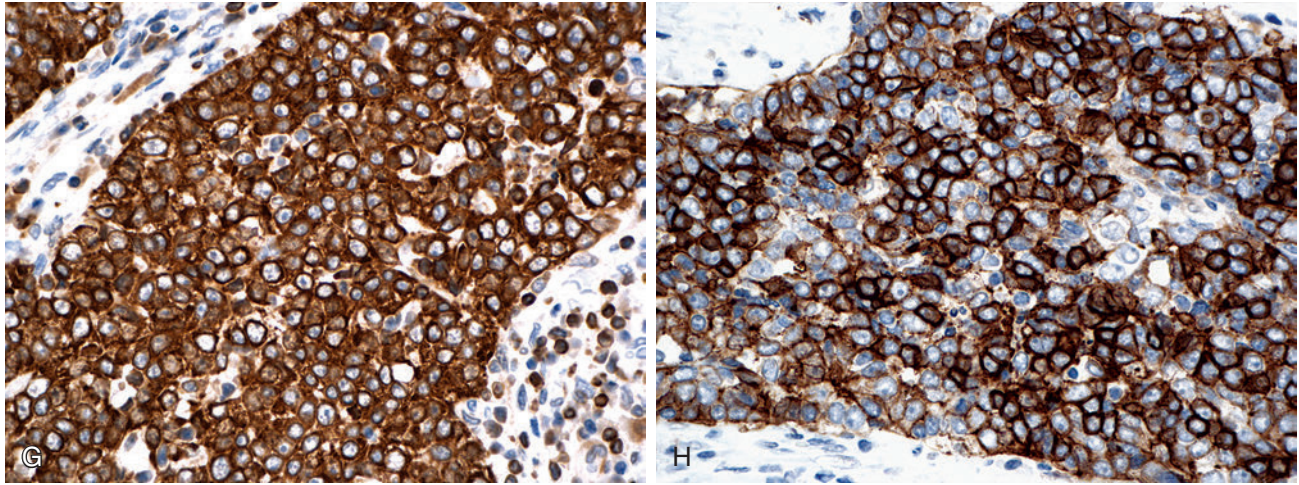


Fig. 28-120. Carcinoma showing thymus-like differentiation (CASTLE).

A, The tumor is demarcated from thyroid parenchyma (*right*) composed of cords and trabecular and solid nests separated by fibrous stroma. **B**, Cords/trabeculae separated by fibrous stroma. **C**, Syncytial-appearing cells with indistinct cell borders, vesicular nuclei, and prominent nucleoli; a sparse inflammatory cell infiltrate. **D**, In this example a more prominent associated inflammatory cell infiltrate is present, in part obscuring the neoplastic cells. **E**, Limited foci with squamous differentiation including associated keratinization may be seen. The neoplastic cells are immunoreactive for **(F)** CD5 (membranous),

**Fig. 28-120, cont'd**

(G) cytokeratin (AE1/AE3), and (H) CD117.

- Lymphocytes:
 - Express markers of both T- and B-cells
- Electron microscopy:
 - Desmosomes, tonofilaments, and elongated cell processes can be seen.

Differential Diagnosis

- Undifferentiated (anaplastic) thyroid carcinoma:
 - PAX8 positive
 - CD5, bcl-2, and CD117 negative
- Metastatic undifferentiated carcinoma (e.g., from Waldeyer tonsillar ring or oropharynx):
 - Nasopharyngeal undifferentiated carcinoma: EBER positive
 - Oropharyngeal undifferentiated carcinoma: p16 positive
 - CD5, bcl-2, and CD117 negative.
- Squamous cell carcinoma
- Follicular dendritic cell sarcoma

Treatment and Prognosis

- Surgical resection with or without radiotherapy is preferred treatment:
 - Lobectomy or subtotal thyroidectomy
 - Neck dissection indicated in the presence of clinically and/or radiographically suspicious or positive cervical lymph node metastasis
- Postoperative radiotherapy is recommended owing to:
 - Considered to be radiosensitive tumors
 - Prognosis generally good
 - Pursue an indolent course.
 - Local recurrence is common.
 - Local recurrence and regional nodal metastasis may occur years following resection.

- Often successfully controlled by surgery or radiotherapy
- 5- and 10-year cause-specific survival rates 90% and 82%, respectively
- Nodal metastasis and tumor extension predict worse prognosis.
- Death attributable to aggressive course with massive local disease or lung metastasis may rarely occur.

SECONDARY OR METASTATIC TUMORS TO THE THYROID (Figs. 28-121 through 28-123 and Box 28-8)

- Thyroid gland may be secondarily involved by malignant tumors originating from other sites:
 - May take the form of direct invasion from a malignant neoplasm of a nearby site or via hematogenous spread from a distant primary malignant tumor
- Among tumors that invade directly into thyroid from an adjacent organ are mucosal tumors of the larynx, pharynx, trachea, and esophagus.
 - By far, squamous cell carcinoma (or one of its histologic variants) is most common type of malignant tumor that invades directly into the thyroid gland.
- Metastatic tumors to thyroid from distant primary site can occur from virtually every organ system (Table 28-13):
 - Most frequent tumors to metastasize to thyroid gland include (in descending order):
 - Renal cell carcinoma (34%)
 - Lung carcinoma (15%)
 - Breast carcinoma (14%)

- Gastrointestinal carcinoma (14%)
- Malignant melanoma (5%)
- Others
- Metastatic tumors to thyroid gland may occur from an occult primary source and simulate appearance of a primary thyroid tumor.

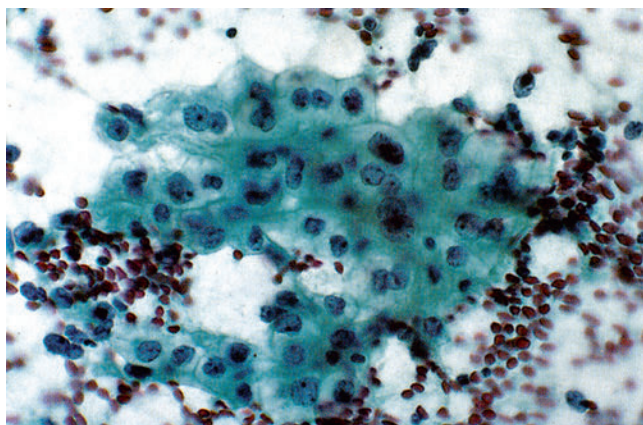


Fig. 28-121. Metastatic renal cell carcinoma, FNAB.

Metastatic renal cell carcinoma to thyroid, fine-needle aspiration biopsy (FNAB) is characterized by cells with clear-appearing cytoplasm, distinct cell borders, vesicular nuclei, and inconspicuous to small nucleoli (Papanicolaou). These features could be those of a primary thyroid clear cell neoplasm. In the presence of such findings clinical history of a renal cell carcinoma would certainly support a diagnosis of a metastasis, but if material is available immunohistochemical staining would be invaluable in determining if the lesion is primary to the thyroid or possibly represents a metastasis.

- Thyroid involvement by metastatic deposits from distant sites most often seen in autopsy material
- Clinically detectable thyroid mass due to metastatic disease occurs in a minority of patients:
 - In patients with a clinically detectable mass, metastatic tumor to the thyroid presents as a rapidly growing thyroid mass of recent onset.
 - Patients are generally euthyroid, although some patients may present with disturbances in thyroid function (hyperthyroidism).
- Radiology:
 - May appear as a single hypofunctioning (“cold”) mass on thyroid scan and as solid and/or cystic lesions on ultrasonography

BOX 28-8 Secondary or Metastatic Tumors to the Thyroid Gland

Epithelial

- Kidney, breast, lung, gastrointestinal, hepatobiliary and pancreas, genitourinary tract, others

Melanocytic/Neuroendocrine

- Malignant melanoma
- Neuroendocrine carcinomas (especially small cell carcinoma)

Hematolymphoid

- Non-Hodgkin malignant lymphoma
- Hodgkin disease
- Leukemia
- Others

Mesenchymal

- Kaposi sarcoma
- Others

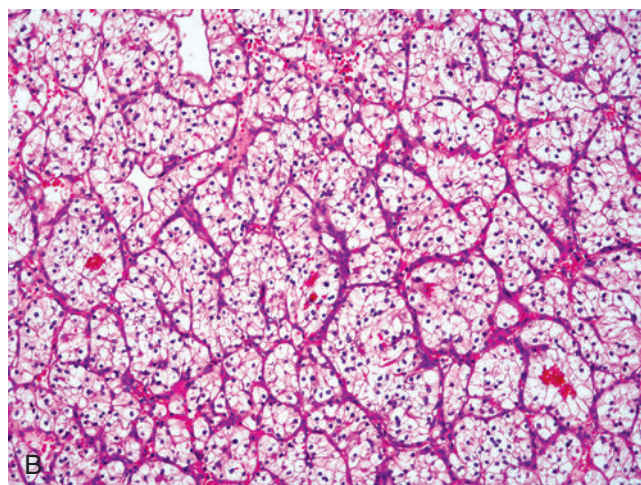
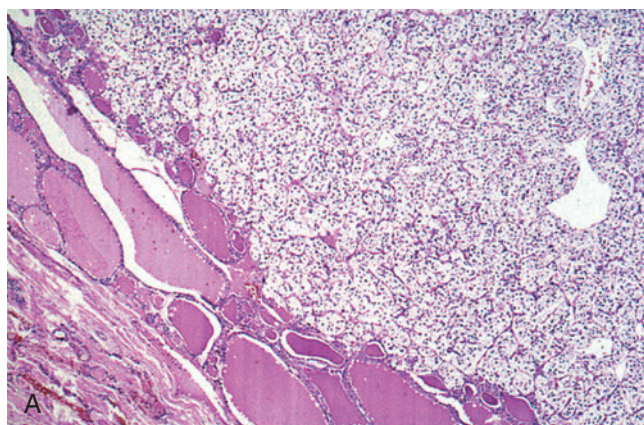


Fig. 28-122. Metastatic renal cell carcinoma to the thyroid gland.

A, A cellular proliferation composed of clear-appearing cells is located within adenomatoid nodule (*lower left*). **B**, Nests and lobules of tumor separated by fibrovascular stroma.

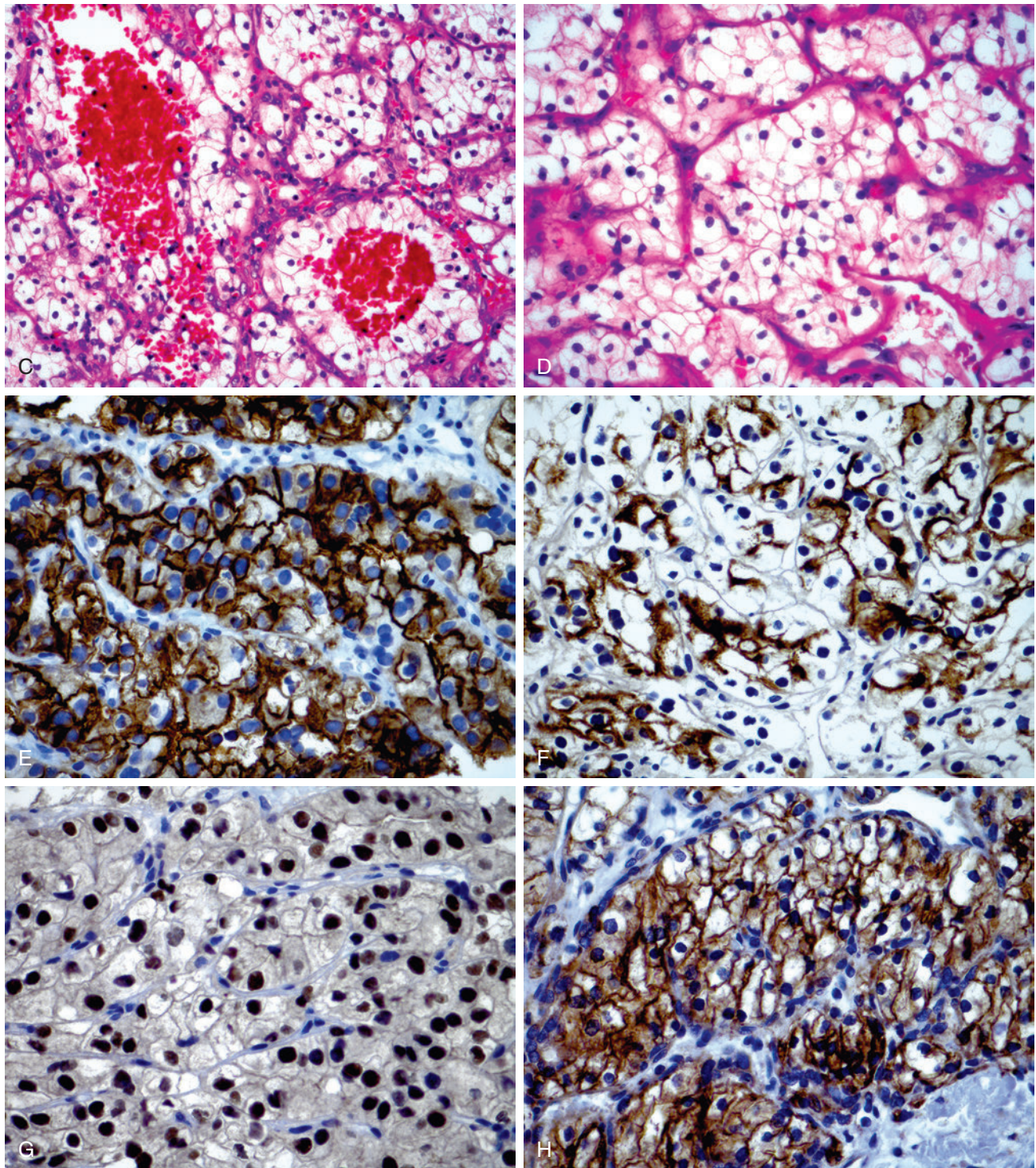


Fig. 28-122, cont'd

C, Instead of colloid, often the central aspect of a metastatic renal cell carcinoma contains red blood cells. This is a helpful but not diagnostic feature seen in renal cell carcinomas and generally not in primary thyroid tumors. **D**, Lesional cells are characterized by clear-appearing cytoplasm with small, round, hyperchromatic nuclei and sharply delineated cell borders. Immunohistochemical staining includes reactivity for **(E)** CD10 (membranous), **(F)** renal cell carcinoma (RCC) antibody, **(G)** PAX2 (nuclear), and **(H)** carbonic anhydrase IX.

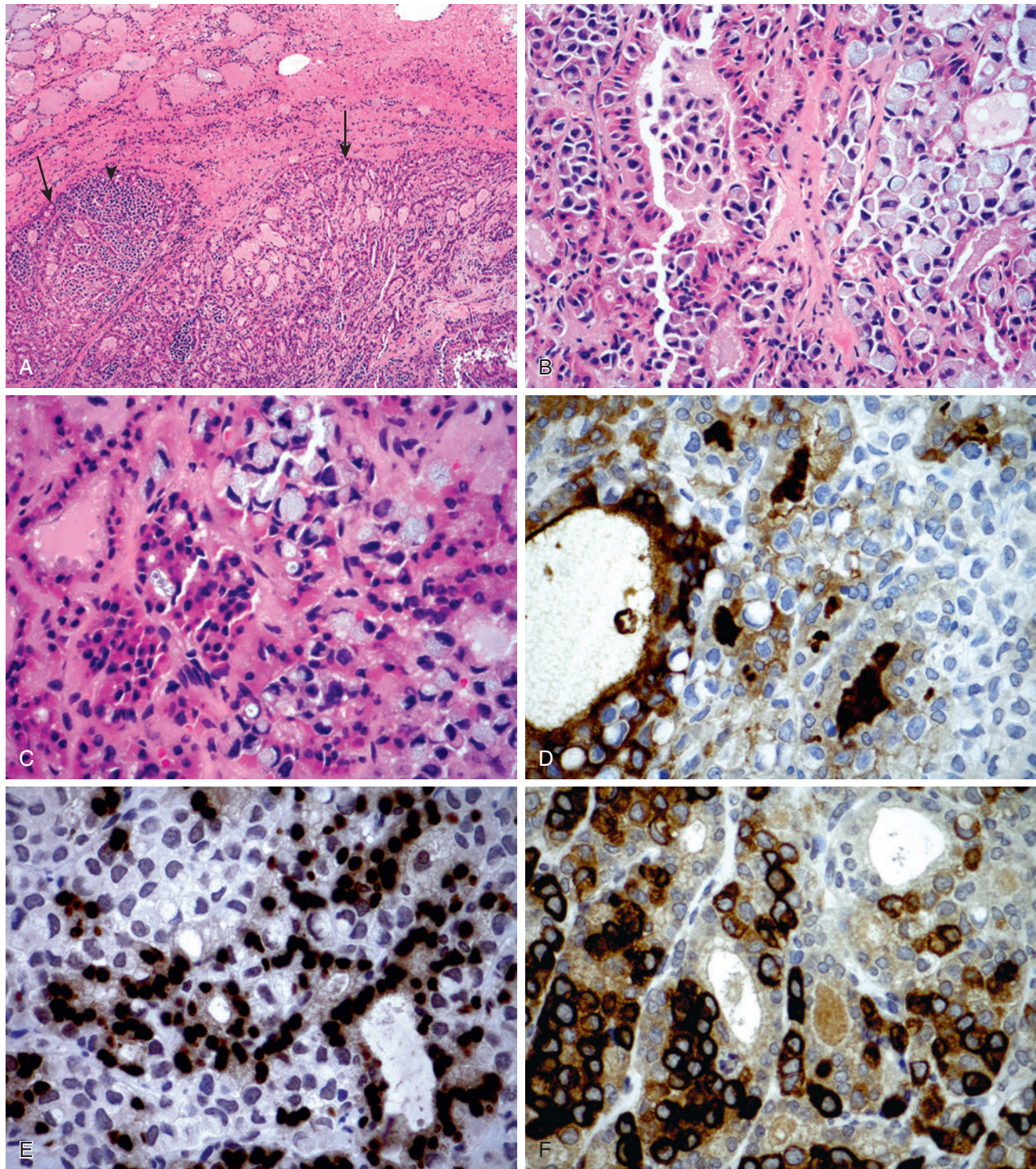


Fig. 28-123. Metastatic lobular carcinoma of the breast to the thyroid gland.

A, At low magnification a circumscribed thyroid lesion composed of follicles with oncocytic cells (*arrows*) as well as an apparent second cellular component composed of darker-appearing nuclei (*arrowhead*). **B** and **C**, Admixture of cells with brightly eosinophilic cytoplasm (follicular cells) as well as cells with signet ring cell appearance containing intraluminal mucinous-appearing material (metastatic lobular carcinoma). Immunohistochemical staining shows **(D)** thyroglobulin restricted to follicular epithelial cells, **(E)** TTF-1 restricted to follicular epithelial cells, and **(F)** mammaglobin restricted to metastatic lobular carcinoma. The findings are those of breast lobular carcinoma metastatic to a follicular adenoma, oncocytic type, a finding that may be referred to as “tumor within tumor” or “tumor-to-tumor” metastasis.

TABLE 28-13 Follicular Tumors with Clear Cells versus Metastatic Renal Cell Carcinoma

Features	Follicular Adenoma/Carcinoma with Clear Cells	Metastatic Renal Cell Carcinoma
Luminal secretion	Colloid; will be PAS positive	No colloid; red blood cells; pseudofollicles
Nested growth with fibrovascular stroma	Present	Present
Cytoplasm	Foamy appearing	Clear with distinct cell borders
Nuclear	Round; dispersed or coarse chromatin	Small, round, hyperchromatic
Glycogen (diastase-sensitive, PAS-positive)	Yes, but colloid will be diastase-resistant	Yes; intensely positive
IHC findings	Thyroglobulin, TTF-1, PAX8 positive CD10, RCC, CAIX, PAX2 negative	Thyroglobulin, TTF-1 negative CD10, RCC, CAIX, PAX2, PAX8 positive

CAIX, Carbonic anhydrase IX; IHC, immunohistochemistry; RCC, renal cell carcinoma antibody; TTF-1, thyroid transcription factor 1.

- Metastatic deposits may simulate appearance of primary thyroid lesion.
- Multiple lesions may be more indicative of metastatic tumor.
- Histology:
 - Metastasis often occurs to pre- or coexisting primary thyroid lesion:
 - Primary thyroid lesions may include:
 - Adenomatoid nodule
 - Thyroid neoplasm (follicular adenoma, follicular carcinoma, papillary carcinoma, medullary carcinoma)
 - Possible clue is presence of thyroid lesion with contrasting morphologies
 - May be referred to as “tumor within tumor” or “tumor-to-tumor” metastasis
 - Renal cell carcinoma may present most difficult metastatic tumor to differentiate from a primary clear cell neoplasm of the thyroid gland (Table 28-13):
- Immunohistochemical staining should allow for confirmation of metastatic tumor and differentiation from primary thyroid neoplasm:
 - Renal cell carcinoma:
 - CD10, renal cell carcinoma (RCC) antibody, PAX2, PAX8, carbonic anhydrase IX positive
 - Thyroglobulin, TTF-1, calcitonin, neuroendocrine markers negative
 - Lung adenocarcinoma:
 - Napsin A, TTF-1 positive
 - Thyroglobulin, TTF-1, calcitonin, neuroendocrine markers negative
 - Breast (mammary duct) carcinoma:
 - Mammaglobin, BRST2, e-cadherin positive
 - Thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers negative
 - Breast (lobular) carcinoma:
 - Mammaglobin, BRST2 positive
 - e-cadherin negative
 - Thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers negative
 - Gastrointestinal carcinoma:
 - CK20, CDX2 (nuclear), villin positive
 - Thyroglobulin, TTF-1, PAX8, calcitonin negative
 - Malignant melanoma:
 - S100 protein, HMB-45, melan-A, tyrosinase, MITF1, Sox10 (nuclear), and vimentin positive
 - Thyroglobulin, TTF-1, PAX8, calcitonin, neuroendocrine markers negative
- Treatment and prognosis:
 - Surgical resection of a metastatic tumor may inadvertently occur when metastatic tumor presents as a metastasis from an occult primary neoplasm.
 - Surgical resection is an acceptable treatment modality even for some tumors that are known to be metastatic to the thyroid (i.e., renal cell carcinoma).
 - External irradiation and chemotherapy may be used in treatment.
 - Despite attempts at controlling disease, prognosis in patients with metastatic tumor to thyroid is generally poor:
 - Death usually occurs within 2 years after identification of metastasis to thyroid
 - Cause of death usually due to widespread metastatic disease from respective primary tumor
 - Exceptionally prolonged survival following surgical resection (lobectomy or total thyroidectomy) may occur in renal cell carcinoma in which metastatic disease is limited to the thyroid gland.

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Unusual Epithelial Tumors of the Thyroid Gland

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Mesenchymal Tumors of the Thyroid Gland

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Thyroid Gland Post Fine Needle Aspiration Biopsy (FNAB)-Related Histologic Changes and Intraoperative Consultation

POST FINE NEEDLE ASPIRATION BIOPSY (FNAB)-RELATED MORPHOLOGIC CHANGES (Figs. 29-1 through 29-11)

- FNAB has tremendous utility as first interventional diagnostic procedure relative to a patient with a thyroid mass.
- Diagnostic sensitivity and specificity of FNAB of a thyroid mass is high.
- In many situations, surgical removal is treatment for a thyroid mass lesion irrespective of diagnosis by FNAB.
- FNAB may result in a number of histologic changes in resected thyroid gland that may create diagnostic challenges:
 - Histologic alterations caused by FNAB may lead to an erroneous diagnosis, such as changing interpretation from a benign process to a malignant one.
 - Pathologists must be aware of diversity of changes that may occur induced by FNAB.
- Post-FNAB histologic changes occur in numerous lesions, including adenomatoid nodules, hyperplastic lesions, follicular adenoma and its variants, follicular carcinoma and its variants, and papillary carcinoma and its variants.
- Oncocytic (oxyphilic) cells may be present in a wide variety of thyroid lesions (e.g., adenomatoid nodules, follicular adenoma, follicular carcinoma, papillary carcinoma, others) and are more prone to retrogressive changes secondary to a traumatic event such as FNAB owing to prominence of oxygen-sensitive mitochondria in these cells:
 - Any compromise to oxygen supply of oncocytic cells may result in retrogressive changes, including:
 - Cyst formation, papillary architecture, hemorrhage, infarction
- Based on type of reaction seen post-FNAB alterations may include acute or chronic changes:
 - Acute changes usually identified within 3 weeks from FNAB to surgical removal and may include:
 - Hemorrhage with hemosiderin-laden macrophages and granulation tissue:
 - Represent most common findings:
 - Localized follicular destruction
 - Capsular alterations
 - Atypical cytologic features with necrosis and mitoses:
 - Nuclear atypia is reactive or reparative, typically occurs near the needle tract, and includes nuclear enlargement (nucleomegaly), hyperchromasia, prominent nucleoli
 - Chronic changes usually identified more than 3 weeks from FNAB to surgical removal and may include (individually or in combination):
 - Metaplasia:
 - Squamous or oncocytic cells
 - Mucous cell may uncommonly be identified.
 - Infarction
 - Nuclear atypia, including nucleomegaly, hyperchromasia, and prominent nucleoli
 - Cyst formation
 - Papillary architecture
 - Fibrosis
 - Calcifications
 - Hemorrhage (recent and remote in form of hemosiderin-laden macrophages) and/or cholesterol granuloma formation
 - Capsular alterations with pseudoinvasive growth and/or epithelial displacement:
 - May take the form of a needle tract in which there is a linear-appearing “bud” into fibrous capsule
 - ◻ Low magnification appearance suggests capsular invasion, but at higher magnification follicular epithelium does not violate capsule.
 - ◻ Rather, needle tract composed of dense fibrosis as well as chronic inflammatory cells infiltrate including macrophages and giant cells with or without hemorrhage

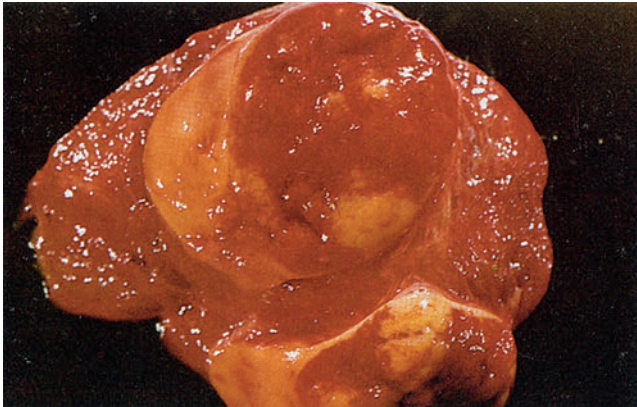


Fig. 29-1. Post-FNAB changes.

Post-FNAB hemorrhage and infarction of a follicular adenoma, oncocytic type.

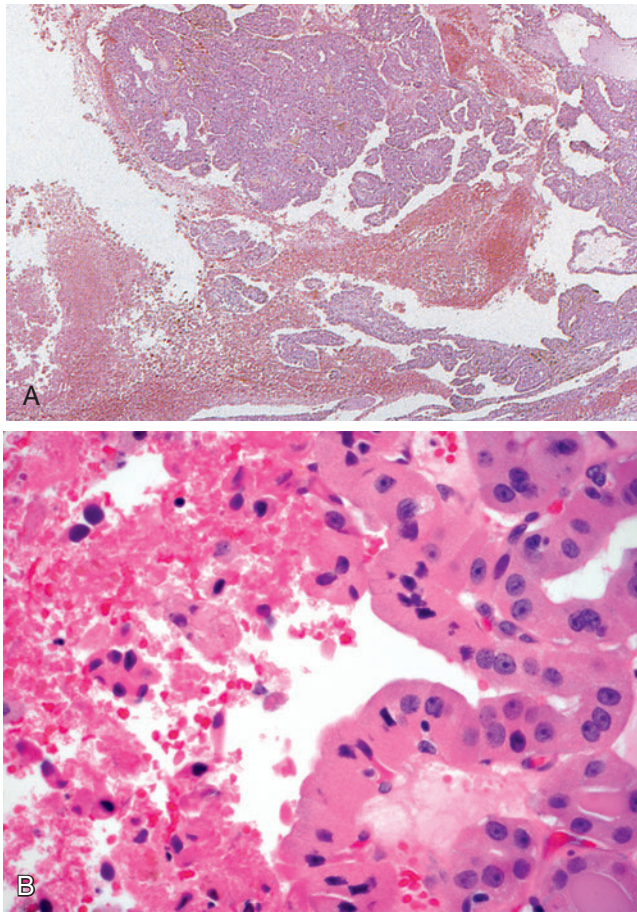


Fig. 29-2. Post-FNAB changes.

A, Post-FNAB changes in this follicular adenoma, oncocytic type, include cystic degeneration, papillary architecture, and fresh hemorrhage. **B**, At higher magnification the follicular cells (*right*) show the presence of granular, brightly eosinophilic cytoplasmic changes (so-called Hürthle cells) with associated hemorrhage and infarction (*left*).

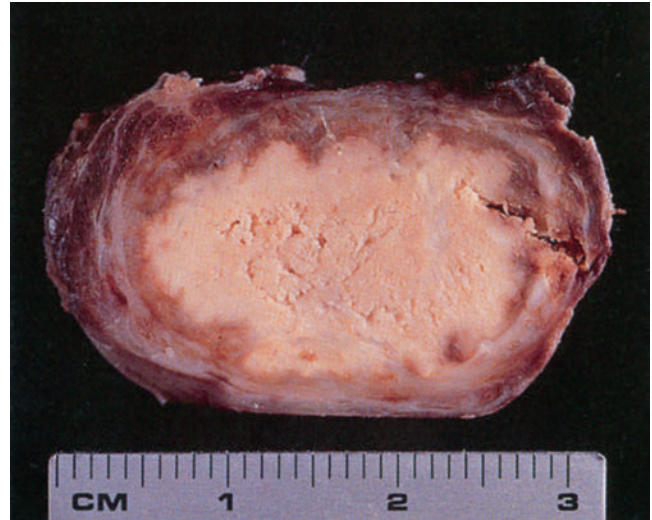


Fig. 29-3. Post-FNAB infarction of a papillary carcinoma.

- (recent and remote, latter in form of hemosiderin deposition); cholesterol granuloma formation may be present.
 - Epithelial displacement
- Vascular alterations, including:
 - Dilated vascular spaces with thrombosis, organization, papillary endothelial hyperplasia (Masson tumor-like reaction), and endothelial cell atypia:
 - May suggest presence of a vascular tumor such as hemangioma or even an angiosarcoma
 - Temporal sequence from the FNAB to surgical removal is an important factor in the interpretation of these findings.
 - Artfactual implantation or “invasion” of tumor cells within endothelial-lined space:
 - In this setting, cells float within vascular lumens and are not adherent to vessel wall and/or have associated fibrin thrombus formation as seen in true vascular invasion.
- Reparative changes may be exuberant, including spindle-shaped cells (fibroblasts) that may simulate a sarcoma and have been referred to as post-FNAB spindle cell nodule.
- Needle tract tumor implantation:
 - Rare occurrence
 - Reported in association with papillary thyroid carcinoma
 - Intervals between FNAB and detection of implantation range from 2 to 131 months
 - Location of carcinoma cells in line of needle insertion include:

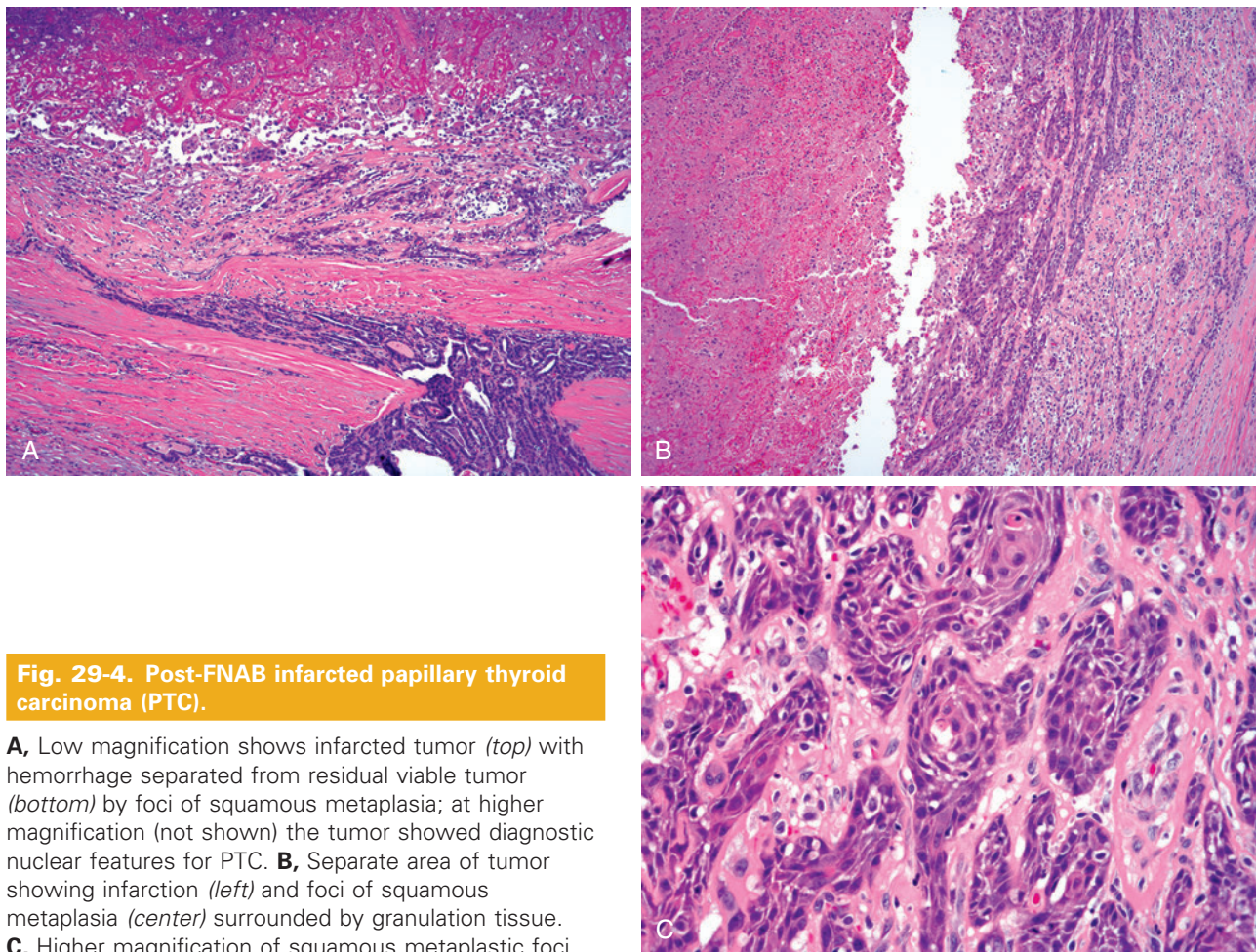


Fig. 29-4. Post-FNAB infarcted papillary thyroid carcinoma (PTC).

A, Low magnification shows infarcted tumor (*top*) with hemorrhage separated from residual viable tumor (*bottom*) by foci of squamous metaplasia; at higher magnification (not shown) the tumor showed diagnostic nuclear features for PTC. **B**, Separate area of tumor showing infarction (*left*) and foci of squamous metaplasia (*center*) surrounded by granulation tissue. **C**, Higher magnification of squamous metaplastic foci.

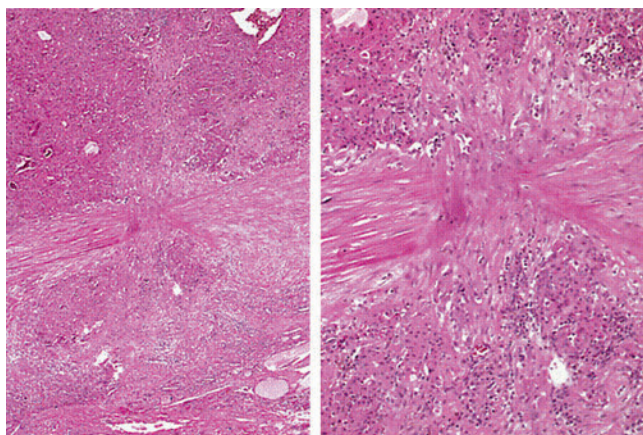


Fig. 29-5. Needle tract and capsular pseudoinvasion.

Left, The appearance at low magnification includes linear-appearing "bud" into fibrous capsule, suggesting capsular invasion. *Right*, At higher magnification, the needle tract bud includes mixed inflammatory cells and hemorrhage.

- Subcutis
- Within strap muscles
- None of the lesions included lymph node components on pathology.
- Implanted tumors surgically removed without recurrence at focal sites

INTRAOPERATIVE CONSULTATION (IOC) (FROZEN SECTION) OF THE THYROID GLAND

(Figs. 29-12 through 29-20)

Indications

- Most effective in cases in which fine-needle aspiration biopsy (FNAB) results are suspicious for malignancy (Bethesda V)
- Render a histologic diagnosis.
- Differentiate a benign lesion (e.g., adenomatoid nodule[s], adenoma) from a malignant neoplasm that may require additional surgery (i.e., total or near total thyroidectomy).

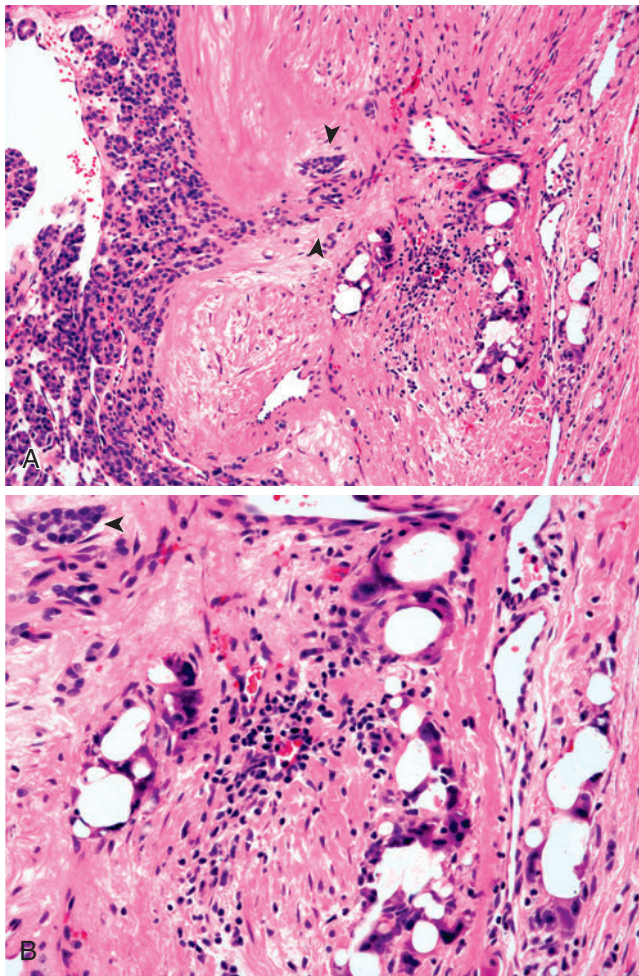


Fig. 29-6. Needle tract with epithelial displacement.

A, B, Follicular epithelial cells (*arrowheads*) displaced along needle tract that includes chronic inflammatory cells, hemorrhage, fibrosis, and foreign body giant cell reaction; follicular epithelium does not violate the capsule.

- Identification of nonsentinel nodal metastasis:
 - Role of sentinel lymph node sampling not established for thyroid tumors
- Incisional biopsy with intraoperative consultation (IOC) may occur:
 - In patients with unresectable disease (e.g., undifferentiated [anaplastic] carcinoma)
 - To ensure adequacy for diagnosis in certain clinical settings (e.g., unresectable disease) or in relationship to certain tumor types (e.g., hematolymphoid tumors)

Surgeon's Expectations

- Establish a correct diagnosis.
- Differentiate a benign (non-neoplastic or benign tumor) from a malignant tumor.

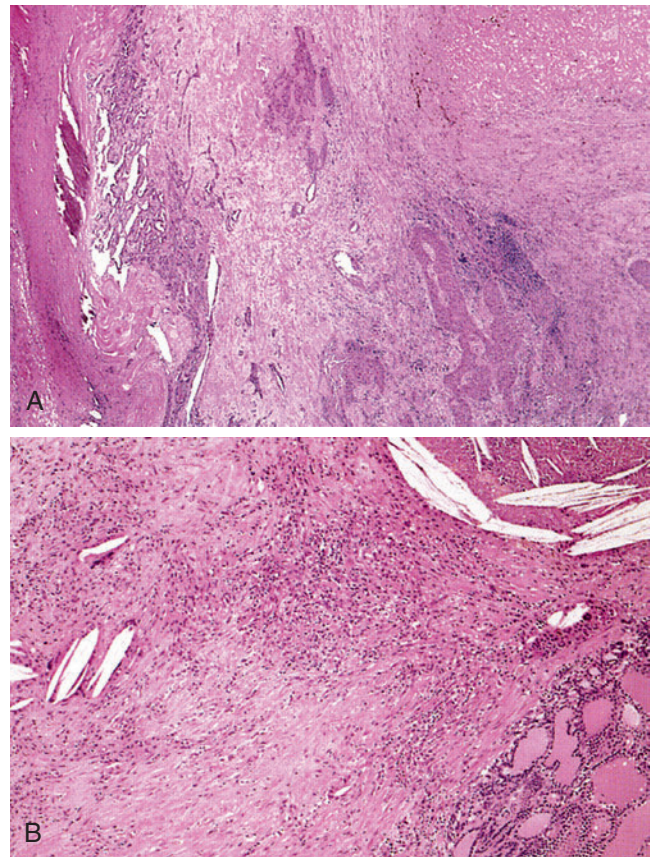


Fig. 29-7. Post-FNAB changes.

Post-FNAB changes in adenomatoid nodule: **(A)** infarction (*upper right*), fibrosis, chronic inflammation, squamous metaplasia, and calcifications; **(B)** granulation tissue and cholesterol granuloma formation.

- Identification of nodal metastasis in cases in which lymph nodes are resected and sent for IOC
- Identify additional findings that may affect treatment.

Specimen Handling

- Lobectomy specimen:
 - Ink exterior of specimen.
 - Serially sectioned in “breadloaf” manner
 - Cut section through center of lesion and measure it.
 - Section to include capsule-to-tumor interface.
 - Weigh gland (optional).
- Subtotal or total thyroidectomy specimen:
 - If removed with preoperative diagnosis of malignancy (e.g., by FNAB):
 - Ink exterior of specimen.
 - Gross examination usually suffices.
 - Weigh gland (optional).

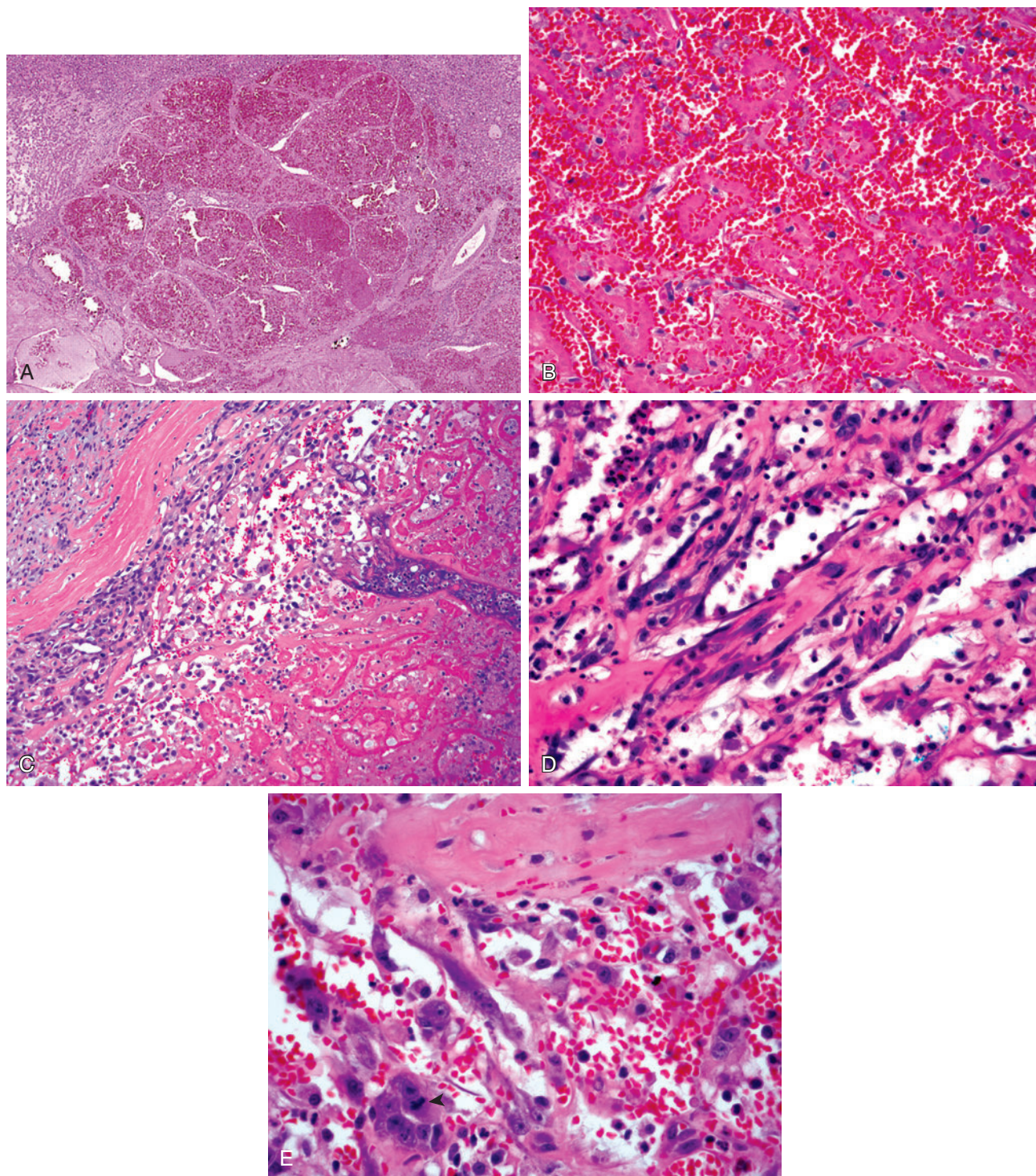


Fig. 29-8. Post-FNAB vascular changes.

Post-FNAB vascular alterations may include **(A and B)** blood-filled spaces simulating the appearance of a hemangioma; **(C through E)** vascular proliferation adjacent to area of infarction simulating an angiosarcoma, including **(C)** dilated, ramifying, and interconnecting channels, **(D)** nuclear atypia, and **(E)** mitotic figures (*arrowhead*).

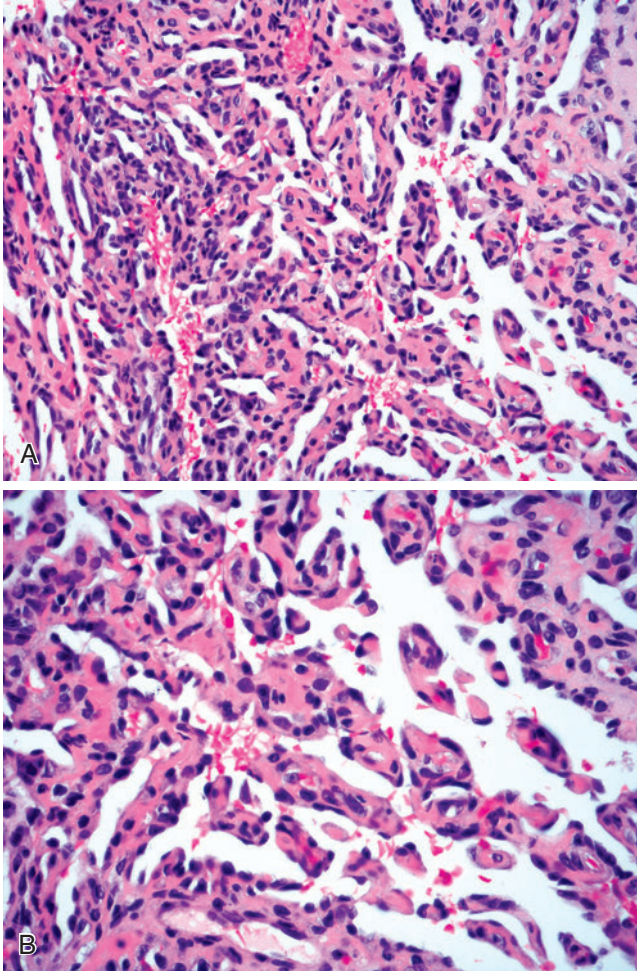


Fig. 29-9. Papillary endothelial hyperplasia.

A, B, Post-FNAB vascular alterations may include papillary endothelial hyperplasia characterized by the presence of numerous papillae projecting into vascular lumens composed of a single layer of endothelium surrounding a collagenized core.

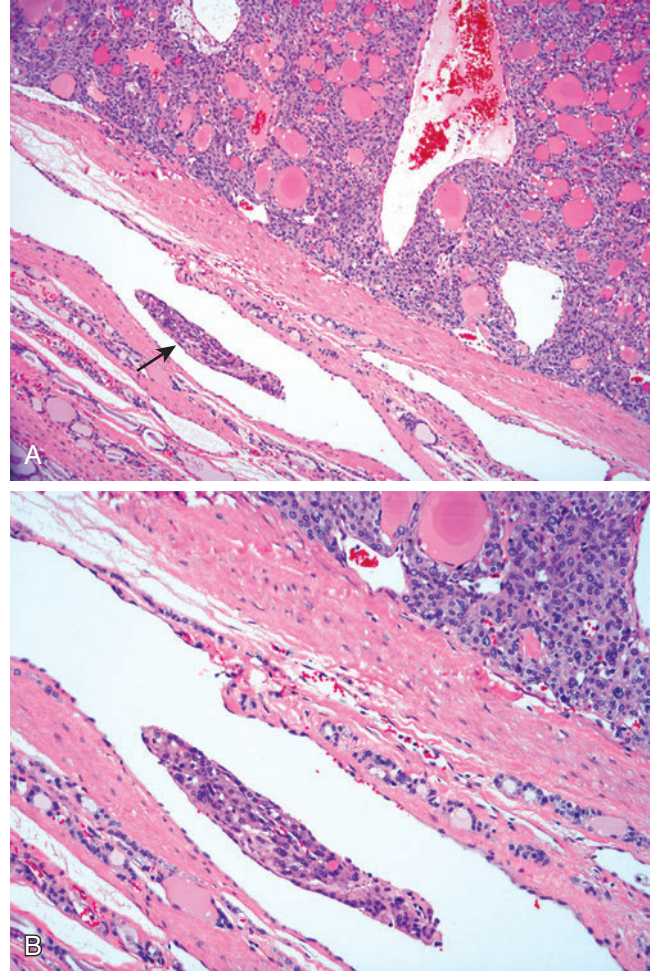


Fig. 29-10. Pseudovascular invasion.

A, Post-FNAB of a follicular adenoma showing artifactual implantation of tumor cells within an intracapsular endothelial-lined vascular space (*arrow*). **B,** At higher magnification, the tumor cells are free floating, the blood vessel lacking adherence to the vessel wall and/or associated fibrin thrombus formation as would be seen in bona fide vascular invasion.

- Follicular adenoma versus follicular carcinoma:
 - Recommendation is that at least four blocks from tumor-to-capsule-to-thyroid interface be examined, but the number of sections is not considered “standard of practice” and number of blocks examined is a decision made by individual pathologist.

Gross Findings

- Observation of macroscopic features important to proper evaluation and sectioning in thyroid resections include:
 - Number of lesions/nodules identified
 - Circumscription/encapsulation versus poorly circumscribed versus invasive
 - Presence of intralesional fibrosis:
 - Often seen in papillary thyroid carcinoma but not a pathognomonic finding
 - Presence of retrogressive changes including cyst formation, hemorrhage, calcifications:
 - Often seen in association with adenomatoid nodule(s)
 - Color:
 - Brown to red color indicative of oncocytic cells

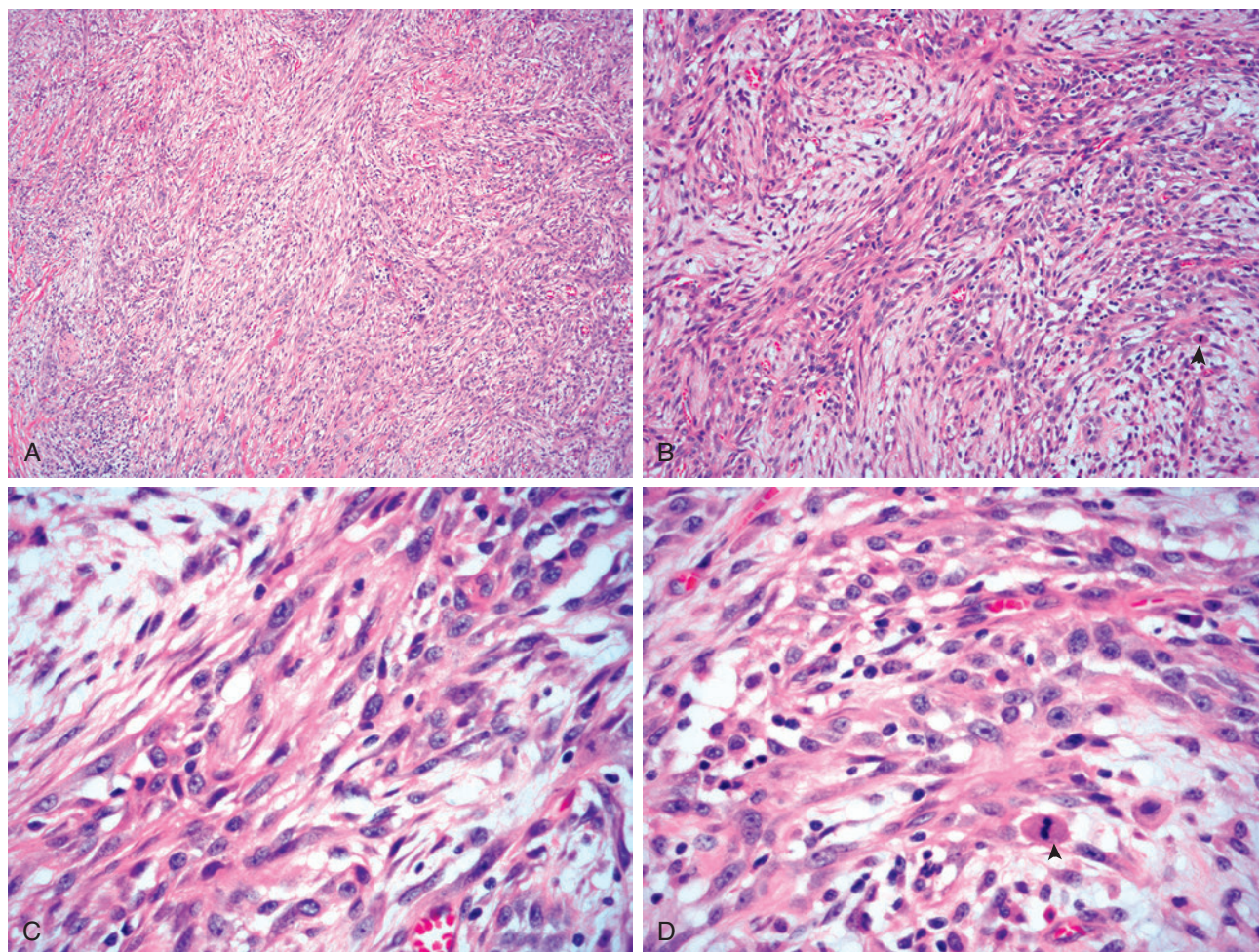


Fig. 29-11. Post-FNAB spindle cell nodule in an adenomatoid nodule.

A and B, Low magnification shows fascicular to storiform growth with scattered mitotic figures (*arrowhead*).
C and D, Spindle-shaped to epithelioid-appearing fibroblasts with enlarged nuclei, prominent nucleoli, and mitotic figure (*arrowhead*).

- Glistening appearance suggests prominence of colloid as may be seen in adenomatoid nodules or follicular adenoma.

Intraoperative Cytology

- Cytologic preparations (touch preps, scrap preps, needle aspiration):
 - Should be performed in all cases as considered essential in IOC of thyroid lesions:
 - May provide cytomorphologic features less well observed on frozen section preparation
 - Used in conjunction with frozen sections as complimentary diagnostic tool
 - Increases diagnostic accuracy

Diagnostic Considerations

See [Table 29-1](#) for diagnostic categories.

- Papillary thyroid carcinoma (PTC)
- Follicular adenoma
- Follicular carcinoma
- Adenomatoid nodules
- Chronic lymphocytic (Hashimoto) thyroiditis
- Medullary thyroid carcinoma (MTC)
- Post-fine-needle aspiration biopsy changes (see first section in this chapter):
 - Cyst formation
 - Fibrosis
 - Hemorrhage

Text continued on p. 1467

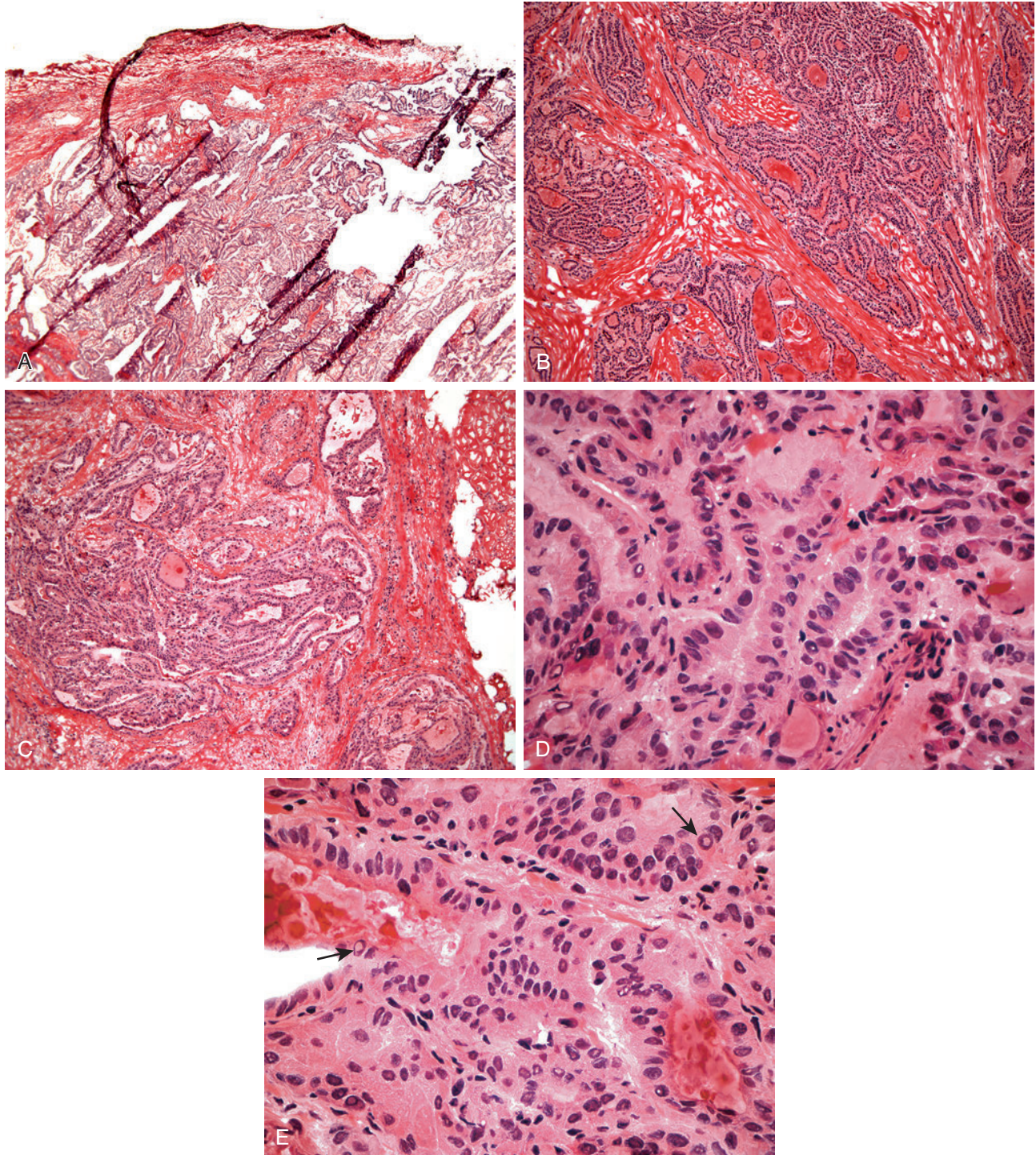


Fig. 29-12. Intraoperative consultation, papillary thyroid carcinoma usual type.

A, Low magnification shows a follicular epithelial lesion with papillary architecture. **B**, Areas showing elongated and irregular-appearing follicles and intratumoral fibrosis. **C**, Papillae, elongated follicles, and intratumoral fibrosis. **D** and **E**, At higher magnification diagnostic nuclear including nuclear enlargement, variation in nuclear size and shape, crowding, overlapping, and intranuclear inclusion (*arrow*); note absence of optically clear nuclei, which is an artifact of fixation and not a feature seen on frozen section.

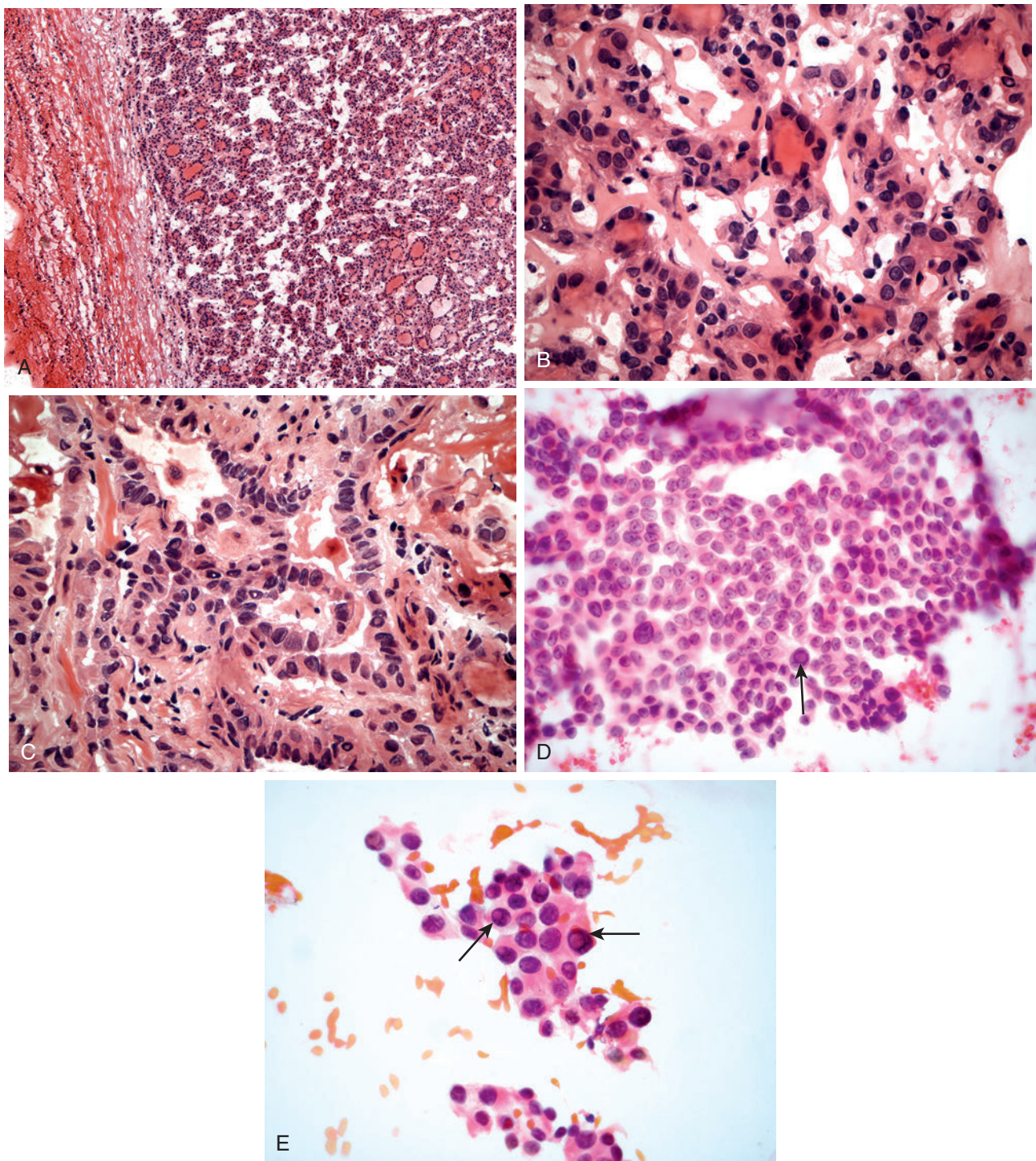


Fig. 29-13. Intraoperative consultation, papillary thyroid carcinoma (PTC), follicular variant.

A, Encapsulated follicular epithelial tumor without invasive growth that is entirely composed of follicular architecture without evidence of papillae. **B**, Areas showed nuclear features suggestive of papillary thyroid carcinoma. **C**, Other areas show the presence of intranuclear inclusions that in conjunction with other nuclear features supports the diagnosis of papillary thyroid carcinoma. **D** and **E**, Cytologic (touch) preparations show unequivocal diagnostic features for PTC, including enlarged nuclei with variation in size and shape, dispersed (very fine)-appearing nuclear chromatin, nuclear grooves, and intranuclear inclusions (*arrows*).

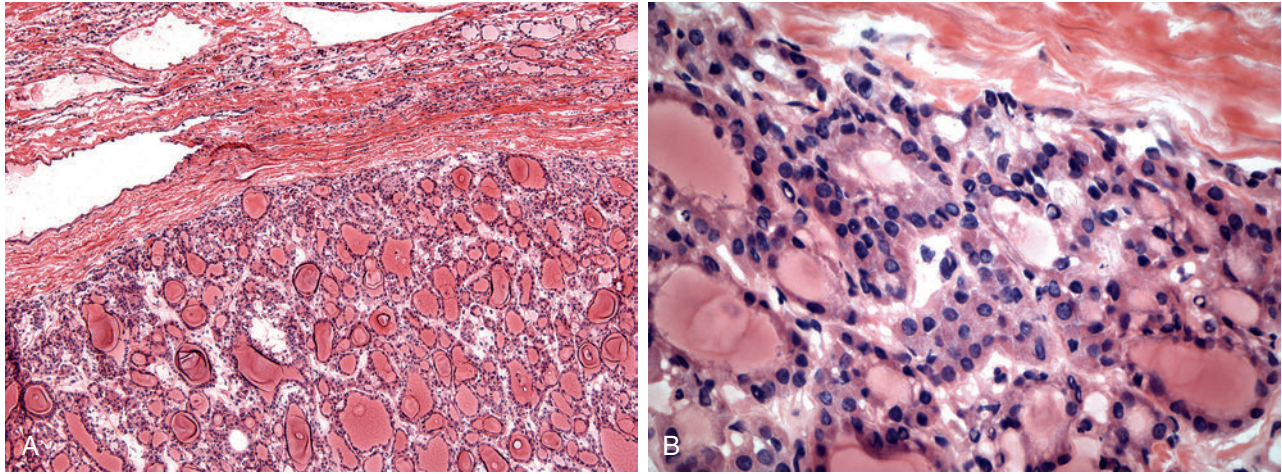


Fig. 29-14. Intraoperative consultation, follicular adenoma.

A, Encapsulated follicular epithelial tumor with no evidence of invasion. **B**, Cytomorphology includes rather uniform-appearing cells with round nuclei and coarse nuclear chromatin lacking nuclear features diagnostic for papillary thyroid carcinoma.

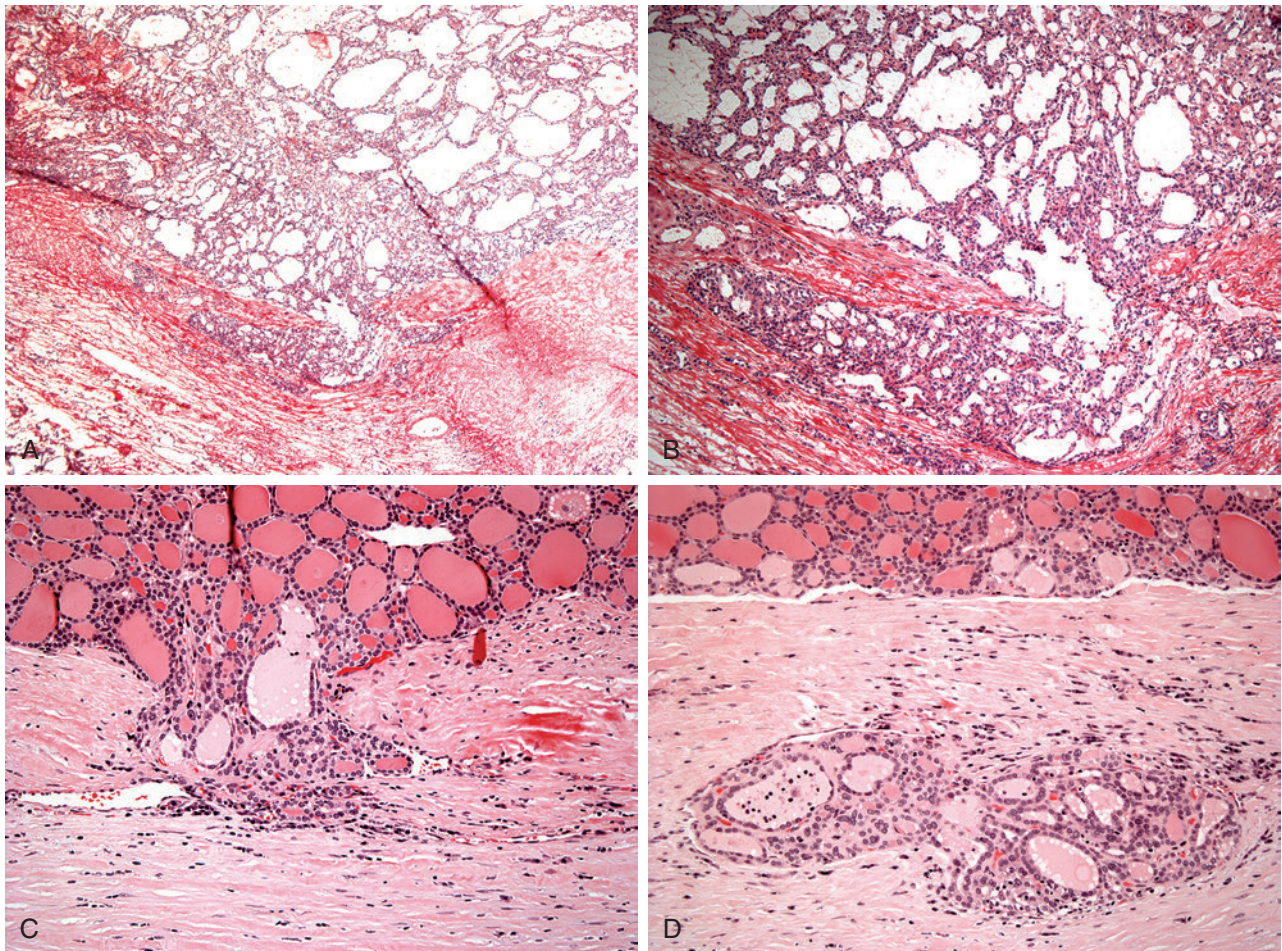


Fig. 29-15. Intraoperative consultation, follicular carcinoma minimally invasive.

A and **B**, Low magnification showing tumor invading into and through its capsule but at the time of IOC definitive evidence of angioinvasion was not identified. **C** and **D**, On permanent section evidence of angioinvasion in the form of tumor within capsular endothelial-lined vascular spaces was seen and confirmed the diagnosis of (minimally invasive) follicular carcinoma.

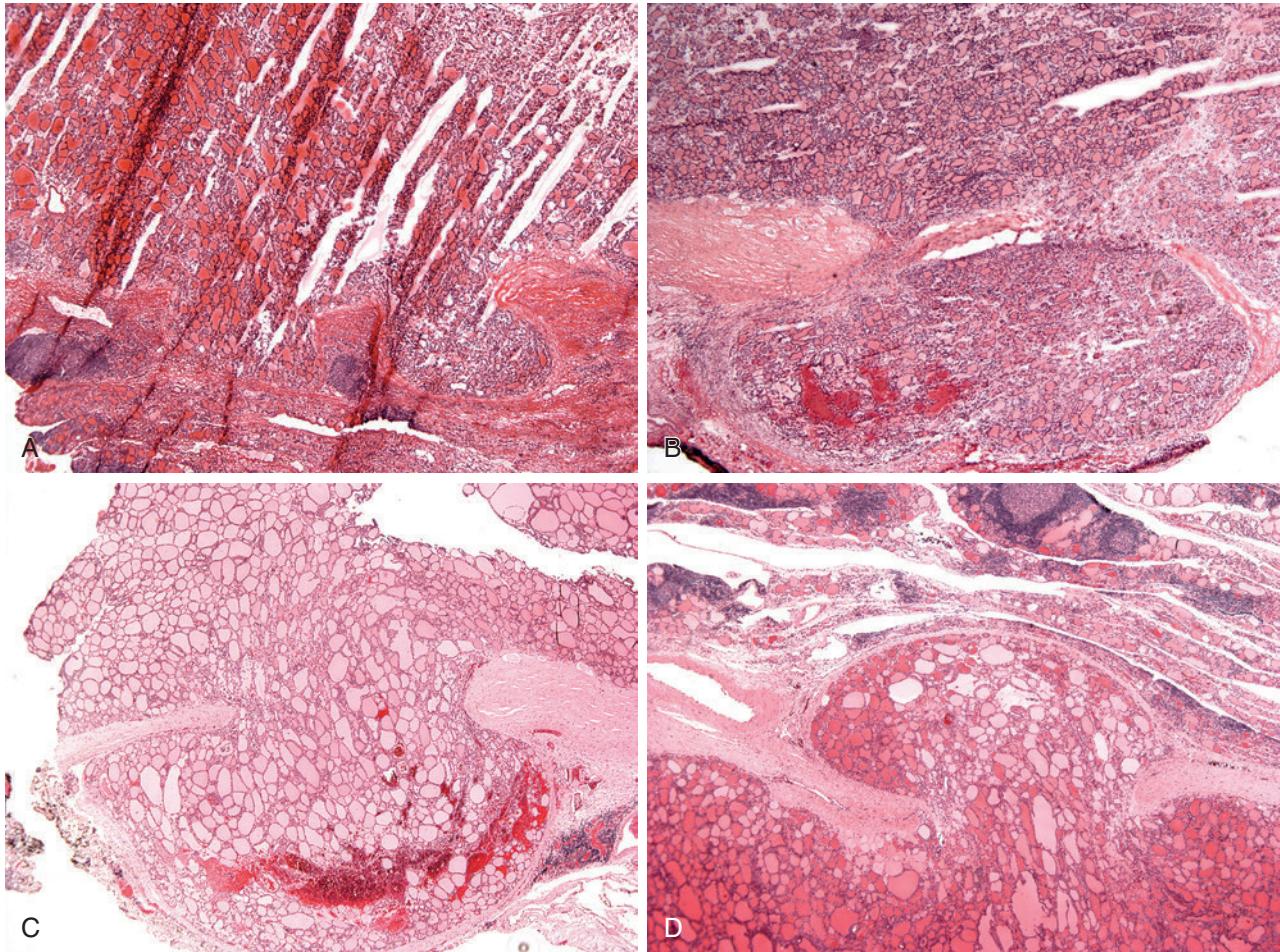


Fig. 29-16. Intraoperative consultation, follicular carcinoma.

A, In this image separate foci of tumor are seen protruding into and through the capsule. **B,** Other areas show mushroom-like protrusion of the tumor completely bifurcating the capsule. **C and D,** Permanent sections confirm the capsular invasion as evidenced by the presence of "mushroom-like" growth through the capsule.

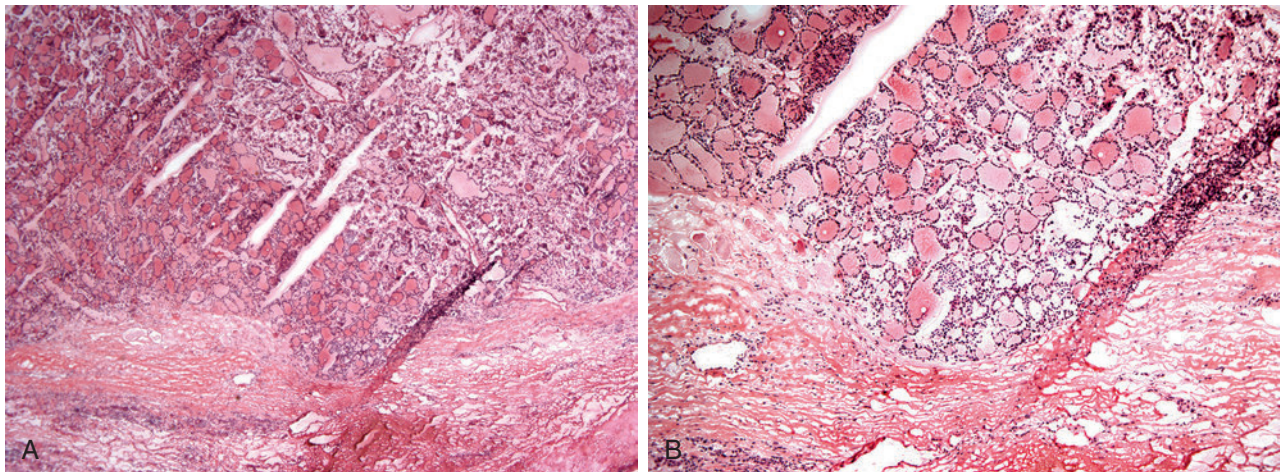


Fig. 29-17. Intraoperative consultation, capsular pseudoinvasion in a follicular adenoma.

A, B, Not infrequently limited protrusion of tumor into the capsule may be seen but the extent of protrusion does not qualify as capsular invasion; angioinvasion was not present.

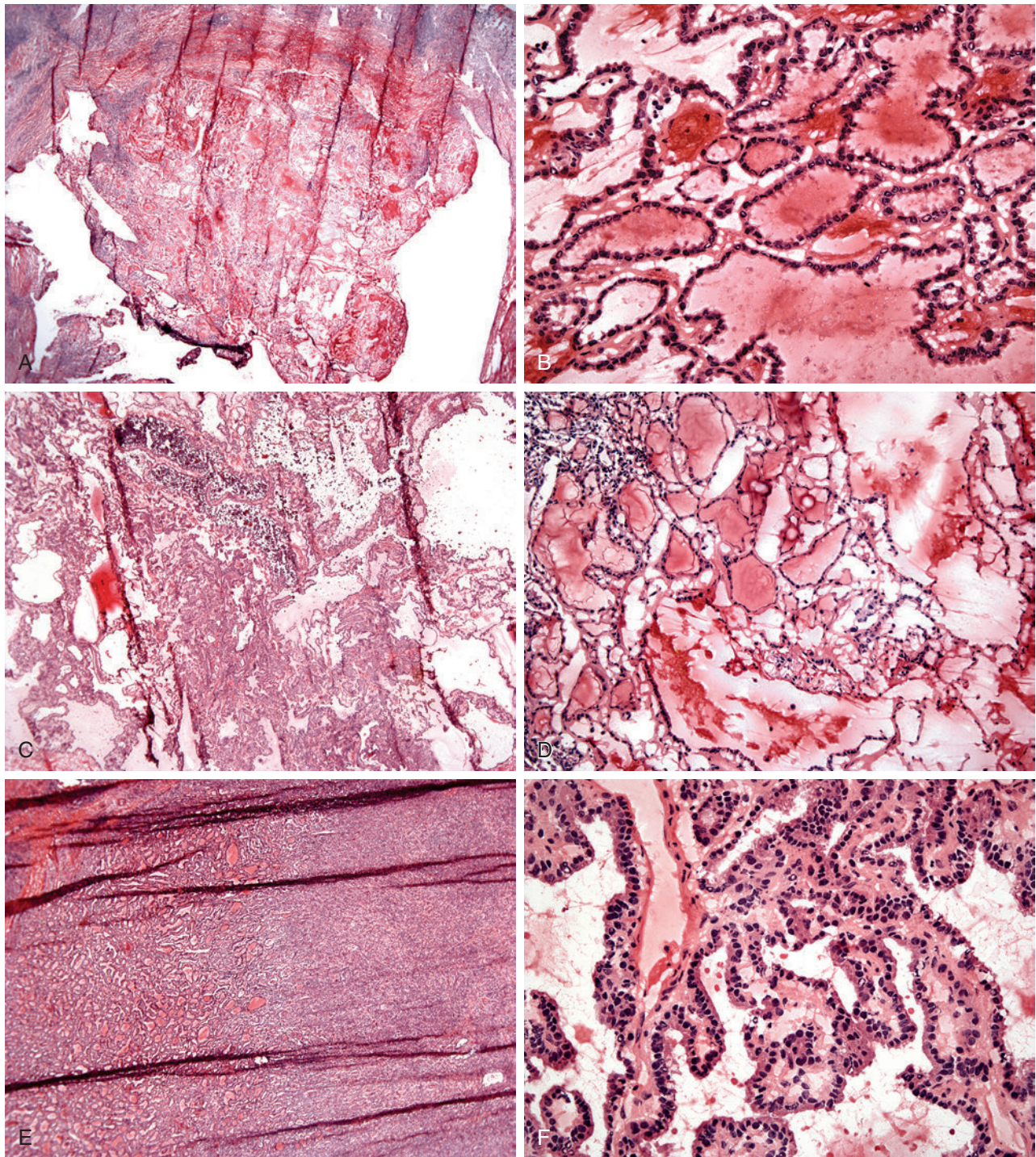


Fig. 29-18. Intraoperative consultation, adenomatoid nodules.

A and B, This lesion was part of multiple nodules that were circumscribed but not encapsulated and composed of colloid-filled follicles with bland nuclear morphology. **C and D,** Retrogressive changes in adenomatoid nodules may include cyst formation and papillary architecture, but there was an absence of nuclear findings associated with papillary thyroid carcinoma (on frozen section and touch preparation, not shown). **E and F,** Cellular adenomatoid nodule—despite the increase cellularity there is an absence of invasion and an absence of nuclear findings associated with papillary thyroid carcinoma (on frozen section and touch preparation, not shown).

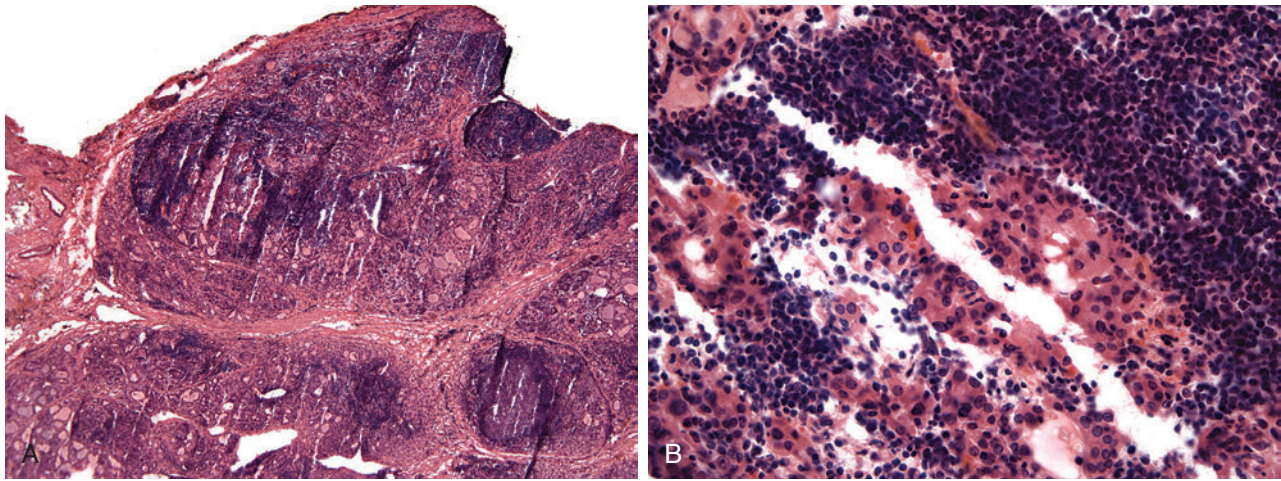


Fig. 29-19. Intraoperative consultation, chronic lymphocytic (Hashimoto) thyroiditis.

A, Thyroid gland characterized by multiple nodules separated by fibrous tissue and associated dense lymphoid infiltrate. **B,** At higher magnification the thyroid follicular cells with oncocytic cytoplasm changes and associated dense lymphocytic cell infiltrate.

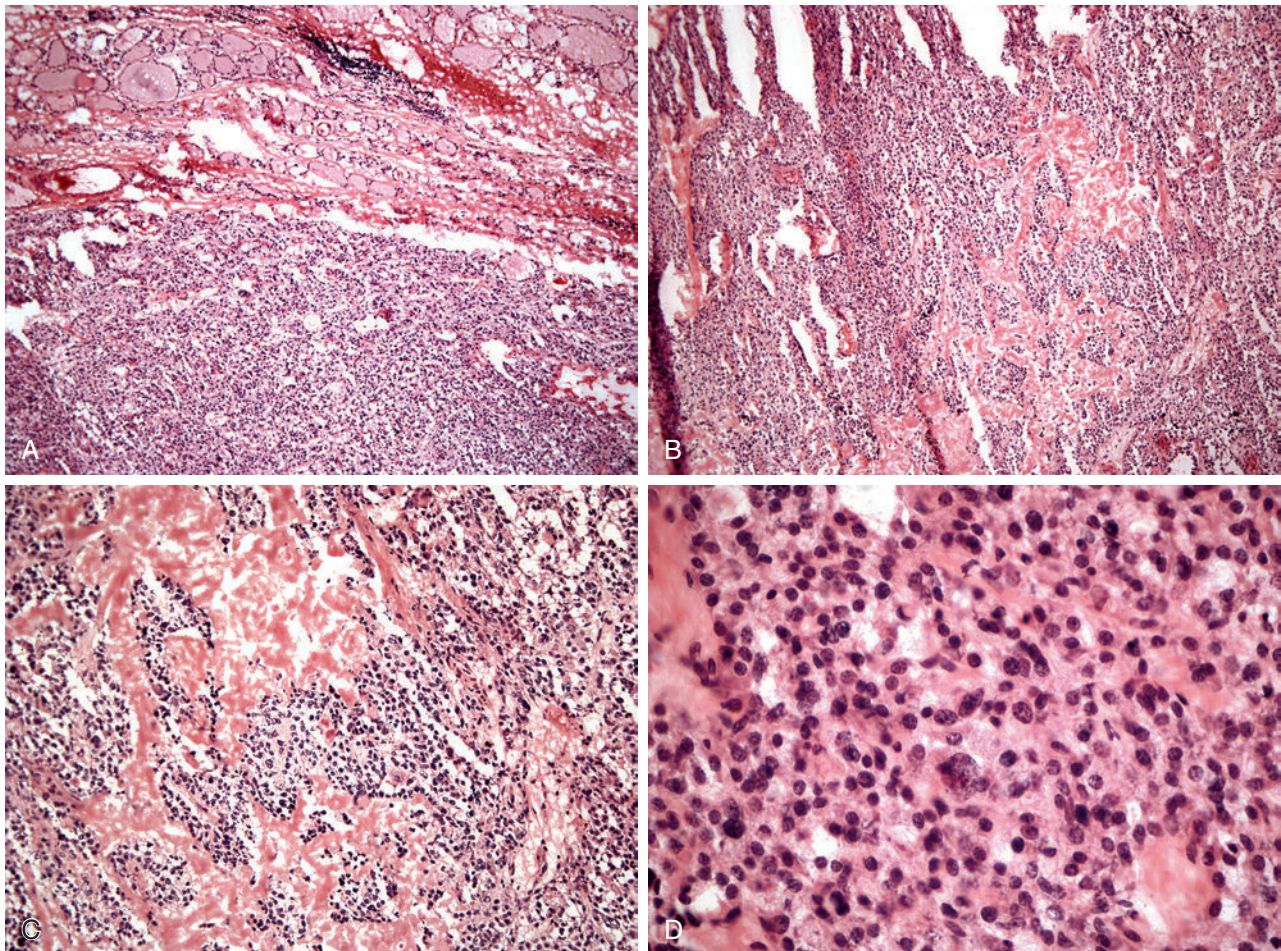
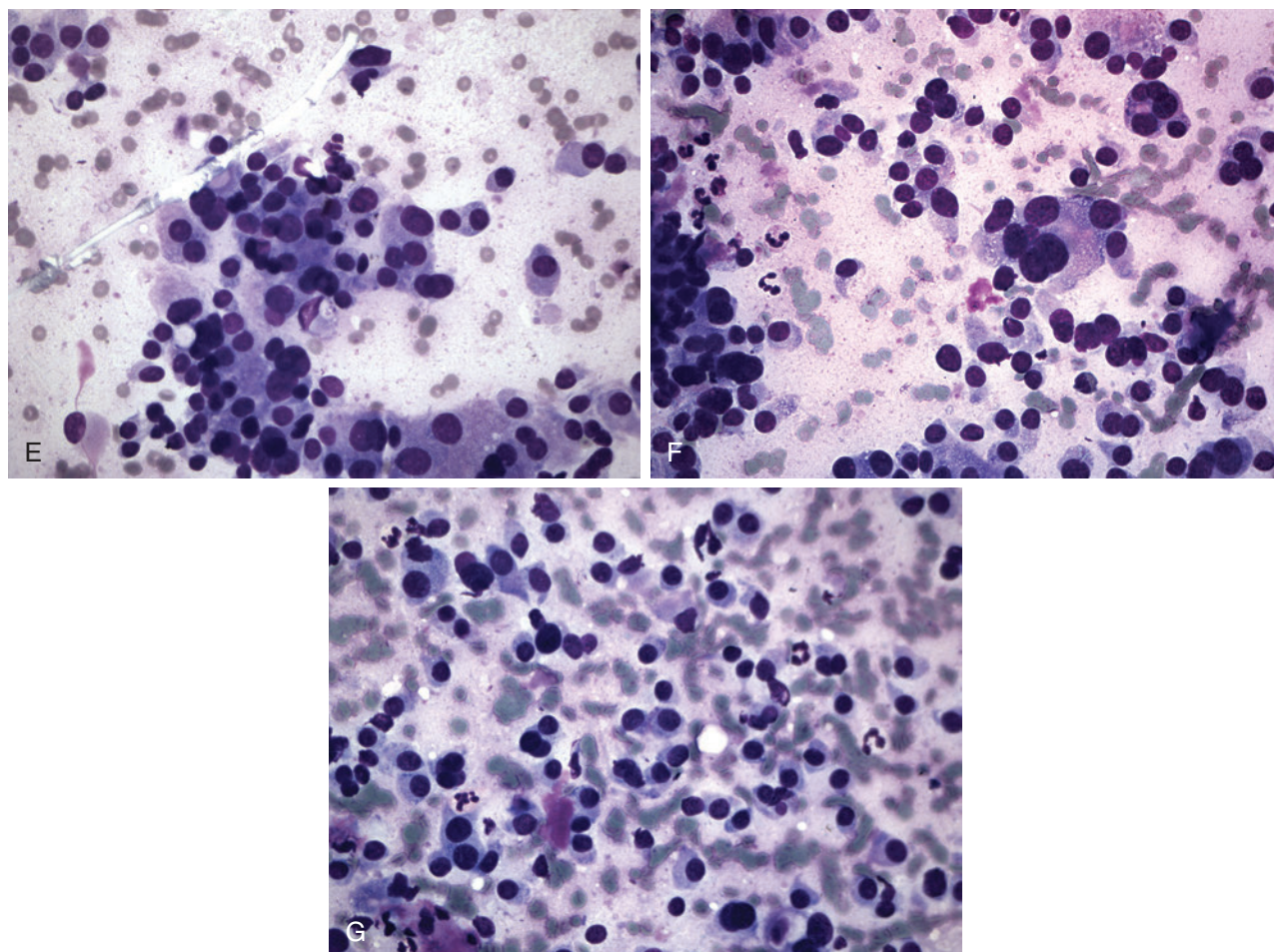


Fig. 29-20. Intraoperative consultation, medullary thyroid carcinoma.

A, Circumscribed cellular tumor lacking evidence of colloid formation demarcated from the adjacent normal thyroid parenchyma (*top*). **B** and **C,** Areas of the tumor show acellular extracellular eosinophilic material that proved to be amyloid. **D,** At higher magnification the tumor cells are composed of variably pleomorphic round nuclei with dispersed nuclear chromatin. Touch preparations at the time of frozen section assist in the diagnosis, showing

**Fig. 29-20, cont'd**

(**E**) nuclear characteristics of medullary thyroid carcinoma including round cells, some with a plasmacytoid appearance, with dispersed nuclear chromatin, (**F**) scattered multinucleated giant cells, and (**G**) extracellular amyloid material.

TABLE 29-1 Intraoperative Consultation: Diagnostic Categories

Lesion	Diagnostic Consideration
Follicular lesion low cellularity/large follicles	Adenomatoid nodules Follicular adenoma
Encapsulated cellular follicular lesion with no invasion	Follicular neoplasm, defer PTC Follicular neoplasm suspicious for malignancy
Follicular lesion with invasion	Follicular carcinoma; PTC, follicular variant
Invasive papillary lesion	PTC and variants
Other	Medullary carcinoma, lymphoma, anaplastic carcinoma

PTC, Papillary thyroid carcinoma.

- Infarction
- Nuclear atypia
- Vascular alterations
- Capsular pseudoinvasion
- Vascular pseudoinvasion

Diagnostic Accuracy of IOC of the Thyroid Gland

- 98% correlation between IOC, including FS and cytologic preparation, and final histologic diagnosis
- Average deferral rate of 11% (compared with average deferral rate of 3% for other sites)
- Reoperation rate 1.4%

Contraindications and Limitations of IOC of Thyroid Gland Lesions

- Not indicated in cases diagnosed as definitive for malignancy (Bethesda VI), including:
 - Papillary thyroid carcinoma
 - Poorly differentiated thyroid carcinoma
 - Medullary thyroid carcinoma
 - Undifferentiated (anaplastic) carcinoma
 - Squamous cell carcinoma
 - Metastatic carcinoma
 - Malignant lymphoma
 - In such cases the preoperative surgical plan includes total thyroidectomy, in which there is no information generated by IOC that would alter surgical approach.
 - Exception to this scenario would be evaluation of lymph nodes for nodal metastasis that may prompt neck dissection at time of IOC.
- Limited to no utility in cases in which FNAB diagnosis is “follicular lesion of undetermined significance” or “follicular neoplasm or suspicious for follicular neoplasm” (Bethesda IV), including those lesions with oncocytic (so-called Hürthle) cells:
 - In many of these cases differential diagnosis primarily includes follicular adenoma versus follicular carcinoma, in which differentiating criteria (i.e., invasive growth) may:
 - Be only focally identified and not readily observed at time of IOC

- Require numerous sections more appropriately performed on permanent section evaluation and not in frozen sections

- Diagnosis of follicular carcinoma:
 - Problematic issue given the fact majority of follicular carcinomas are low grade and may show only focal/limited evidence of capsular invasion and/or angioinvasion on permanent section
 - Guidelines include at least four sections be taken from the tumor-to-capsule-to-stromal interface, but foci of invasion may not be evident even in multiple sections.

SUMMARY

- IOC of thyroid gland lesions is most effective where FNAB is suspicious for but not definitively diagnostic of carcinoma.
- Not indicated in cases diagnosed as definitive for malignancy by FNAB
- Is at best of limited value and arguably of no value in the diagnosis of minimally invasive (low-grade) follicular carcinoma

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Embryology, Anatomy, and Histology of the Parathyroid Glands

EMBRYOLOGY

- Parathyroid glands are of endodermal origin and originate as symmetric, nodular epithelial proliferations on the dorsal aspects of the third and fourth pharyngeal pouches around the fifth week of gestation.
- Superior gland develops from the fourth pharyngeal pouch, which is connected with the pharynx, from which it separates. The fourth pharyngeal pouch is a complex bilobed structure composed of a ventral component; the ultimobranchial body, which fuses with the lateral aspect of the thyroid lobe; and a dorsal epithelial proliferation, which separates to become the superior thyroid gland, assuming the usual adult position along the posteromedial aspect of the thyroid gland. The superior parathyroid glands tend to be more constant in position than the inferior glands.
- Inferior parathyroid glands develop from the third pharyngeal pouch, also a complex bilobed structure, associated with the thymus, from which it separates after migrating caudally to a position near the lower pole of the thyroid gland.
- Most common “anomaly” of the parathyroid glands is ectopia, which usually represents a variation in embryologic migratory pattern.

- Parathyroid agenesis is very rare:
 - DiGeorge syndrome includes:
 - Complete or partial absence of the third and fourth pharyngeal pouches and their derivatives: the thymus, the parathyroid glands, and the C cells
 - Disease is manifested by multiple facial malformations, hypoplasia of the thyroid, hypoparathyroidism, and cardiac abnormalities.

ANATOMIC CONSIDERATIONS

(Fig. 30-1)

- Most individuals have at least four parathyroid glands; approximately 13% of the population has supernumerary glands, ranging in number from one additional gland to as many as 12 glands in rare instances.
- Rare individuals with fewer than four glands have been reported; however, there is doubt in at least some of the cases that all of the glands were identified.
- Supernumerary glands may be well formed (about half of the cases) or may be less distinct aggregates of parathyroid tissue located near the normal glands.

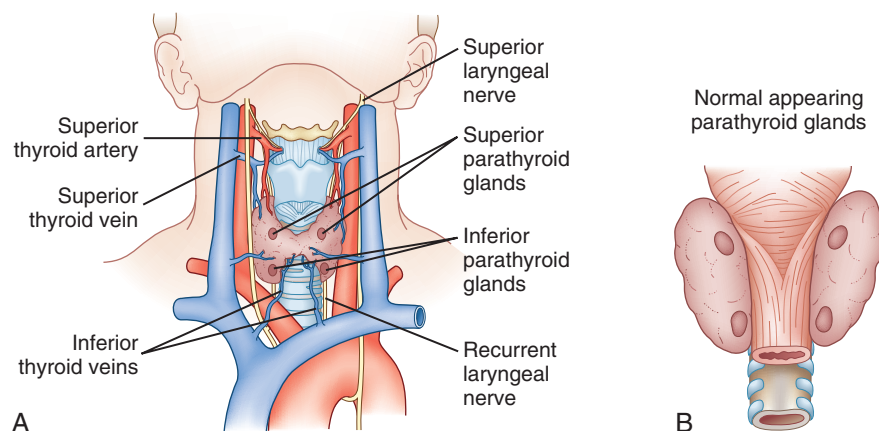


Fig. 30-1. Anatomy of the parathyroid glands.

(From Miller FR, Netterville JL: *Surgical management of thyroid and parathyroid disorders*, Med Clin North Am 83(1):247, 1999, Fig. 1.)

- There is considerable variation in the location of the parathyroid glands in adults, though their distribution follows a predictable pattern based on their embryologic development.
- The superior glands are more constantly placed than the lower glands:
 - The superior glands are located along the posterior edge of the thyroid superior to the intersection between the recurrent laryngeal nerve and the inferior thyroid artery (approximately 80%).
 - 20% are found posterior to the upper pole of the thyroid, where they may be intimately associated with the thyroid capsule
 - The superior glands may rarely be retroesophageal or retropharyngeal, or even intrathyroidal.
- The lower glands are more variably placed:
 - Although the most common location is around the posterolateral or inferior aspects of the lower pole of the thyroid gland (approximately 60%), they may be found within the portion of the thymus that is adjacent to the lower pole of the thyroid.
 - Because the inferior glands pursue a lengthy developmental migratory course, they may be found from the level of the hyoid bone to the mediastinum, where they may be situated in thymic tissue or in the pericardium.

BLOOD SUPPLY AND LYMPHATICS

- Arteries and veins:
 - Blood supply is from the superior and inferior thyroid arteries or from anastomoses between the superior and inferior thyroid arteries.
 - If glands are ectopic in location, the arterial supply may be from the esophageal or pharyngeal arteries.
 - Venous drainage:
 - Upper glands via superior or lateral thyroid vein
 - Lower glands via lateral or inferior thyroid vein
- Lymphatics:
 - Originates from subcapsular plexus into the superior deep cervical, pretracheal, paratracheal, retropharyngeal, and inferior deep cervical lymph nodes

INNERVATION

- Derived from the sympathetic ganglia (superior or middle cervical ganglia) either directly or indirectly through a plexus in the fascia of the posterior surface of the thyroid lobes:
 - Nerves are probably vasomotor rather than secretomotor.

HISTOLOGY (Figs. 30-2 through 30-4; Table 30-1)

- Parathyroid glands are soft yellow-brown to dark brown, circumscribed ovoid structures; some parathyroid glands are bilobed or flattened.
- Normal size and weight (see Table 30-1):
 - Each gland measures approximately 3 to 6 mm in length.
 - Combined weight increases from early infancy (mean, 5 to 9 mg) to the third or fourth decade (mean for males, 120 mg; for females, 142 mg).
 - The actual parenchymal cell mass represents about 74% of the weight of adult parathyroid glands.
- Capsule of the parathyroid glands consists of delicate fibrous tissue.
- Within the glands there is an arborizing meshwork of arterioles, venules, and a myriad of capillaries that give the glands an extremely rich blood supply.
- Parathyroid glands in infants and children:
 - Very cellular, with little stromal collagen and very few stromal fat cells
 - Number of stromal fat cells begins to increase around puberty and continues to increase until the third to fifth decades.
 - Stromal fat is variable in its distribution among individuals as well as within a single gland, making the relative percentage of stromal fat a tenuous feature in evaluation of parathyroid proliferations.
 - Chief cells arranged in solid sheets with minimal intervening stroma
 - Oncocytic (oxyphilic) and transitional oncocytic cells are not normally observed.
 - Chief cells are small and have faintly eosinophilic cytoplasm with less intracellular fat than the cells of adult parathyroid glands.
 - More variable architectural features appear, beginning in puberty with the accumulation of more stromal tissue.
- Adult parathyroid glands:
 - Composed predominantly of chief cells (although they are larger and contain more intracytoplasmic fat than the chief cells in children):
 - Nuclei are round and tend to be rather hyperchromatic due to a coarse chromatin pattern typical of neuroendocrine cells.
 - Cytoplasm is amphophilic or slightly eosinophilic to somewhat clear.
 - Parenchymal cells of adult parathyroid glands are arranged in solid groups, cords, nests, and follicle-like structures, with intervening stromal tissue:

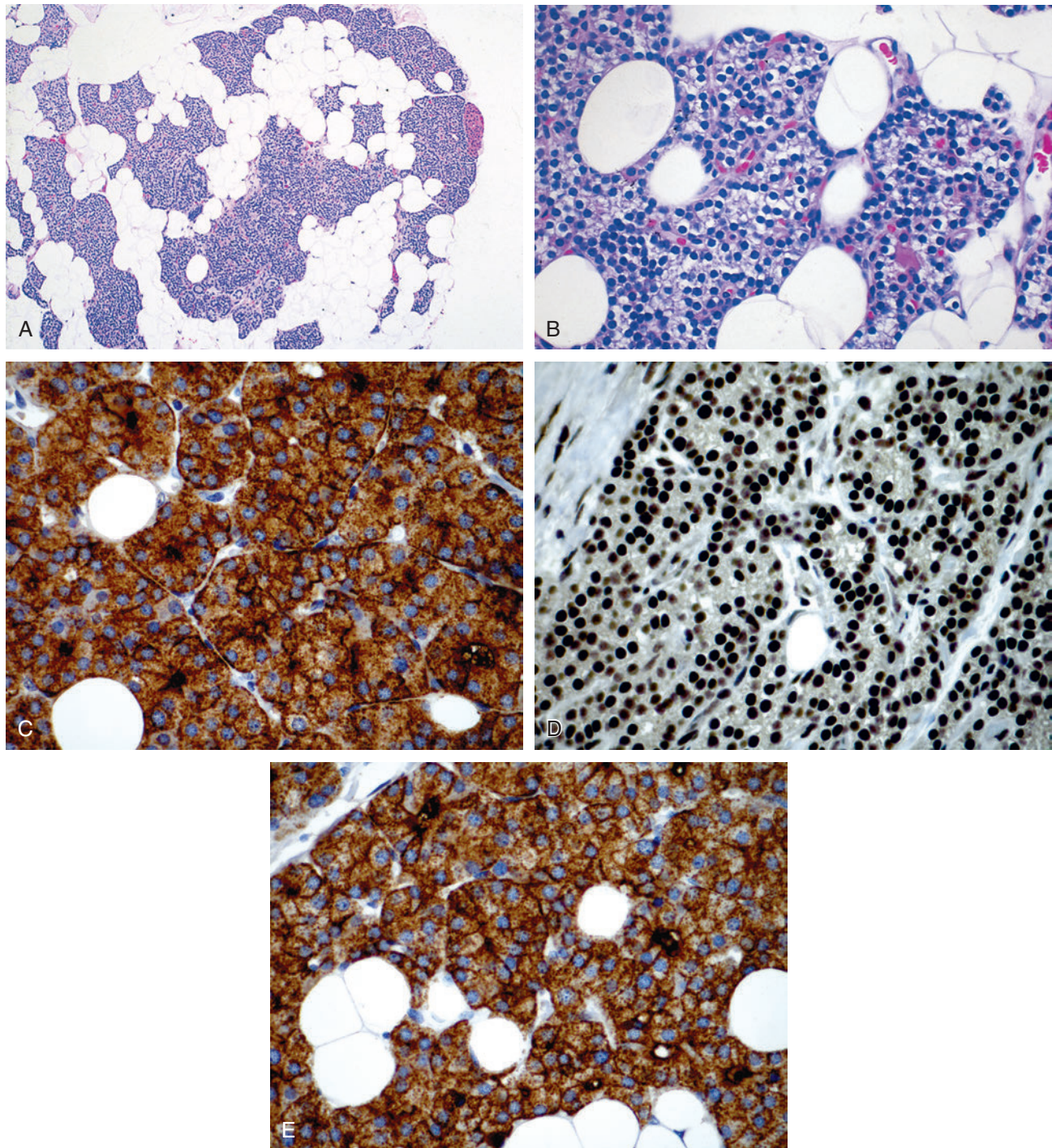


Fig. 30-2. Normal parathyroid gland.

A, Normal parathyroid gland in an adult composed of chief cells and abundant intraparenchymal mature fat. **B**, Solid groups of chief cells that have small hyperchromatic, round nuclei and clear appearing cytoplasm. The chief cells stain for **(C)** parathyroid hormone, **(D)** parafibromin (nuclear staining), and **(E)** chromogranin.

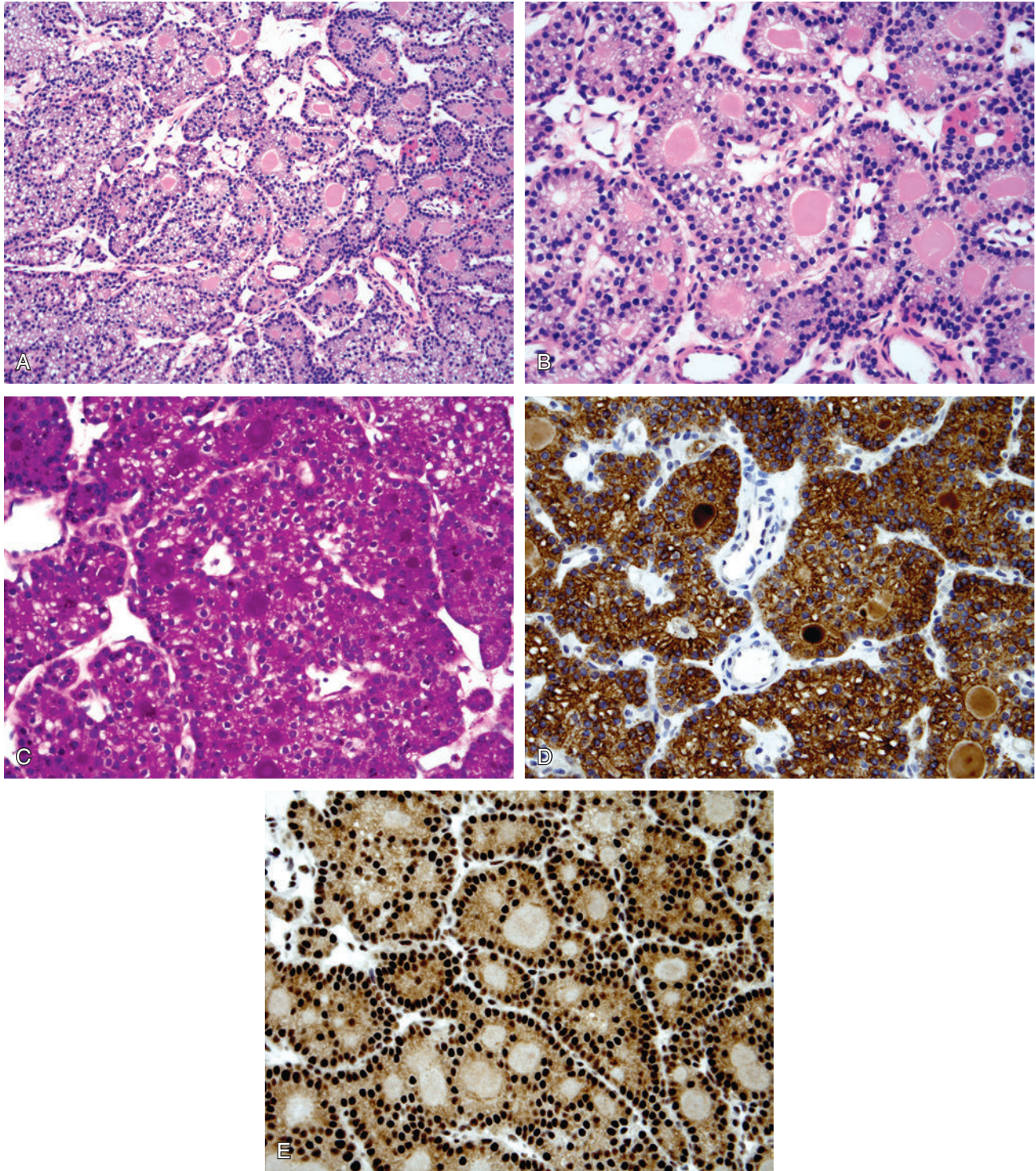


Fig. 30-3. Normal parathyroid gland.

A and B, The normal parathyroid gland may include a follicular growth pattern with central colloid-like material simulating the appearance of thyroid follicles. **C,** The eosinophilic colloid-like material is PAS-positive. Parathyroid gland origin is confirmed by immunohistochemical staining for **(D)** parathyroid hormone and **(E)** parafibromin (nuclear staining) but is negative for thyroglobulin and TTF1 (not shown).

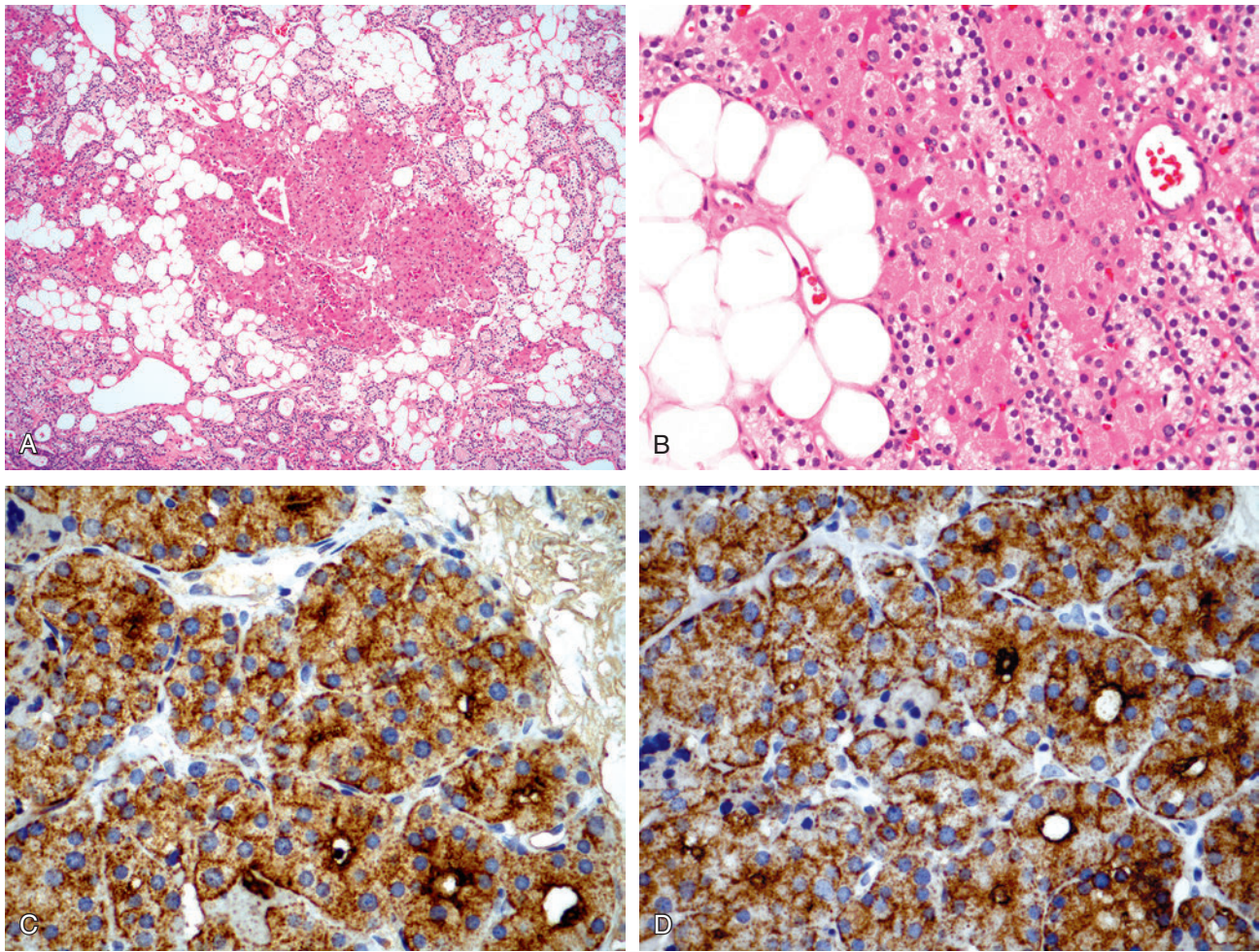


Fig. 30-4. Normal parathyroid gland.

The normal parathyroid gland in adults may include oncocytic cells (**A**) interspersed with the chief cells as a nodular focus. Note the presence of abundant intraparenchymal mature fat. **B**, At higher magnification the oncocytic cells are characterized by brightly eosinophilic-appearing cytoplasm. Oncocytic cells are immunoreactive for (**C**) parathyroid hormone (PTH) and (**D**) chromogranin but the staining for these markers tends to be less intense as compared with PTH and chromogranin staining in association with chief cells.

TABLE 30-1 Comparison of Normal Parathyroid Tissue to Abnormal Parathyroid Tissue

Parameter	Normal Range	Abnormal Changes
Number	Usually 4, sometimes 5	Ectopia
Size	Length 3-6 mm Width 2-4 mm Thickness 0.5-2.0 mm	Enlarged gland greater than 6 mm
Weight	Approx. 30 mg each: men: 120 ± 3.5 mg women 142 ± 5.2 mg	Any gland weighing greater than 60 mg
Percentage fat	Approximately 17%, rarely more than 50%; more in women than in men	Complete absence or very few intraparenchymal fat cells
Intracytoplasmic lipid	Abundant	Absent or scanty

Modified from Chan JKC: The parathyroid gland. In Fletcher CDM: Diagnostic histopathology of tumors, ed 4, Philadelphia, 2013, Elsevier Saunders, p 1274.

- Follicle-like structures often contain eosinophilic PAS positive material that resembles colloid:
 - Colloid-like material is not immunoreactive for thyroglobulin or thyroid transcription factor 1 (TTF1).
 - Resemblance of this colloid-like substance to amyloid at a light microscopic and ultrastructural level has been noted.
- Prominent lipid droplets are present in 70% to 80% of the chief cells.
- Chief cells, which are “active” in the secretory process, contain little or no cytoplasmic lipid; they also contain more secretory granules as evidenced by silver stains or by chromogranin staining.
- Women generally have a higher percentage of stromal fat than men.
- Generally stromal fat represents about 50% of total stromal volume.
- Stromal fat content is affected by several variables, including nutrition, body habitus, general state of health, and heredity.
- Immunohistochemical staining in normal parathyroid gland chief cells includes:
 - Parathyroid hormone (PTH), parafibromin (nuclear stain), chromogranin A, cytokeratins (CK8, CK18, CK19), and CD4
 - No reactivity for thyroglobulin, TTF1, PAX8, and calcitonin
 - Cyclin D1 present in approximately 6% of cases
- Oncocytic cells and transitional oncocytic cells are also found in the adult parathyroid:
 - Oncocytic cells are larger than chief cells and have striking eosinophilic granular cytoplasm.
 - Ultrastructural studies indicate that the cytoplasmic granularity results from the enormous number of mitochondria in these cells.
 - Nuclei of oncocytic cells are usually pyknotic.
 - Immunoreactivity includes:
 - Parathyroid hormone (PTH) and chromogranin A but less intense staining as compared to chief cells; chromogranin may be negative.
 - Parafibromin (nuclear stain)
 - Cytokeratins (CK8, CK18, CK19) are positive although less intense as compared to chief cells.
 - No reactivity for thyroglobulin, TTF1, PAX8, CD4, and calcitonin
 - Oncocytic cells may be interspersed in small groups among the chief cells, or they may form nodules.
 - Relative number of oncocytic cells and the tendency to form oncocytic cell nodules increase with age.
 - In older individuals oncocytic nodules (single, multiple) are common.
 - Transitional oncocytic cells appear to represent an intermediate phase in the transition from chief cells to oncocytic cells.
 - Although the oncocytic cells in normal glands do not seem to be actively secreting parathyroid hormone, hyperfunctioning oncocytic neoplasms have been reported.

FURTHER READING

References may be accessed online at ExpertConsult.com.

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Parathyroid Glands: General Considerations

HYPERPARATHYROIDISM

Definition: Hyperparathyroidism is the state of elevated serum parathyroid hormone (PTH) as a result of excessive secretion (overproduction).

- Hyperparathyroidism is the most common pathologic condition affecting the parathyroid glands.
- Causes of hyperparathyroidism due to parathyroid-related disorders are listed in [Box 31-1](#).
- Parathyroid-independent hypercalcemic disorders are listed in [Box 31-2](#).
- Hyperparathyroidism is divided into primary, secondary, and tertiary categories.
- Reference range for intact PTH in normal adults is 10-65 pg/ml.

Primary Hyperparathyroidism

Definition: Inappropriately elevated PTH secretion due to intrinsic abnormality of parathyroid gland(s), in the

BOX 31-1 Causes of Hyperparathyroidism Due to Parathyroid-Related Disorders

Primary

- Parathyroid proliferative disease, including:
 - Adenoma (approximately 85% of cases)
 - Hyperplasia (approximately 13% of cases)
 - Carcinoma (approximately 2% of cases)
- Syndromes associated with hyperparathyroidism include (see Section 10 for more complete discussion):
 - Multiple endocrine neoplasia (MEN)-1
 - MEN-2A
 - Hyperparathyroidism-Jaw syndrome
 - Less common syndromes associated with hyperparathyroidism include:
 - Familial hypocalciuric hypercalcemia
 - Familial hypercalcemic hypercalciuria
 - Neonatal severe primary hyperparathyroidism
 - Familial isolated hyperparathyroidism
- Rarely may be associated with parathyroid cyst

Secondary

- Chronic renal failure (most common)
- Dietary vitamin D deficiency or abnormalities of vitamin D metabolism
- Malabsorption
- Pseudohypoparathyroidism

Tertiary

- Same as secondary hyperparathyroidism

absence of known stimulus for PTH secretion causing elevation of serum calcium (hypercalcemia) with decreased serum phosphate (hypophosphatemia); hypercalciuria is common.

Clinical

- Current reported annual incidence is 0.04 per 1000 persons.
- Causes for primary hyperparathyroidism include the group of lesions collectively referred to as *parathyroid proliferative disease* composed of ([Fig. 31-1](#)):
 - Parathyroid adenoma: approximately 85% of cases
 - Parathyroid hyperplasia: approximately 13% of cases
 - Parathyroid carcinoma: approximately 2% of cases
- Syndromes associated with hyperparathyroidism include (see Section 10 for more complete discussion):
 - Multiple endocrine neoplasia (MEN)-1
 - MEN-2A
 - Hyperparathyroidism-Jaw syndrome
 - Less common syndromes associated with hyperparathyroidism include:
 - Familial hypocalciuric hypercalcemia
 - Familial hypercalcemic hypercalciuria
 - Neonatal severe primary hyperparathyroidism
 - Familial isolated hyperparathyroidism
- Rarely, primary hyperparathyroidism is associated with parathyroid cyst.

BOX 31-2 Parathyroid-Independent Hypercalcemia

- Hypercalcemia of malignancy
- Vitamin D intoxication
- Granulomatous diseases
 - Sarcoidosis
 - Other
- Hyperthyroidism
- Vitamin A intoxication
- Adrenal insufficiency
- Thiazide diuretics
- Milk-alkali syndrome
- Renal failure
- Immobilization
- Other

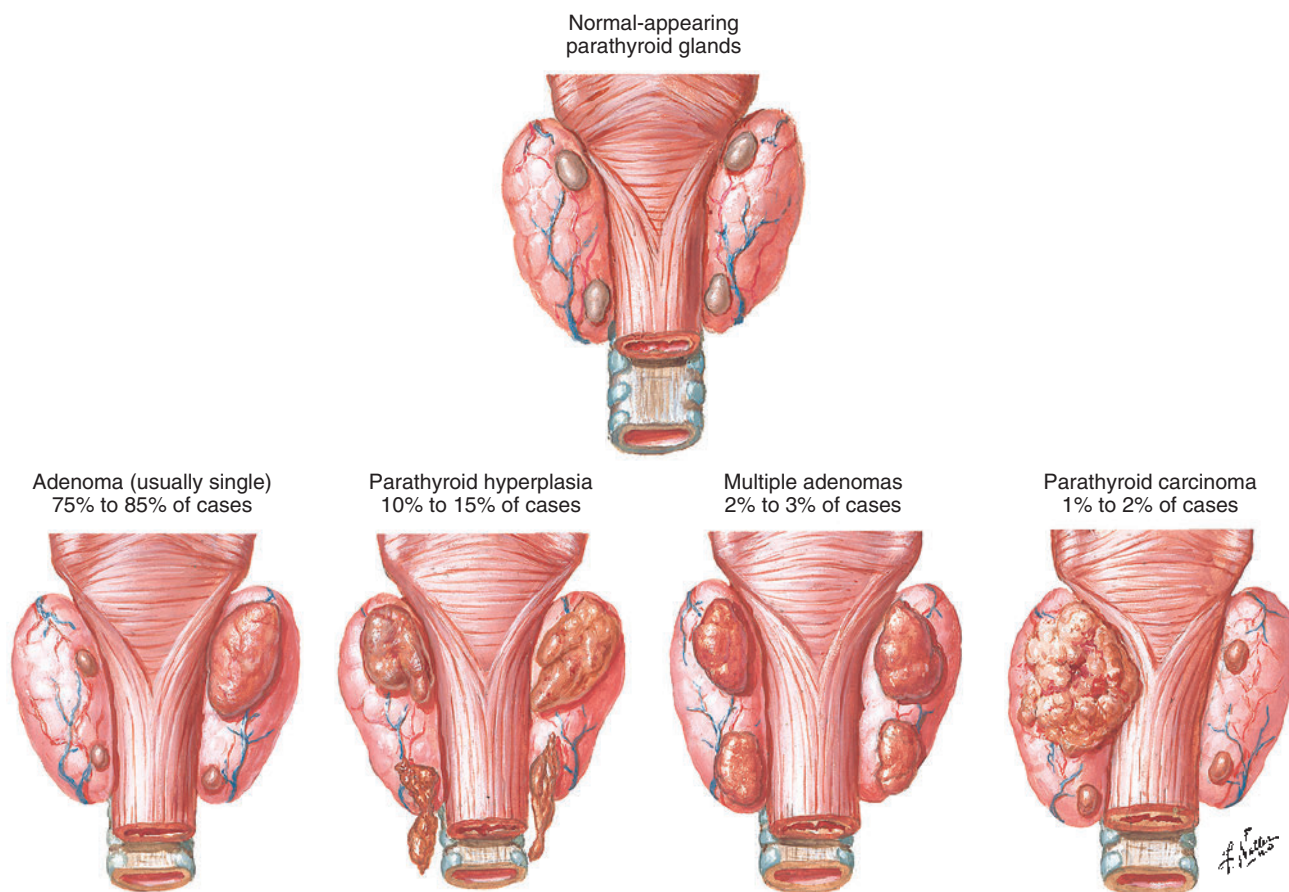


Fig. 31-1. Normal parathyroid glands and parathyroid gland abnormalities.

Drawings of the normal-appearing parathyroid glands and the appearance of the major causes of hyperparathyroidism.

(Modified from www.netterimages.com. From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-93, p 2661.)

- More common in women than in men; primarily occurs in middle and older ages with a mean age of occurrence in the sixth decade of life; may occur over a wide age range from the second to ninth decades of life.
- Symptoms are related to the level and duration of serum calcium elevation:
 - Patients are commonly asymptomatic or present with vague complaints, such as lethargy, weakness, polyuria, polydipsia, arthralgia, constipation, and depression.
 - Rather nonspecific presentation has been encountered more often in the past two decades when routine biochemical testing has resulted in an overall increase in the prevalence of primary hyperparathyroidism by detection of clinically silent cases.
- “Classical” primary hyperparathyroidism was characterized by:
 - Advanced bone disease: *osteitis fibrosa cystica* with increase of osteoclastic bone resorption accompanied by fibrovascular marrow replacement and increased osteoblastic activity:
 - Radiographic evidence of general demineralization of bone
 - Subperiosteal resorption most evident in the phalanges of the hands
 - Bone cysts, often multiple, with a tendency to occur in central medullary portions of the metacarpals, ribs, and pelvis
 - Osteoclastomas or “brown tumors” found in jaws, long bones, and ribs
 - Pathologic fractures
 - Renal manifestations:
 - Nephrolithiasis: recurrent and severe; stones composed of calcium phosphate
 - Nephrocalcinosis: presence of bilateral, extensive mineralization in renal pyramids and medullary regions
 - Other manifestations:
 - Conjunctival calcifications
 - Band keratopathy

- Hypertension
- Peptic ulcer disease
- Pancreatitis (acute and chronic)
- Signs and symptoms of severe classical primary hyperparathyroidism, including advanced bone disease and recurrent nephrocalcinosis are uncommon as compared with their incidence two to three decades ago:
- Diffuse osteopenia, with or without compression fractures, articular chondrocalcinosis, and other joint disorders, such as pseudogout and true gout, are currently more frequent findings.
- Biochemical findings include:
 - Elevated serum calcium, which is most accurately reflected by the serum ionized calcium value, because the regulated fraction of calcium is that which is not bound to plasma proteins
 - Decrease in serum inorganic phosphorus resulting from increased urinary loss of phosphates induced by the action of parathyroid hormone at the renal tubular level, as reflected by decreased tubular reabsorption of phosphate or by increased renal phosphate clearance
 - Corresponding increase in urinary cyclic AMP usually accompanies these parathormone-induced alterations in urinary phosphate metabolism
- Serum levels of parathyroid hormone vary depending on the type of assay:
 - Currently preferred assay quantitates intact parathyroid hormone molecule rather than only a cleavage product, as was measured in earlier procedures.
 - Normal serum value for intact parathyroid hormone is 210 to 310 pg/ml.
- Patients with mild symptoms may have significant morbidity due to bone disease.
- Increased mortality rates due to cardiovascular disease may occur.

Secondary Hyperparathyroidism

Definition: An increase in parathyroid parenchymal cell mass of multiple glands in response to a known clinical stimulus for increased secretion of parathyroid hormone. These conditions are usually characterized by hypocalcemia and hyperphosphatemia.

Tertiary Hyperparathyroidism

Definition: An absolute increase in parathyroid parenchymal cell mass associated with autonomous hyperfunction and resultant hypercalcemia in a patient with previously known secondary hyperparathyroidism following implementation of dialysis or renal transplantation.

BOX 31-3 Causes of Hypoparathyroidism Due to Parathyroid-Related Disorders

- Iatrogenic:
 - Postsurgical removal of parathyroid glands
 - Following ^{131}I ablative therapy
- Agenesis
- Familial hypoparathyroidism
- Idiopathic or autoimmune hypoparathyroidism
- Secondary tumors
- Pseudohypoparathyroidism

HYPOPARATHYROIDISM

Definition: Clinical disorder characterized by hypocalcemia and hyperphosphatemia due to deficiency in parathyroid hormone.

Clinical

- Causes of hypoparathyroidism due to parathyroid-related disorders are listed in [Box 31-3](#).
- Hypoparathyroidism may occur as a transient (acute) phenomenon or as a chronic disease.
 - Transient acute hypoparathyroidism may occur following parathyroid or thyroid surgery or following radioactive iodine ablation therapy:
 - Hypocalcemia is mild and may not require treatment.
 - Chronic hypoparathyroidism is uncommon; causes include:
 - Iatrogenic:
 - Postsurgical removal of parathyroid glands
 - Following ^{131}I ablative therapy of the thyroid gland in the treatment of Graves disease
 - Agenesis:
 - Complete or partial failure of development
 - Develops in association with other third and fourth branchial pouch abnormalities, including the thymus and thyroid C-cells, as in DiGeorge syndrome, which is characterized by:
 - ◻ Absence of cell-mediated immunity
 - ◻ Hypoparathyroidism
 - ◻ Congenital defect of the heart and great vessels
 - ◻ DiGeorge syndrome may be a neurocristopathy.
 - Association with other congenital defects in a syndrome referred to as 22q11.2 deletion syndrome or CATCH 22 syndrome:
 - ◻ Cardiac defect, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia, and 22q11 deletion
 - ◻ Includes DiGeorge syndrome, conotruncal anomaly face syndrome, and velocardiofacial syndrome.

- GATA-3:
 - Transcription factor functionally involved with the development of parathyroid glands (as well as) breast, urothelial, epidermal, T lymphocyte
 - Mutations in GATA-3 result in hypoparathyroidism characterized by hypocalcemia and low PTH
- Familial hypoparathyroidism:
 - Congenital or inherited mutation of a transcription factor called glial cell missing homolog B (*GCMB*) (6p23) expressed in the PTH-secreting cells of the developing parathyroids.
 - Several mutations in *GCMB* reported to cause hypoparathyroidism
 - Gene responsible for X-linked recessive hypoparathyroidism linked to Xq26-Xq27
- Idiopathic or autoimmune hypoparathyroidism:
 - Seen in conjunction with autoimmune polyglandular syndrome (APS) type I syndrome also referred to as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED):
 - Rare autosomal-recessive disorder caused by mutation of a single gene named autoimmune regular gene (*AIRE*), which results in a failure of T-cell tolerance within the thymus
 - Disorder by chronic mucocutaneous candidiasis, chronic hypothyroidism, and Addison disease
 - Patients have antibodies directed against other endocrine organs such as adrenal glands, ovaries, thyroid gland.
- Secondary tumors and/or infiltrative disease, including:
 - Metastatic tumors
 - Iron overload such as hemochromatosis and in patients with thalassemia major following numerous transfusions
 - Copper deposition in Wilson disease
- Pseudohypoparathyroidism:
 - Idiopathic and inherited forms of PTH resistance characterized by end-organ resistance to parathyroid hormone due to partial deficiency of the α subunit of the stimulatory G protein ($G_{s\alpha}$), encoded by the *GNAS* gene resulting in low serum calcium, high serum phosphate, and appropriately high serum parathyroid hormone
 - Albright hereditary osteodystrophy (AHO), also known as pseudohypoparathyroidism, type 1a includes:
 - Hypocalcemia and hyperphosphatemia
 - Short stature
 - Rounded face
 - Foreshortened fourth metacarpals
 - Obesity
 - Subcutaneous calcifications
 - Defect in the PTH receptor or in its cAMP-mediated signal transduction
 - Measurement of cAMP in urine following infusion of synthetic PTH is used to establish the diagnosis of PTH resistance.
 - Subclassification into five disorders based on presence of AHO and renal resistance to PTH
 - Pseudopseudohypoparathyroidism is used to refer to patients with the phenotype of AHO but with normal biochemical parameters (lack of PTH unresponsiveness).
- Predominant clinical signs and symptoms of hypocalcemia are:
 - Neuromuscular irritability, including:
 - Perioral paresthesias
 - Tingling in the fingers and toes
 - Tetany (spontaneous or latent):
 - Chvostek sign: ipsilateral contractions of the facial nerve on percussion of the facial nerve below the zygoma
 - Trousseau sign: carpal spasm (may be painful) following 3 minutes of occlusive pressure with a blood pressure cuff
 - EKG abnormalities from hypocalcemia include:
 - Prolonged QT intervals
 - Marked QRS and ST segment changes that may mimic acute myocardial infarction or conduction abnormalities
 - Ventricular arrhythmias (rare complication of hypocalcemia)
 - CNS abnormalities:
 - Convulsions
 - Irritability and depression
 - Psychosis
 - Basal ganglia calcifications with extrapyramidal manifestations
 - Increased intracranial pressure with papilledema
- Total serum calcium includes free (biologically active) and protein bound components, and the major binding protein is albumin:
 - Measurements of total calcium must include concurrent measurement of albumin.
- In comparison to nonparathyroid related hypocalcemia, parathyroid dysfunction includes:
 - Low serum calcium due to lack of PTH-mediated bone resorption and urinary calcium reabsorption

- Increased serum phosphate due to impaired renal function
- Low serum $1,25(\text{OH})_2\text{D}_3$ and decreased $1,25(\text{OH})_2\text{D}_3$ intestinal calcium absorption (further exacerbating the hypocalcemia)
- Low or undetectable PTH levels:
 - PTH levels may be inappropriately normal if some degree of PTH production is preserved.
 - Elevated PTH levels may be present in syndrome associated with resistance to the biologic effects of PTH.
- Acute hypocalcemia is a medical emergency requiring prompt attention:
 - In the presence of neuromuscular irritability, IV calcium is administered until the effects of hypocalcemia abate.
- Treatment of hypocalcemia should be directed at its underlying cause and includes exogenous calcium and vitamin D replacement therapy.
- Vigilant monitoring of the patient to assess efficacy of treatment and to prevent complications is indicated:
 - Daily monitoring of serum calcium for the first month of therapy
 - Measurement of serum PTH and 24-hour urinary calcium excretion is performed within 2 to 4 weeks of institution of therapy.

FURTHER READING

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Non-Neoplastic Lesions of the Parathyroid Glands

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE PARATHYROID GLANDS

(Box 32-1)

BOX 32-1 Non-Neoplastic Lesions of the Parathyroid Glands

- Parathyroid hyperplasia
 - Primary chief cell hyperplasia
 - Water-clear cell hyperplasia
- Parathyroiditis
- Parathyroid cyst

PRIMARY CHIEF CELL HYPERPLASIA (Figs. 32-1 through 32-5, Table 32-1)

Definition: Non-neoplastic increase in parenchymal cell mass of multiple parathyroid glands in the absence of a known clinical stimulus for increased secretion of parathyroid hormone.

Clinical

- Responsible for approximately 13% of cases of hyperparathyroidism
- An autopsy incidence of 7% has been reported.



Fig. 32-1. Parathyroid hyperplasia.

This gland was one of three enlarged glands in a patient with primary hyperparathyroidism. The gland has a variegated nodular appearance.

- Affects females more often than males (F:M = 3:1); incidence increases with age
- Occurrence:
 - Sporadic cases represent 80% of patients with primary chief cell hyperplasia.
 - 20% have familial disease, usually associated with one of the multiple endocrine neoplasia syndromes, although familial parathyroid hyperplasia without other endocrine abnormalities also occurs.
- See under hyperparathyroidism for signs, symptoms, and laboratory findings (see Chapter 31).
- Approximately 20% of patients with primary chief cell hyperplasia have one of the multiple endocrine neoplasia syndromes (MEN):
 - Association is most frequent in MEN type 1 (MEN-1, Wermer syndrome).
 - Parathyroid proliferative disease is seen in 30% to 40% of patients with MEN-2A (Sipple syndrome), but is rare in MEN-2B (Gorlin syndrome).
- MEN-1 (Wermer syndrome) includes:
 - Autosomal-dominant transmission with variable penetrance:
 - Germline mutation on chromosome 11q13

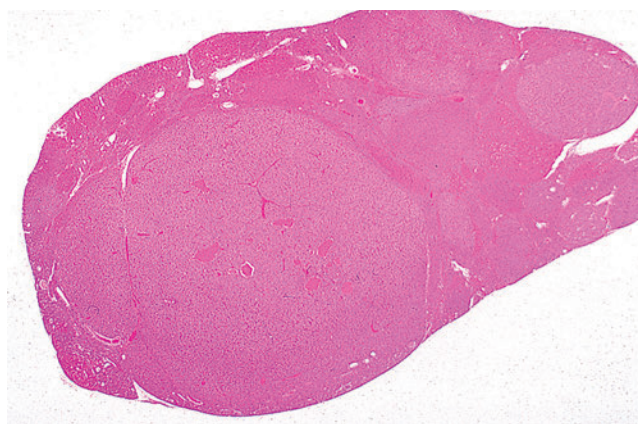


Fig. 32-2. Parathyroid hyperplasia.

The multinodular appearance of this gland is the result of proliferation of groups of cells with different cytologic features; the entire gland is affected by the proliferative process; no rim of normal parathyroid tissue is seen.

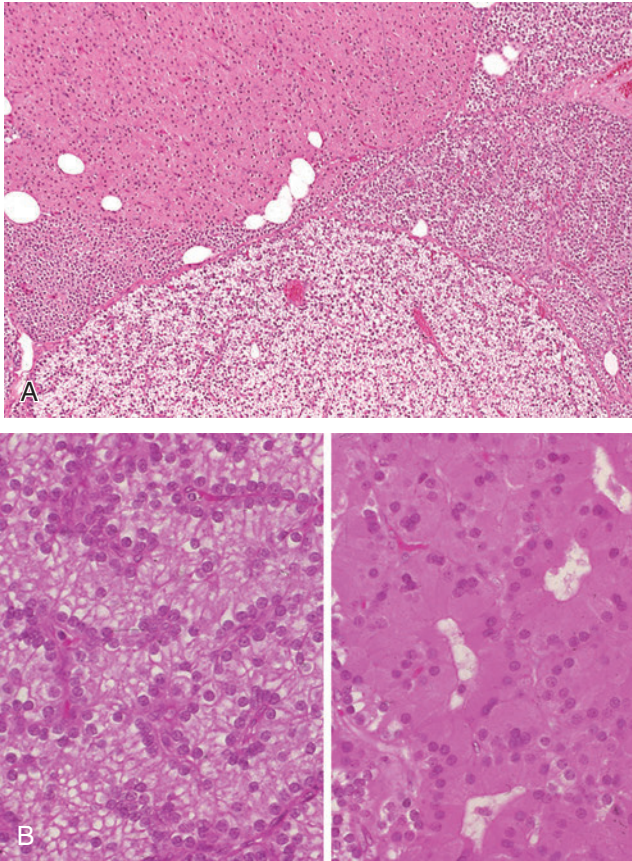


Fig. 32-3. Parathyroid hyperplasia.

A, The nodules within the gland are composed of those with clear cells and another with oncocytic cells.

B, Different areas of the same hyperplastic gland may contain predominantly chief cells (*left*) or oncocytic cells (*right*).

- 90% of patients have parathyroid hyperplasia; less often associated with parathyroid neoplasms (adenoma and carcinoma)
- Pancreatic or duodenal endocrine tumors (gastrinoma, insulinoma, glucagonoma)
- Gastrointestinal endocrine cell hyperplasia or neoplasia (functioning and nonfunctioning)
- Anterior pituitary adenoma (functioning and nonfunctioning)
- Some patients also develop pulmonary and thymic neuroendocrine neoplasms, adrenal cortical neoplasms, and thyroid follicular neoplasms.
- MEN-2:
 - Includes MEN-2A (Sipple syndrome) and MEN-2B (Gorlin syndrome)
 - MEN-2A and MEN-2B:
 - Autosomal-dominant transmission:
 - Germline mutations in *RET* proto-oncogene located on chromosome 10q11.2

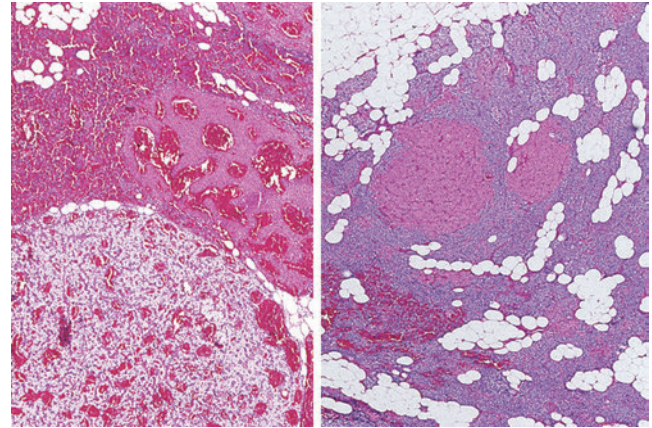


Fig. 32-4. Parathyroid hyperplasia.

The hyperplastic features may be unevenly distributed among the four glands or even within a single gland. *Left*, Nodules and areas of solid growth with high cellularity. *Right*, Area showing a higher percentage of lipocytes admixed with diffuse cellular areas of chief cells and scattered small oncocytic nodules.

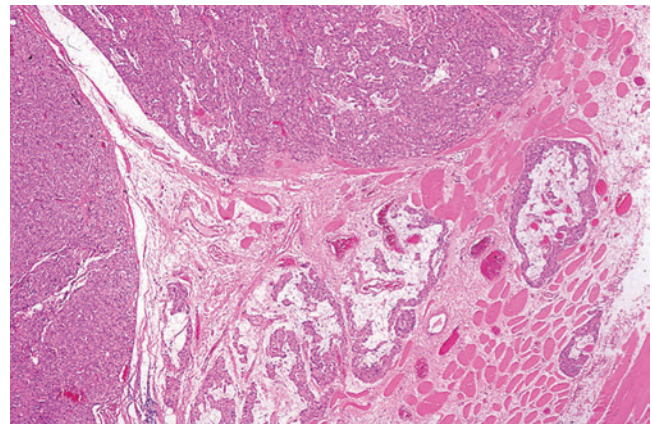


Fig. 32-5. Recurrent parathyroid hyperplasia.

Recurrent parathyroid hyperplasia in parathyroid auto-grafted into the forearm. This patient had a history of chronic renal failure with secondary hyperparathyroidism. His hypercalcemia recurred several months after subtotal parathyroidectomy with autoimplantation of portions of parathyroid gland into the soft tissue of the forearm. The irregular islands of cellular parathyroid tissue may appear to be infiltrating skeletal muscle. This pattern, and even the presence of mitotic figures in the parathyroid tissue, do not indicate malignancy.

- MEN-2A (Sipple syndrome):
 - Characterized by development of bilateral C-cell hyperplasia, thyroid medullary carcinoma, pheochromocytoma, and parathyroid hyperplasia
- MEN-2B (Gorlin syndrome): characterized by development of bilateral C-cell hyperplasia,

TABLE 32-1 Comparative Features of Parathyroid Proliferative Diseases

	Hyperplasia	Adenoma	Carcinoma
Gender; age	Slight female predilection; most common in 5th-6th decades	More common in women; most common in 4th decade	Equal gender predilection; wide age range
Clinical	Asymptomatic or complaints of lethargy, weakness, polyuria, polydipsia, arthralgia, constipation, and depression	Similar to hyperplasia	Similar to hyperparathyroidism of benign etiology but more severe due to the higher serum calcium levels; higher proportion of renal disease (nephrolithiasis) and bone disease; peptic ulcer disease; palpable neck mass more common than in adenoma
Serum calcium	11.7 mg/dl (average)	12.5 to 13.5 mg/dl	Often >14 mg/dl
Intraoperative findings	2 or more glands enlarged, easily dissected; enlargement may be asymmetric	1 gland enlarged; easily dissected; more frequent in lower glands or ectopic sites	1 gland enlarged; often adherent to surrounding tissues
Weight	Total gland weight usually <1 g, but may be up to 5 g	0.3 to 1.0 g commonly, but may weigh several grams in patients with bone disease	>1.5 g (often much larger)
Capsule	Circumscribed by capsule of parathyroid gland, may be incomplete No compressed rim of atrophic or normal parathyroid tissue	Thin tumor capsule, often surrounded by rim of uninvolved parathyroid, which may appear atrophic	Thickened capsule; rim of normal parathyroid rarely seen
Gross appearance	Gray-brown, soft Cut surface may be homogeneous or nodular Lacks fibrous bands	Red-brown, firm Usually homogeneous, lacks fibrous bands but may appear nodular	Gray-white, firm, often lobulated or irregular Fibrous bands often produce coarse nodularity
Histologic pattern	Diffuse or nodular, sometimes follicular or acinar	Diffuse or nodular, frequently follicular or acinar	Predominantly solid or diffuse; may include trabecular, organoid, spindle, or follicular
Cytologic features	Chief cells predominate; transitional and oncocytic cells often present	Chief cells predominate, but mixture of chief, transitional, and oncocytic cells may be seen; rarely, purely oncocytic	Cells usually resemble chief cells, but variable cytoplasmic oncocytic change may be seen; cell borders often indistinct
Intracytoplasmic lipid	Decreased	Decreased in tumor; abundant in atrophic rim of parathyroid	Usually absent
Stromal fat cells	Scanty to absent	Usually absent in tumor; present in rim of atrophic parathyroid	Absent
Nuclear morphology	Normal to slightly increased N-to-C ratio; usually without nuclear pleomorphism	Nuclei enlarged, with variability in size; scattered groups of large pleomorphic, hyperchromatic nuclei, or multinucleated cells	Increased N-to-C ratio; enlarged atypical nuclei; often with very monotonous (bland appearing) nuclei
Nucleoli	Inconspicuous to small	Inconspicuous to small	Frequently prominent and enlarged
Mitoses	Common (60% of cases; most with <1 mitotic figure/10 HPF)	Common (70% of cases; most with <1 mitotic figure/10 HPF)	Common (80% of cases), may include atypical mitoses
Capsular and vascular invasion	Absent	Absent; entrapment of tumor cells may occur in capsule if degenerative changes present	Capsular invasion present in two thirds; may involve only capsule or extend into adjacent tissues Vascular invasion present in up to 15%; usually in capsular vessels

TABLE 32-1 Comparative Features of Parathyroid Proliferative Diseases—cont'd

	Hyperplasia	Adenoma	Carcinoma
Remainder of gland	Entire gland is abnormal	Normal or atrophic	Normal
Degenerative changes	May be seen in very large glands; includes hemorrhage, areas of fibrosis, and cystic change	Common, especially in larger adenomas; includes hemorrhage, fibrosis, and cystic change, sometimes calcification	Tumor cell necrosis; calcification and cystic changes may be present
Treatment	Subtotal parathyroidectomy with surgical removal of three glands leaving a remnant of the fourth or total parathyroidectomy* with autotransplantation of parathyroid tissue in forearm	Surgical removal of the enlarged gland	En bloc resection, including ipsilateral thyroid lobe and adjacent soft tissues
Prognosis	Excellent	Excellent	Up to 50% of patients are cured by en bloc resection; considered an indolent malignancy even in presence of recurrence or metastasis with long survival even after recognition of tumor recurrence; morbidity and mortality correlate to complications of severe hypercalcemia
Recurrence and metastasis	Recurrence in approximately 16% of cases due to inadequate neck exploration and may not be evident for years	Absent	Recurrence in two thirds of patients usually within 3 years of the first surgery; metastasis is 35%, is a late event usually preceded by local recurrence; most commonly to lung, cervical lymph nodes, and liver
Familial and/or MEN association	Yes, in approximately 20% of cases	Uncommon	Rare

g, Grams; HPF, high power fields; MEN, multiple endocrine neoplasia syndrome; N-to-C, nuclear-to-cytoplasmic.

*Particularly in cases of familial hyperparathyroidism.

medullary thyroid carcinoma, pheochromocytomas, and oral and gastrointestinal ganglioneuromatosis

Radiology

- Radiographic imaging techniques applied to localization of hyperfunctioning parathyroid glands include retrograde phlebectomy with serum parathormone assays, CT scanning, ultrasonography, magnetic resonance imaging (MRI), thallium subtraction scanning, and technetium-99m sestamibi imaging.
- Imaging procedures have been significantly less effective in localizing glands in cases of hyperplasia as compared with parathyroid adenomas or carcinomas.
- Technetium-99m sestamibi has been effective in localizing up to 60% of hyperplastic glands; it has been more widely used in the evaluation of patients

with recurrent hyperparathyroidism after parathyroid resection.

Pathology

Cytology

- Cytologic findings in aspirate smears of parathyroid hyperplasia and parathyroid adenoma are indistinguishable and allow only documentation of “parathyroid proliferative disease.”

Gross

- Although all four glands may be enlarged, it is not uncommon for hyperplasia to be somewhat asymmetric, with two or three glands being much larger than the others.
- In some cases one gland is so much larger than the others that the gross appearance suggests an adenoma, emphasizing the importance of sampling

grossly “normal” glands to facilitate accurate discrimination between hyperplasia and adenoma, because increased cellularity of the smaller glands may be the key to recognizing the multiglandular nature of the proliferation.

- Glands may be diffusely enlarged or may be nodular, particularly with increasing size.
- Cystic change may be present but is not common.
- Total gland weight in primary chief cell hyperplasia is variable and has been reported as:
 - <1 g in 54% of patients
 - 1 to 5 g in 28% of patients
 - 5 to 10 g in 18% of patients
- Glands are usually soft and tan-brown
- Distinction between hyperplastic and adenomatous glands generally cannot be made by gross examination.

Histology

- Primary chief cell hyperplasia results from an increase in parenchymal cell mass, predominantly involving chief cell proliferation; however, oncocytic cells may be present as well.
- Chief cell hyperplasia may be diffuse or nodular:
 - Chief cells may be arranged in solid sheets, cords, acinar-like, or follicular structures or commonly mixed patterns are identified.
 - Variable nodularity
 - Nodules may be small (micronodular), solitary, or multiple.
- Small follicular structures may contain PAS-positive material resembling dense colloid; this material is thyroglobulin negative.
- Stromal fat cells are absent or markedly decreased in number in most areas, although foci of stromal fat cells may mimic normal gland:
 - Variations in distribution of fat cells and variability in the density of the chief cells, particularly in a nodular hyperplasia, may yield a confusing histologic picture.
 - Areas with residual fat may mimic a rim of “normal” gland, particularly when they are adjacent to large nodules, which generally lack fat cells, may suggest a diagnosis of adenoma, again emphasizing the importance of microscopic examination of multiple glands and the need for processing multiple sections of larger glands.
- Although circumscribed by the delicate fibrous capsule of the gland, hyperplasia may also involve nests of parathyroid tissue in the soft tissue of the neck (“parathyromatosis”):
 - This phenomenon may be the cause of recurrent disease after an apparently complete resection of the grossly evident hyperplastic glands.
 - Should not be mistaken for “invasion” as one would see in carcinoma; the lack of a fibroblastic

reaction or infiltrative contour, absence of an intravascular location of these nests, and lack of other histologic features of carcinoma should help exclude malignancy.

- Hyperplastic cells usually contain less intracytoplasmic fat than normal or atrophic parathyroid tissue when demonstrated by oil red O or Sudan black stains; however, some hyperplastic parathyroid tissue may contain abundant intracytoplasmic fat:
 - Intracytoplasmic fat may be more abundant in the chief cells between hyperplastic nodules, whereas it is usually absent in cells within the nodules.
 - The term lipohyperplasia has been used in cases of hyperplastic glands with abundant fat:
 - Presence of fat in this setting makes the diagnosis of hyperplasia challenging.
 - Biopsies may contain only fat or be predominantly of fat with limited parenchymal cells.
 - The clinical setting and enlargement of multiple glands is important in the diagnosis of lipohyperplasia.
- Although mitotic figures may be seen, they usually number less than 1 per 10 high-power fields; some cases demonstrate mitotic rates of 1 to 5 per 10 high-power fields; however, atypical mitoses are not present.
- Immunohistochemistry:
 - Chief cells are positive for parathyroid hormone (PTH), parafibromin (nuclear), cytokeratins, chromogranin A:
 - Staining for PTH and chromogranin A is less intense as compared with normal (nonhyperplastic) chief cells.
 - Calcitonin and synaptophysin typically negative but in small percentage of cases may be focally positive
 - PAX8 (nuclear) reactivity present in approximately 40% of hyperplasia and adenomas
 - Negative for thyroglobulin and TTF-1
- Electron microscopy:
 - Cells contain abundant mitochondria, endoplasmic reticulum, and large Golgi areas, as well as characteristic secretory granules.
- Cytogenetics and molecular genetics:
 - Chief cell hyperplasia associated with MEN: see previously

Differential Diagnosis

- Parathyroid proliferative disease, especially adenoma and also carcinoma ([Table 32-1](#))
- Lithium therapy for psychiatric disorders has been associated with a form of hyperparathyroidism similar to primary hyperparathyroidism with hypercalcemia and elevated serum parathormone levels;

chief cell hyperplasia and “adenomas” have been described in these patients:

- Hyperparathyroidism resolves after discontinuing lithium therapy
- Patients requiring lithium may be treated successfully with subtotal parathyroidectomy.
- Humoral hypercalcemia of malignancy (HHM) is an important clinical differential diagnostic consideration in patients suspected of having primary hyperparathyroidism:
 - HHM is independent of the extent of metastatic disease involving bone and is characterized by hypercalcemia, hypophosphatemia, and elevated urinary cyclic AMP levels.
 - Unlike hyperparathyroidism, serum parathormone, and 1,25-dihydroxyvitamin D are suppressed.
 - Mechanism for hypercalcemia appears to be increased bone resorption due to a humoral factor known as parathyroid hormone-related protein.
 - This form of hypercalcemia was most frequent in patients with squamous cell carcinoma (lung, upper aerodigestive tract, and female genital tract), renal cell carcinoma, and transitional cell carcinoma.
 - A second mechanism of hypercalcemia associated with malignancy is related directly to the osteolytic effect of bone metastases; this form of hypercalcemia is more common in patients with breast carcinoma and hematologic malignancies; these patients have suppressed levels of parathormone, but urinary cyclic AMP is not elevated and parathyroid hormone-related protein has not been implicated.
- Familial benign hypercalcemia or familial hypocalciuric hypercalcemia:
 - Autosomal-dominant condition
 - Caused by inactivating mutations in the calcium sensing receptor (*CASR*) gene, leading to a general calcium-hyposensitivity, compensatory hypercalcemia, and hypocalciuria
 - Should be suspected in young patients with presumptive diagnosis of hyperparathyroidism and family history
 - Hypercalcemia often starts in childhood.
 - Persistent hypercalcemia following subtotal parathyroidectomy for presumed primary hyperparathyroidism
 - Many patients are asymptomatic or have vague symptoms.
 - Signs and symptoms of hypercalcemia are rare.
 - Calcium:creatinine clearance ratio is traditional test to diagnose this disorder:
 - Patients have low urinary calcium excretion relative to serum calcium levels, elevated serum

magnesium levels, parathyroid hormone levels are usually elevated but lower than in primary hyperparathyroidism

- Histologically, parathyroid glands are normal or show mild chief cell hyperplasia.

Treatment and Prognosis

- Subtotal parathyroidectomy with complete removal of three glands, leaving a remnant of the fourth, is the most widely accepted therapy.
- Total parathyroidectomy with autotransplantation of remnants of parathyroid tissue in the forearm is also a common surgical therapy.
- Recurrence rate of hyperparathyroidism following subtotal parathyroidectomy is approximately 16%:
 - Recurrences may not be evident for several years.
 - Recurrences may be due to inadequate neck exploration, which may result from diagnosis of “adenoma” in cases of asymmetric hyperplasia.
 - Less frequent causes include failure to recognize supernumerary or ectopic glands, parathyromatosis, or surgical implantation of hyperplastic tissue in the soft tissue of the neck.

WATER-CLEAR CELL HYPERPLASIA (Figs. 32-6 and 32-7)

Definition: Non-neoplastic increase in parenchymal cell mass of multiple parathyroid glands by proliferation of large cells with clear, vacuolated cytoplasm, in the absence of a known clinical stimulus for increased secretion of parathyroid hormone.

Synonym: Wasserhelle cell hyperplasia

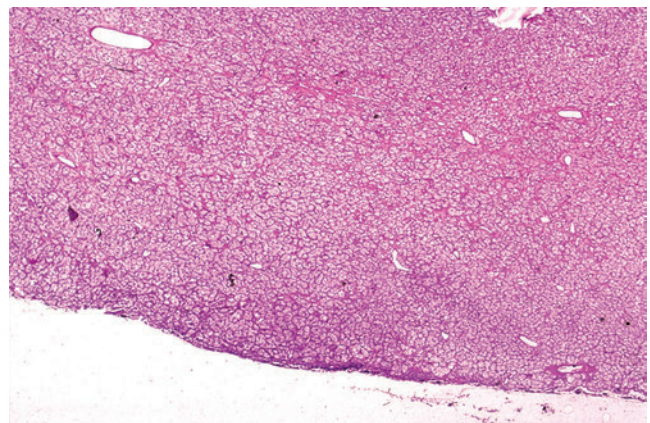


Fig. 32-6. Water-clear cell hyperplasia.

In water-clear cell hyperplasia the glands are usually markedly enlarged and are replaced by a diffuse proliferation of clear cells with no stromal fat, although in other examples, limited intraparenchymal fat may be present.

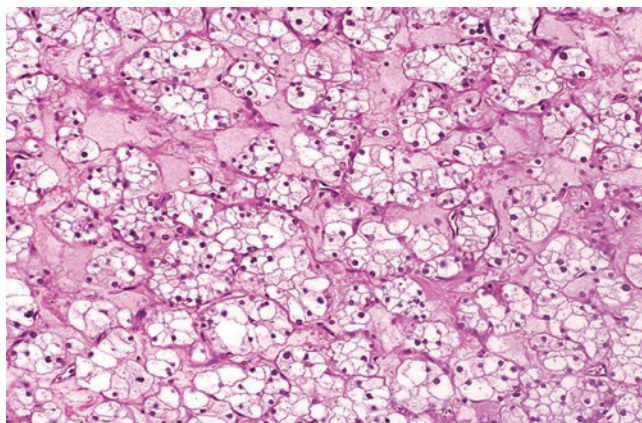


Fig. 32-7. Water-clear cell hyperplasia.

In contrast to the cells in chief cell hyperplasia, the cells in water-clear cell hyperplasia show more abundant, clear appearing cytoplasm, a much lower nuclear-to-cytoplasmic ratio, and the presence of distinct cell membranes.

Clinical

- Slightly more common in men than in women (M:F = 1.4:1); most common in fifth decade
- Very rare cause of hyperparathyroidism:
 - Reason for the virtual disappearance of water-clear cell hyperplasia in the population is not known; some suggest that it represents an advanced form of primary chief cell hyperplasia.
 - Decreasing incidence and severity of chief cell hyperplasia as a result of routine biochemical screening of patients lends some support to this theory
 - Electron microscopic appearance of water-clear cell hyperplasia sufficiently distinctive from primary chief cell hyperplasia to doubt that it develops from pre-existing chief cell hyperplasia
- Hypercalcemia and symptoms are usually more severe than in chief cell hyperplasia:
 - Mean serum calcium, 13.2 mg/dl, compared with 11.7 mg/dl in cases of chief cell hyperplasia
- Nephrolithiasis occurs in 90% of patients, in contrast to a rate of 53% of patients with chief cell hyperplasia during the same period.
- Overall incidence of bone disease similar to chief cell hyperplasia, with occasional patients presenting with osteitis fibrosa cystica
- No documented association with multiple endocrine neoplasia or other familial syndromes

Pathology

Gross

- Usually all four glands are enlarged, although asymmetry is common, and the upper glands are often larger than the lower glands.

- Mean total gland weight >10 g in 47% of cases; combined weight under 1 g not reported
- Involved glands are dark brown and may exhibit cystic change, areas of fibrosis, or hemorrhage; nodularity within the glands is uncommon, but the gland contour is often irregular.

Histology

- Glands are usually diffusely replaced by large clear cells, with little or no remaining stromal adipose tissue.
- Cells are from 10 to 40 μ in diameter, with distinct cell borders arranged in sheets, cords, or sometimes in acinar groups.
- Cytoplasm appears clear with distinct cell membranes but may contain many small vacuoles, which give a finely reticulated pattern in hematoxylin-eosin stained sections:
 - Vacuoles are more readily apparent in plastic-embedded thin sections.
 - Glycogen is demonstrable in the cytoplasm with periodic acid Schiff.
 - Neutral fat stains are negative.
- Nuclei are small, round to ovoid, rather hyperchromatic, and are basally oriented in the polyhedral to slightly columnar cells.
- Scattered multinucleated cells and occasional large hyperchromatic nuclei may be observed.
- Immunohistochemistry:
 - Parathyroid hormone (PTH), parafibromin (nuclear), cytokeratins, chromogranin A positive:
 - Staining for PTH and chromogranin A less intense as compared with normal (nonhyperplastic) chief cells
 - Calcitonin staining may focally be present.
 - Cyclin D1 expression present in majority of cases (approximately 61%)
 - Negative for thyroglobulin and TTF-1
- Electron microscopy:
 - Clear cells contain numerous membrane-bound vacuoles, many of which appear “empty”; however, some contain electron-dense material similar to the smaller typical parathyroid secretory granules, which are also scattered through the cytoplasm.

Differential Diagnosis

- Primary chief cell hyperplasia
- Parathyroid adenoma (particularly if only one gland has been sampled or if the hyperplasia is very asymmetric)
- Metastatic renal cell carcinoma with differentiation based on the presence in parathyroid hyperplasia of:
 - Biochemical findings of hyperparathyroidism
 - Positive immunohistochemistry for PTH, parafibromin, and chromogranin

- Absence of renal cell carcinoma (RCC) antibody, CD10, PAX2, PAX8, and CAIX
- Follicular thyroid neoplasm with clear cell features:
 - Presence of thyroglobulin, TTF1, and PAX8 differentiates thyroid from parathyroid lesions.

Treatment and Prognosis

- Subtotal parathyroidectomy is the preferred therapy.
- Recurrent hyperparathyroidism found in 45% of cases, probably because too large a remnant of parathyroid gland was preserved at original operation.

SECONDARY HYPERPARATHYROIDISM

Definition: An increase in parathyroid parenchymal cell mass of multiple glands in response to a known clinical stimulus for increased secretion of parathyroid hormone; usually characterized by hypocalcemia and hyperphosphatemia.

Clinical

- Causes of secondary hyperparathyroidism include chronic renal failure (most common), dietary vitamin D deficiency or abnormalities of vitamin D metabolism, malabsorption, and pseudohypoparathyroidism.
- Occurs over broad age range, reflecting the incidence of chronic renal failure, the most common cause of secondary hyperparathyroidism
- Symptoms of secondary hyperparathyroidism are related primarily to parathyroid hormone-mediated bone resorption, which results in osteomalacia and osteitis fibrosa cystica.
- Abnormal calcium deposits may be seen, including:
 - In the soft tissues, particularly in a periarticular distribution
 - Cutaneous calciphylaxis:
 - Uncommon
 - Mainly seen in renal failure-associated hyperparathyroidism
 - Progressive cutaneous vascular calcification
 - Potentially lethal
- Laboratory studies reveal elevation of parathyroid hormone levels with hypocalcemia and hyperphosphatemia.

Pathology

Gross

- Not significantly different from that of primary chief cell hyperplasia; there may be uniform enlargement of all glands or the enlargement may be asymmetric
- Glands are yellow-brown to gray, with weights ranging from 0.12 to 6 g.

Histology

- Proliferation includes chief cells, oncocytic cells, and transitional cells.
- Increased parenchymal cell mass varies depending on the duration of disease, as does the number of residual stromal fat cells:
 - In advanced disease the fat cells are absent.
- Parenchymal cells may grow in sheets, cords, or acinar structures.
- Nodular aggregates of chief cells or oncocytic cells are common in very enlarged glands; areas of fibrosis, cystic change, and calcification may be present.
- Oncocytic cells seem to be a more common component than in primary chief cell hyperplasia.

Differential Diagnosis

- Primary chief cell hyperplasia
- Parathyroid adenoma

Treatment and Prognosis

- Subtotal parathyroidectomy is the preferred treatment:
 - Remnant of parathyroid gland may be left in situ or transplanted to the soft tissue of the forearm.
 - Auto-transplantation of parathyroid tissue into the forearm musculature following total parathyroidectomy may be associated with graft failure and hypoparathyroidism, or with recurrent hyperparathyroidism due to hyperplasia of the transplanted remnant of parathyroid.
- Recurrence of hyperparathyroidism is a common problem in patients with chronic renal failure, since the stimulus for hypersecretion of parathyroid hormone is frequently not correctable.
- Recurrent hyperplasia may be associated with a multifocal proliferation of islands of parathyroid tissue in the adipose tissue and skeletal muscle, sometimes rather widely separated from the original site of transplantation:
 - Hyperplastic cells may be somewhat more pleomorphic than the original parathyroid proliferation and may even be mitotically active.
 - These changes should not be interpreted as evidence of malignancy.

TERTIARY HYPERPARATHYROIDISM

Definition: An absolute increase in parathyroid parenchymal cell mass associated with autonomous hyperfunction and resultant hypercalcemia in a patient with previously known secondary hyperparathyroidism following implementation of dialysis or renal transplantation.

Clinical

- Tertiary hyperparathyroidism occurs over a broad age range, reflecting the incidence of chronic renal failure.
- Hypercalcemia usually develops several years after the diagnosis of renal disease.
- Hypercalcemia due to tertiary hyperparathyroidism represents a serious threat to renal grafts and requires prompt surgical therapy.
- Laboratory findings are similar to those of primary hyperparathyroidism.
 - Increase in parathyroid parenchymal cell mass of multiple glands in response to a known clinical stimulus for increased secretion of parathyroid hormone. These conditions are usually characterized by hypocalcemia and hyperphosphatemia.
- The cause of autonomous hyperfunction of the parathyroids in patients with treated renal failure is not known; an elevation of the “set point” for serum calcium has been postulated; this would result in stimulation of parathyroid tissue in spite of normal serum calcium levels.
- There is also evidence that the sheer mass of parathyroid tissue in patients with tertiary hyperparathyroidism may cause autonomous function.
- Removal of the bulk of the hyperplastic tissue results in a readily suppressible remnant.

Pathology

Gross

- The glands may be diffusely enlarged or nodular. Patients with nodular hyperplasia tend to have more striking, but asymmetric, gland enlargement.
- Parathyroid glands with diffuse hyperplasia are 10 to 20 times the size of normal parathyroid glands; those with nodular hyperplasia were 20 to 40 times normal size.

Histology

- 95% of patients with tertiary hyperparathyroidism have hyperplasia; only 5% are found to have adenomas.
- Chief cells predominate in hyperplasia due to tertiary hyperparathyroidism; however, oncocytic and transitional cells may be seen in either diffuse or nodular hyperplasia. Rarely, areas with water-clear cells may be present.
- Areas of hemorrhage, recent or remote, as well as fibrosis and calcification are common.
- Mitotic figures are uncommon, as is nuclear pleomorphism.
- Stromal fat cells are sparse but are more often present in areas between nodules. This distribution may suggest a diagnosis of “adenoma”; however, multinodularity is more consistent with a hyperplastic process.

Differential Diagnosis

- Parathyroid adenoma:
 - The rare parathyroid adenomas responsible for tertiary hyperparathyroidism are indistinguishable from parathyroid adenomas associated with primary hyperparathyroidism.

Treatment and Prognosis

- Subtotal parathyroidectomy is the preferred therapy.
- Recurrent hyperparathyroidism has been seen in approximately 8% of patients after surgery.

PARATHYROID CYST

(Figs. 32-8 through 32-10)

Definition: Cystic lesion associated with a parathyroid parenchymal cell lining or associated parathyroid tissue in the cyst wall; these lesions may represent either hyperplasia or adenomas with cystic degeneration or developmental cysts (if nonhyperfunctioning).

Clinical

- Rare lesion
- More common in women than in men; occur in adults
- Symptoms may be due to the presence of an asymptomatic neck mass that preoperatively may be mistaken for a thyroid lesion, thyroglossal duct cyst, or branchial cleft cyst; may be incidentally discovered during surgery or by radiographs (especially in the case of mediastinal parathyroid cysts) or, rarely, to hypercalcemia (as in other cases of primary hyperparathyroidism); pressure symptoms may result in symptoms including dyspnea and stridor due to tracheal compression or hoarseness and vocal cord palsy due to compression of the recurrent laryngeal nerve.
- May be nonfunctional or functional with elevated levels of parathyroid hormone
- Patients may be either normocalcemic or hypercalcemic:
 - Hypercalcemia is associated with the usual biochemical pattern of primary hyperparathyroidism.
- Most are located in the neck arising from any of the parathyroid glands although more commonly arise in association with the lower parathyroid glands; mediastinal parathyroid cysts have been reported.
- Rarely reported in association with MEN-1
- Radiology:
 - On imaging parathyroid cysts are large and unilocular with varying MR imaging and CT findings, depending on their protein content.

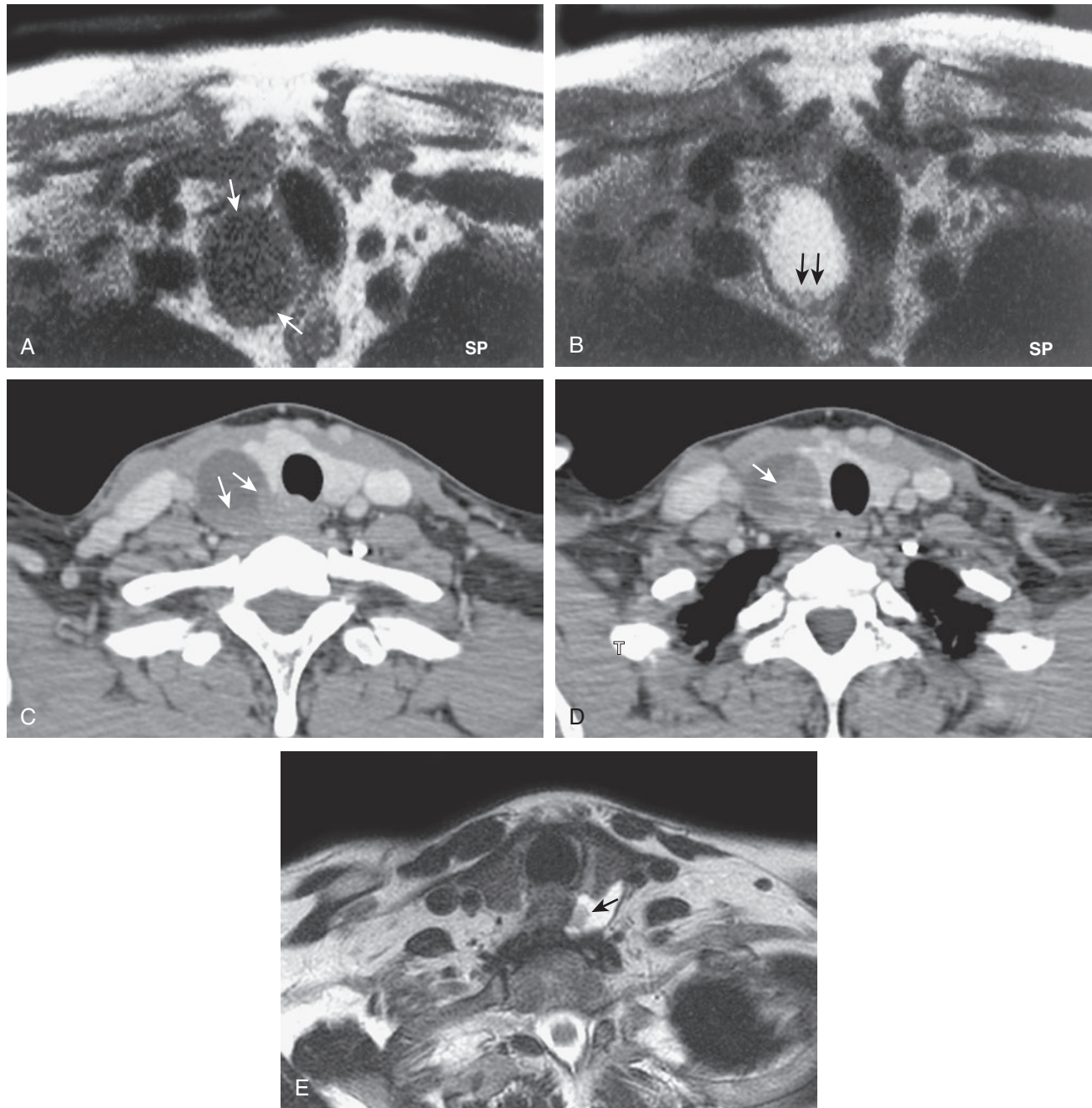


Fig. 32-8. Parathyroid cysts.

A, Unenhanced axial T1-weighted MR image shows a unilocular 3-cm cyst (*arrows*) in the right paratracheal region, just below the inferior pole of the right thyroid lobe. **B**, Corresponding axial T2-weighted MR image shows the hyperintense cyst. Note the small hemorrhage level (*arrows*) in the dependent portion of the cyst, which was confirmed at pathology. **C** and **D**, Axial contrast-enhanced CT scans show a cystic mass adjacent to the posterior right thyroid lobe. The cyst has nodules within it (*arrows*). This was a functioning parathyroid cyst. **E**, Axial T2-weighted MR image shows a cystic mass behind the left thyroid lobe with a nodule within it (*arrow*). This is a functioning parathyroid cyst. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-111, p 2675.)



Fig. 32-9. Parathyroid cyst.

Gross appearance of a (unilocular) parathyroid cyst.

- Origin for parathyroid cysts is unknown; considerations include developmental and degenerative:
 - Developmental due to cystic change in remnants of a branchial pouch or from gland-like structures (called canals of Kürsteiner) in the fetal parathyroid glands
 - Degenerative due to cystic change in a pre-existing lesion (e.g., adenoma, hyperplasia)

Pathology

Cytology

- Fine-needle aspiration has been useful in identification of some parathyroid cysts preoperatively, particularly palpable cervical lesions.
- Aspirated cyst fluid may contain clusters of cells in microacinar or papillary-like groups with the coarse chromatin and finely granular cytoplasm with poorly defined cell borders.
- The cellular component may be difficult to distinguish from follicular thyroid epithelium; immunohistochemistry for thyroglobulin and chromogranin may be helpful if adequate tissue is present.
- Assay of the cyst fluid for parathormone can be used to establish the diagnosis of a parathyroid cyst.

Gross

- Most parathyroid cysts are unilocular with a well-defined capsule and a cyst wall that may be thin and translucent with a gray-white appearance; in some cases the wall has a tan-yellow appearance due to the presence of a rim of parathyroid tissue.
- Cysts vary in size; although many smaller cysts obviously represent cystic change in a parathyroid adenoma, some as large as 10 cm have been described.

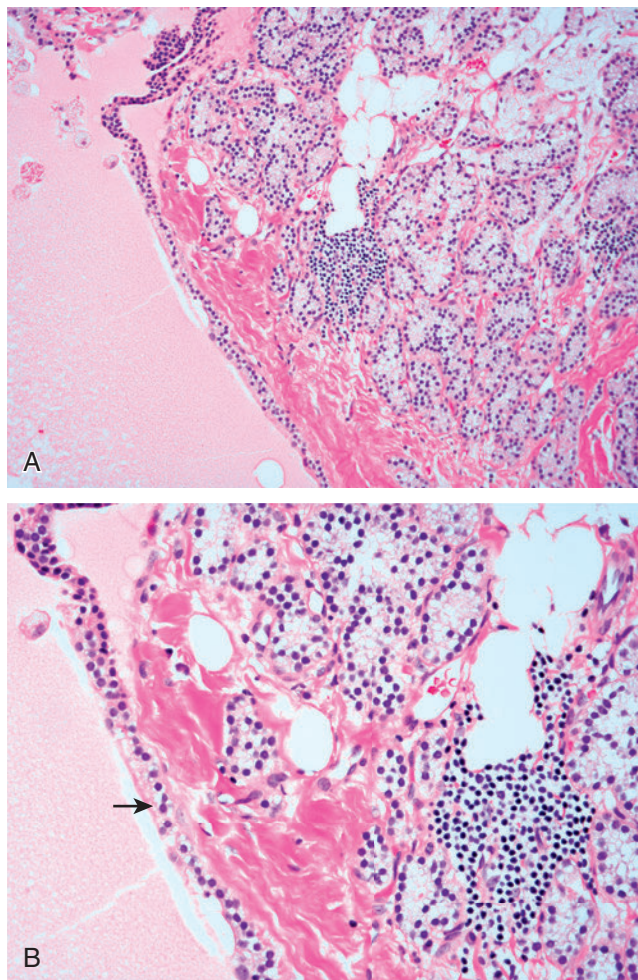


Fig. 32-10. Parathyroid cyst.

A, Intraparenchymal unilocular cyst surrounded by islands of normal parathyroid parenchyma. **B**, At higher magnification the cyst is lined by a single flattened layer of chief cells (arrow) histologically similar to the chief cells in the surrounding parathyroid gland.

- The cyst fluid is thin and colorless to yellow, although sometimes it may be bloody; the cyst fluid may be rich in parathyroid hormone.

Histology

- The cyst may be lined by flattened epithelium or by recognizable chief cells.
- Islands of parathyroid tissue are present within or adjacent to the cyst wall; this parathyroid tissue may appear normal or may represent a parathyroid adenoma or a hyperplastic parathyroid gland.

Differential Diagnosis

- Cystic thyroid neoplasm or adenomatoid nodule
- Lymphangioma
- Thymic cyst

- Bronchogenic, neurenteric, or esophageal foregut cysts
- Pericardial or pleural cysts

Treatment and Prognosis

- Preferred treatment is surgical removal.
- If hypercalcemia is present the approach should include investigation of the status of other parathyroid glands intraoperatively if the cyst is cervical or postoperatively if the lesion is intrathoracic.

CHRONIC PARATHYROIDITIS

(Fig. 32-11)

Definition: Infiltration of the parathyroid gland by mature lymphocytes (mixed B- and T-cells) and plasma cells with glandular atrophy and fibrosis.

Synonyms: Autoimmune parathyroiditis; hyperplastic parathyroiditis

Clinical

- Focal lymphocytic infiltrate of the parathyroid glands has been found at autopsy in approximately 10% of patients who were euparathyroid.
- Uncommon finding that may be seen in patients with hypoparathyroidism, or even more rarely in primary chief cell hyperplasia
- Possible autoimmune cause postulated:
 - Histologic changes equivalent to those seen in association with chronic lymphocytic (Hashimoto) thyroiditis, an autoimmune disease
 - In some patients with chronic parathyroiditis there are autoimmune diseases of other organs.
- Experimental model in rabbits has shown induction of autoimmune parathyroiditis following ozone inhalation.

Pathology

Gross

- May be seen in grossly normal glands, as an incidental finding, or in enlarged glands with hyperplasia

Histology

- Scattered aggregates of lymphocytes and plasma cells are present in the gland.
- Parathyroid parenchyma appears nodular separated by fibrous tissue with associated lymphocytes and plasma cells:
 - The inflammatory cell infiltrate may vary from scattered aggregates to diffuse infiltrate.

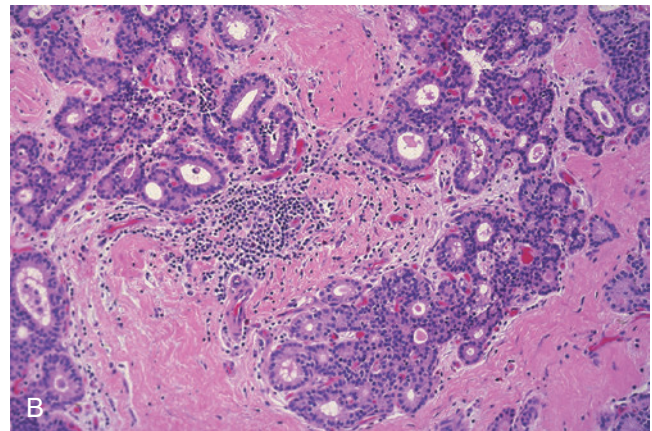
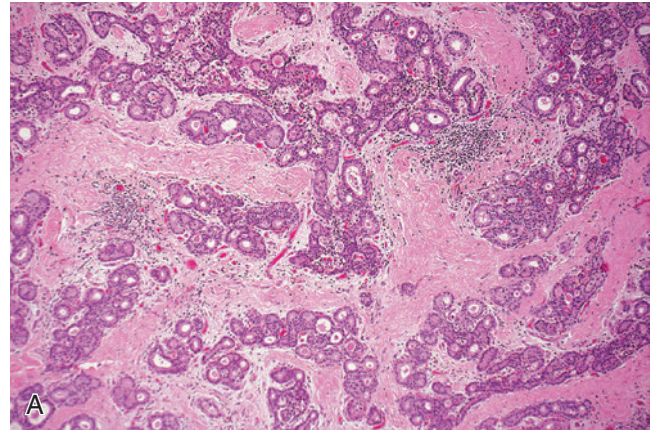


Fig. 32-11. Chronic parathyroiditis.

Chronic parathyroiditis characterized by a nodular-appearing parenchyma separated by fibrous tissue with associated inflammatory cell infiltrate.

- Lymphoid follicles with or without germinal centers may be present.
- Scattered aggregates of lymphocytes may be found in otherwise normal glands as an incidental finding.

Treatment and Prognosis

- The significance of parathyroiditis is often unclear.
- Clinical findings and treatment are based on the underlying process involving the parenchymal cells if clinically evident disease is present.

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Neoplasms of the Parathyroid Glands

CLASSIFICATION OF NEOPLASMS OF THE PARATHYROID GLANDS

(Box 33-1)

BOX 33-1 Neoplasms of the Parathyroid Glands

- Parathyroid adenoma
- Parathyroid carcinoma
- Secondary neoplasms

PARATHYROID ADENOMA

(Figs. 33-1 through 33-22, Table 33-1)

Definition: Benign neoplasm of the parathyroid parenchymal cells, including chief cells and/or oncocytic cells.

Clinical

- More common in females (F:M = 3 to 4:1); occur over a broad age range but are most frequently discovered in the fourth and fifth decades.
- Represents the major cause of primary hyperparathyroidism
- Clinical findings are essentially the same as those associated with primary hyperparathyroidism due to hyperplasia (see Chapter 32).
- As in primary hyperparathyroidism due to hyperplasia, the symptomatology in patients with parathyroid adenomas is changing as a result of routine biochemical screening and early detection:
 - Hypercalcemia may be incidentally discovered in asymptomatic patients, and many patients complain only of fatigue, weakness, or depression.
 - Nephrolithiasis is documented in 69% of men and in 36% of women with adenomas overall, but the incidence has been decreasing in recent years to between 5% and 20%.
 - Severe bone disease, once a common complication, is now rare; however, osteopenia is often present, and joint disease similar to that found in patients with parathyroid hyperplasia occurs.
- Serum calcium levels are generally higher than in patients with primary chief cell hyperplasia but not usually as high as in parathyroid carcinoma.
- Hypophosphatemia, hyperphosphaturia, and elevated serum parathormone levels are found.
- Rarely parathyroid adenomas present as a palpable mass.
- Radiology:
 - Several imaging methods have been used for localization of hyperfunctioning parathyroid tissue, including retrograde phlebotomy for determination of serum parathormone levels, CT scanning, ultrasonography, magnetic resonance imaging (MRI), thallium subtraction scanning, and technetium-99m sestamibi imaging.
 - Technetium-99m sestamibi imaging appears to be the most useful, with localization of more than 90% of adenomas, and has been most widely used in patients with anatomic distortion due to previous surgery and in patient who are high surgical risks; however, more routine utilization has gained support.
 - Multidimensional CT (referred to as 4D-CT) emerging technique used in detection when a lesion is not identified by more conventional techniques (e.g., ultrasonography, sestamibi imaging)
- May be associated with hyperparathyroidism-jaw tumor syndrome (HPT-JT):
 - Autosomal-dominant disorder with germline mutation in *HRPT-2* gene on chromosome 1q25-31
 - Characterized by:
 - Parathyroid adenoma or carcinoma
 - Fibro-osseous lesions of the jaw (e.g., ossifying fibroma of mandible or maxilla): 30% of cases
 - Renal cyst, hamartoma, carcinoma: 20% of cases
 - Approximately 80% of patients develop hyperparathyroidism:
 - Usually presents late in adolescence
 - Hypercalcemia tends to be severe.
 - Higher incidence of parathyroid carcinoma in comparison with patients with MEN-1 and MEN-2A
 - Renal lesions may include:
 - Renal cysts, polycystic renal disease, renal hamartoma
 - Papillary renal cell carcinoma, renal cortical adenomas, Wilms tumor
- 90% of adenomas are found in parathyroid glands in their usual locations:
 - Lower glands are more commonly involved.

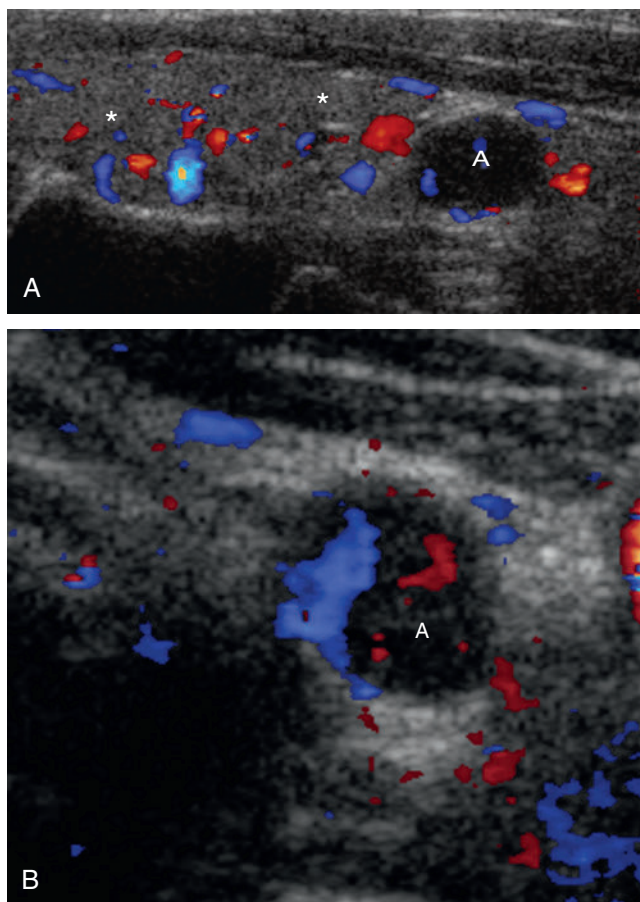


Fig. 33-1. Classic parathyroid adenoma identified on ultrasonography.

A, Sagittal ultrasonographic image shows a hypoechoic, well-defined mass (A) just below the inferior pole of the right thyroid gland (*). **B**, Transverse ultrasonographic image with color flow Doppler shows the increased peripheral arch of vascularity of the mass frequently seen with adenomas (A). (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-95, p 2663.)

- Ectopic parathyroid adenomas:
 - Parathyroid adenomas may occur in any location in which parathyroid tissue may be found, including ectopic sites such as the mediastinum, retroesophageal soft tissue, within the thyroid gland, or in thymic tissue
 - Ectopic adenomas, especially intrathyroidal ones, may be missed by clinical evaluation and/or surgical exploration:
 - Intrathyroidal parathyroid adenomas may be misinterpreted by pathologic evaluation as a thyroid follicular lesion or medullary thyroid carcinoma.

- Reports of adenomas occurring in supernumerary glands include tumors arising in the vagus nerve, pericardium, or other soft tissue sites in the neck.

Pathology

Cytology

- Occasionally enlarged parathyroid glands, either hyperplastic or, more commonly, adenomatous, have been serendipitously subjected to fine-needle aspiration as a clinically suspected “solitary thyroid nodule”; reports of ultrasonically guided fine-needle aspiration for localization and confirmation of parathyroid proliferative disease have appeared.
- An awareness of the typical cytologic appearance of parathyroid tissue can be helpful during intraoperative examination of biopsies during a neck exploration for hyperparathyroidism, as examination of touch preparations provides a rapid means of confirming the presence of parathyroid tissue.
- Aspirates of parathyroid tissue typically contain numerous naked nuclei, as well as small sheets of cells, sometimes forming acinar or follicular structures; small aggregates of dense colloid-like material may be seen but are not numerous.
- The cells are generally small, with predominantly round nuclei; anisonucleosis in scattered cells and occasional large, atypical, naked nuclei are common.
- The cytoplasm is granular and may exhibit scattered large metachromatic granules with a May-Grünwald-Giemsa or Romanowsky stain; Papanicolaou-stained cells have clear to finely granular cytoplasm.
- The nuclei are generally hyperchromatic with coarse chromatin typical of neuroendocrine cells.
- The distinction from follicular epithelium of the thyroid may be difficult, although the cells are usually smaller than those of the thyroid:
 - Immunohistochemical staining for PTH, parafibrin, chromogranin, thyroglobulin, and TTF1 may be helpful in this differential diagnosis.

Gross

- Adenomas are almost always solitary (see below for Double Adenoma).
- Adenomas have rounded borders, are firm, brown to tan, and are contained within a delicate capsule; they may be ovoid or lobulated.
- A remnant of uninvolved parathyroid tissue at the periphery of the tumor may be visible.
- Cystic change may be present, and when marked may mask the neoplastic nature of the proliferation; marked cystic degeneration is frequently associated with scarring and calcification.
- There is significant variation in weight, with most between 0.3 and 1.0 g.

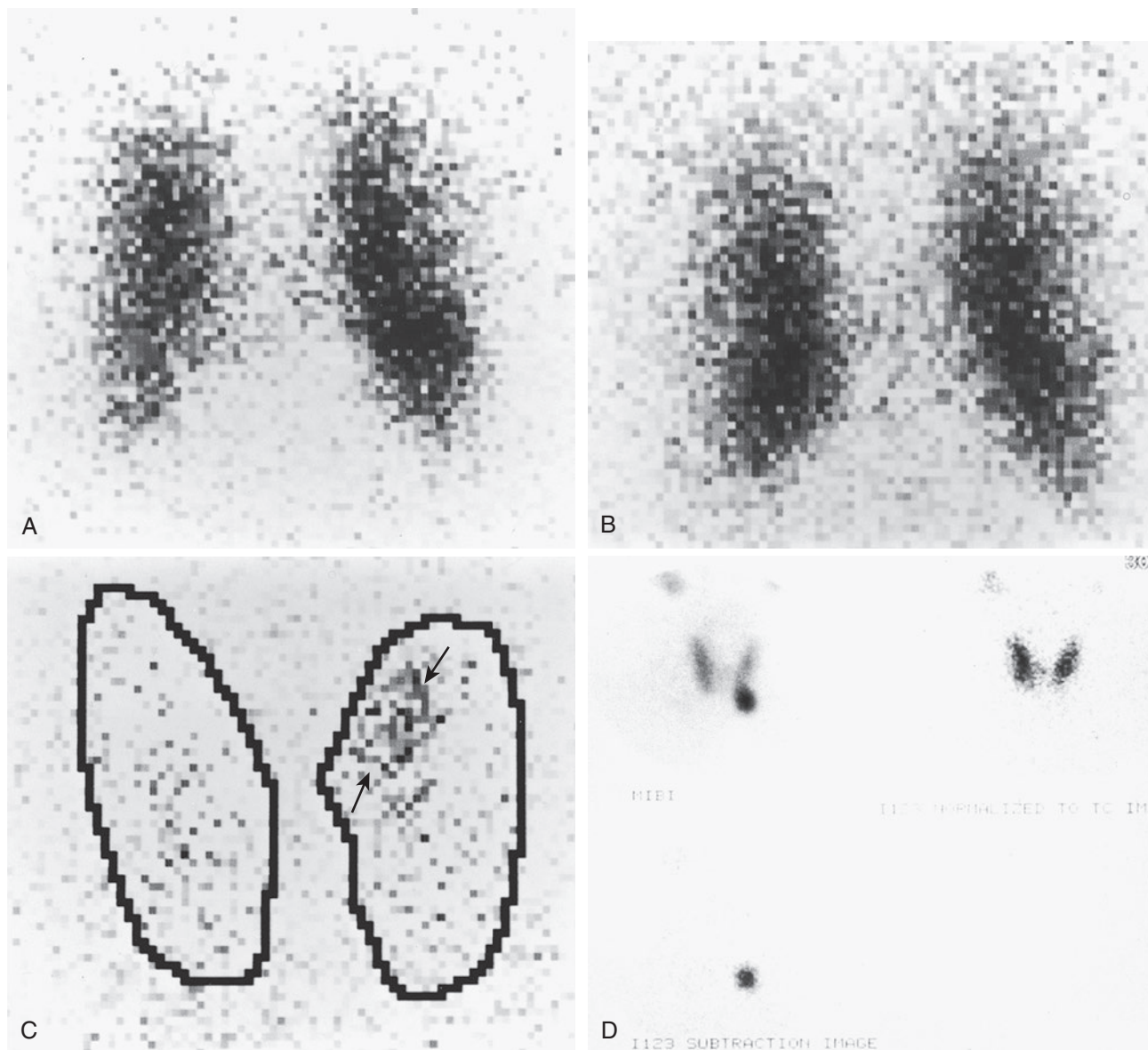


Fig. 33-2. Parathyroid adenoma.

Parathyroid adenoma detected by $^{201}\text{Tl}/^{99\text{m}}\text{Tc}$ -pertechnetate subtraction imaging (**A** to **C**) and by $^{99\text{m}}\text{Tc}$ -sestamibi subtraction imaging with ^{123}I (**D**). **A**, $^{99\text{m}}\text{Tc}$ -pertechnetate concentrated within the thyroid gland. **B**, ^{201}Tl concentrated within thyroid and parathyroid glands. **C**, Computer techniques allow technetium concentrated in the thyroid gland to be subtracted from thallium that accumulates within thyroid and parathyroid tissue. After thyroid subtraction, a parathyroid adenoma is noted as a focus of increased thallium uptake (arrows). **D**, $^{99\text{m}}\text{Tc}$ -sestamibi subtraction imaging with ^{123}I shows an adenoma below the inferior pole of the left lobe of the thyroid gland. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-103, p 2669.)

Histology

- Well circumscribed and uncommonly surrounded by a thin fibrous capsule:
 - Complete encapsulation not commonly seen
- Hypercellular proliferation lacking intraparenchymal fat cells with diffuse growth; vague nodularity may be present and rarely may be multinodular.
- A rim of non-neoplastic parathyroid tissue found in association with only about half of the adenomas:
 - Very helpful finding, if present, in making the distinction between adenoma and hyperplasia
 - “Rim” generally contains abundant stromal fat cells, in contrast to the very cellular adenoma.

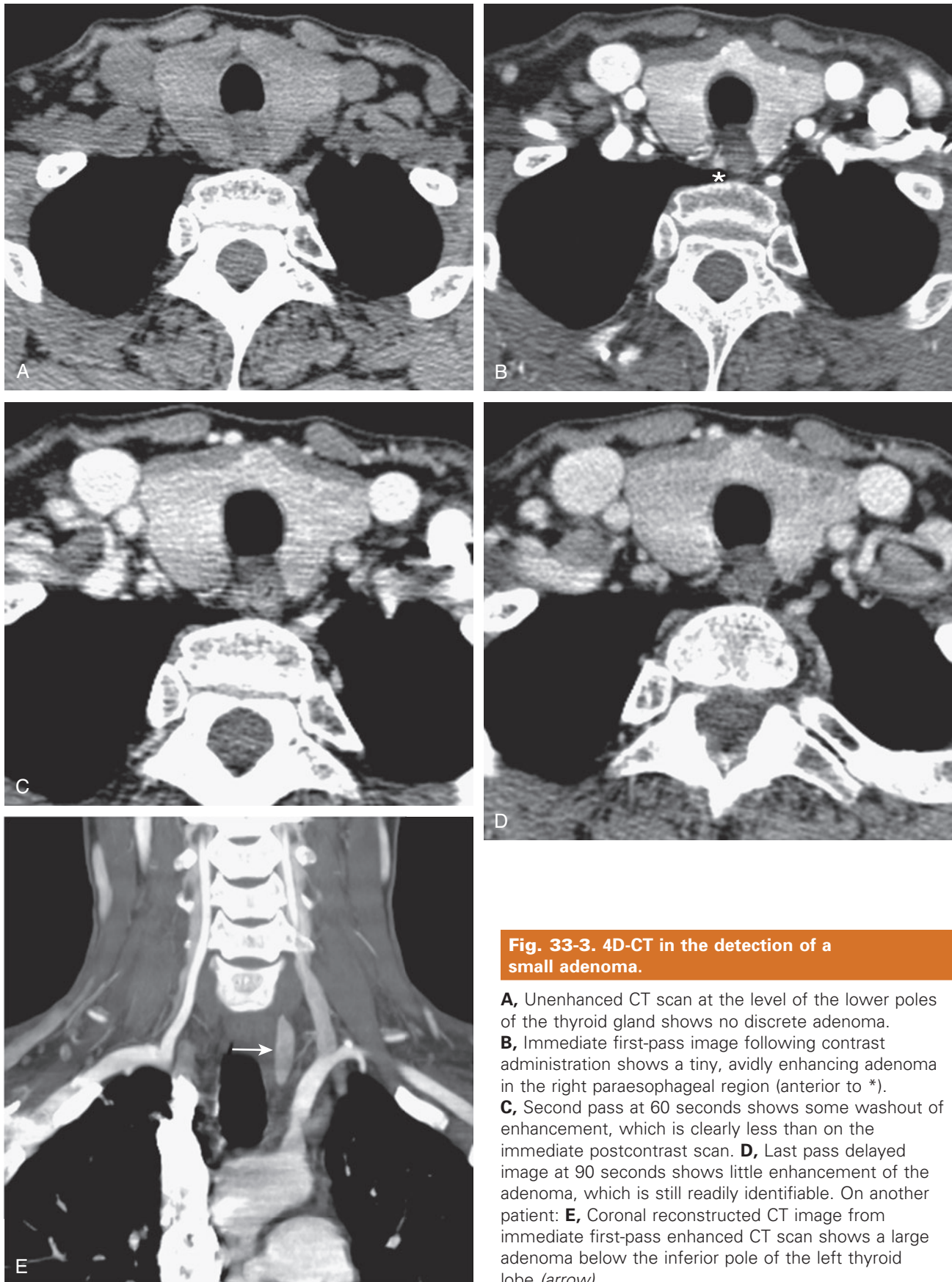


Fig. 33-3. 4D-CT in the detection of a small adenoma.

A, Unenhanced CT scan at the level of the lower poles of the thyroid gland shows no discrete adenoma. **B**, Immediate first-pass image following contrast administration shows a tiny, avidly enhancing adenoma in the right paraesophageal region (anterior to *). **C**, Second pass at 60 seconds shows some washout of enhancement, which is clearly less than on the immediate postcontrast scan. **D**, Last pass delayed image at 90 seconds shows little enhancement of the adenoma, which is still readily identifiable. On another patient: **E**, Coronal reconstructed CT image from immediate first-pass enhanced CT scan shows a large adenoma below the inferior pole of the left thyroid lobe (arrow).

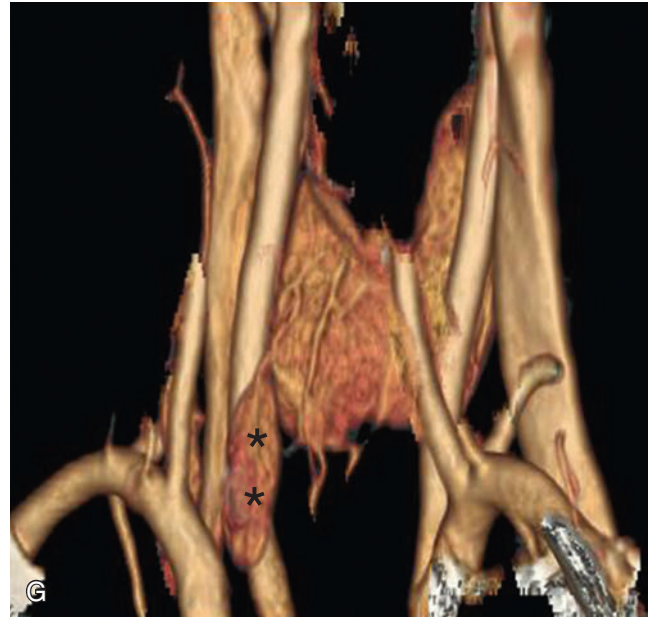
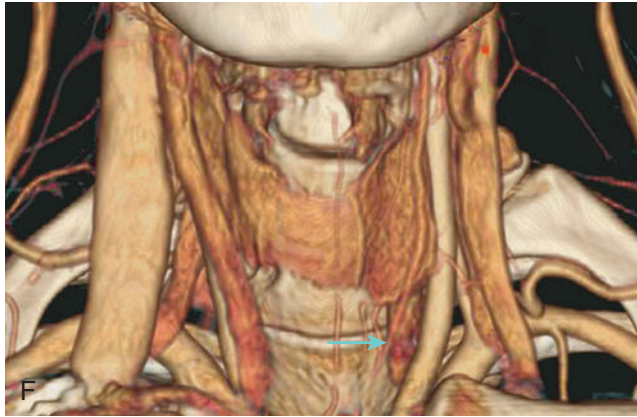


Fig. 33-3, cont'd

F, Coronal maximum intensity projection image in anterior projection shows the adenoma (*arrow*). **G**, Coronal maximum intensity projection image in the posterior projection shows the adenoma (*) posterior to the common carotid artery. (Cases courtesy of Dr. Lawrence Ginsberg. From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-101, p 2667.)

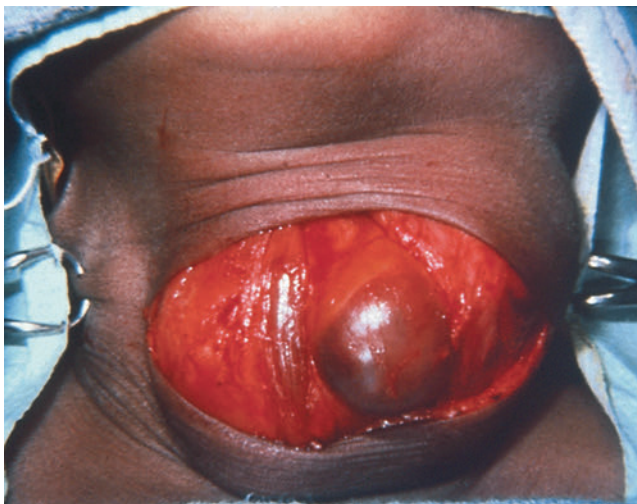


Fig. 33-4. Parathyroid adenoma.

Parathyroid adenoma appearing as a large encapsulated lesion bulging into the operative field. Adenomas are typically easily dissected free of adjacent structures; difficulty in removing a parathyroid tumor should raise suspicion for a parathyroid carcinoma.

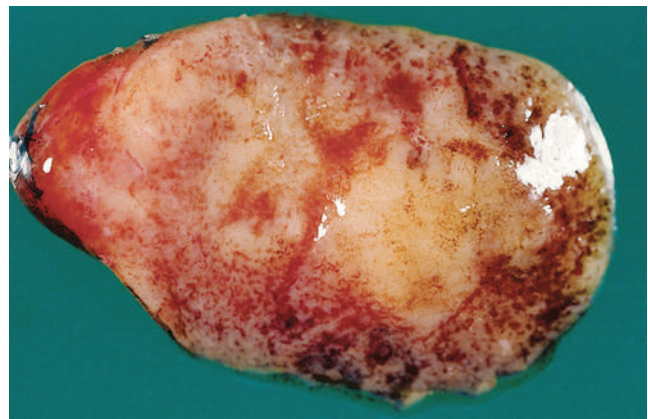


Fig. 33-5. Parathyroid adenoma.

Cut section of a parathyroid adenoma shows a homogeneous, light tan appearance; a delicate inconspicuous capsule is present. A remnant of uninvolved parathyroid tissue is not grossly visible.

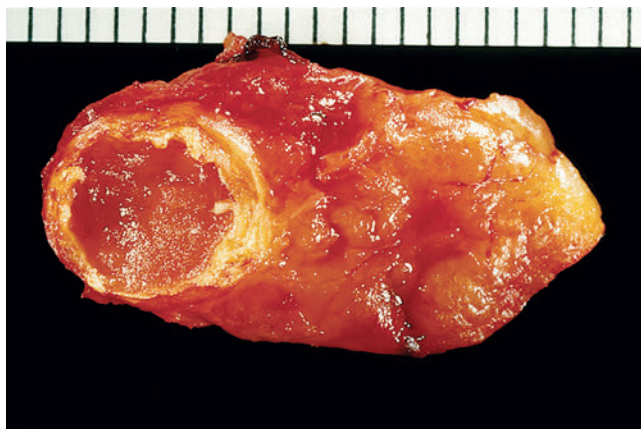


Fig. 33-6. Parathyroid adenoma.

Parathyroid adenoma appearing as a nodular focus with cystic change and associated calcification.

- Nuclei of residual normal or atrophic parathyroid gland typically smaller than the nuclei of the adenoma.
- Growth patterns include solid (diffuse) sheets, cords, nests, acini, follicles, and microcysts:
 - Follicle formation may contain eosinophilic “colloid-like” material.
 - Distinct trabecular pattern is uncommon.
- Predominantly composed of chief cells:
 - Nuclei round and regular with central to slightly basal location within the cell and have inconspicuous nucleoli; usually lack significant pleomorphism:
 - Cells with hyperchromatic enlarged nuclei as well as multinucleated cells are common and can be found scattered throughout the tumor or may be clustered in small foci; these scattered atypical nuclei are not an indicator of malignancy in the absence of other evidence of a malignancy (see section on [parathyroid carcinoma](#)).
 - Cytoplasm varies, including slightly eosinophilic, amphophilic, clear, or oxyphilic.
 - Chief cells of an adenoma frequently larger than the non-neoplastic chief cells in the uninvolved rim of parathyroid tissue, if one is present
 - Oncocytic cells may be seen in variable numbers, focally admixed with chief cells or as nodular aggregates.
- Mitotic figures are identifiable in many adenomas, but usually number fewer than 1 per 10 high-power fields; mitotic rates as high as 4 mitoses per 10 high-power fields have been described in occasional cases.
- Delicate vascular network composed of thin fibrovascular stroma, sinusoid-like blood vessels or capillaries traverse the neoplasm.

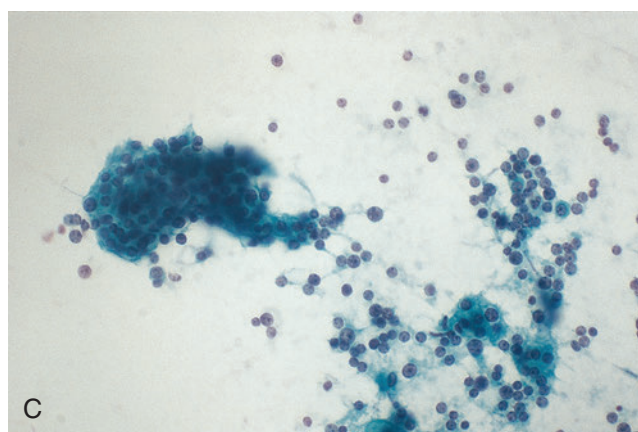
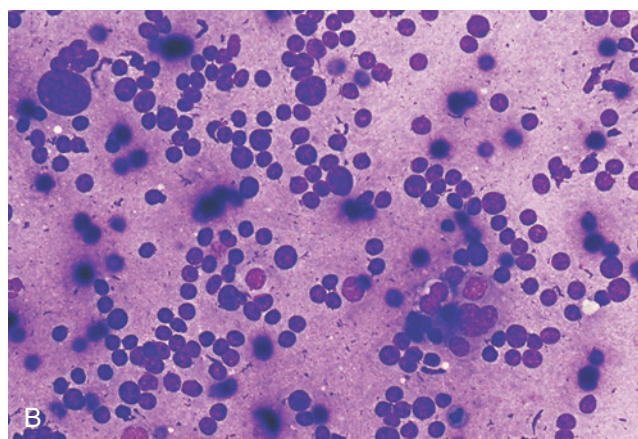
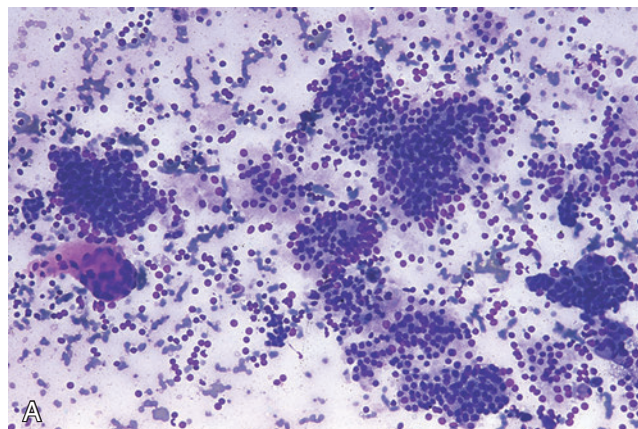


Fig. 33-7. Parathyroid adenoma, fine-needle aspiration.

A, Cellular smear with cohesive groups of small epithelial cells and fragments of pink colloid-like material may suggest a follicular neoplasm of thyroid origin; the colloid-like material, however, is somewhat sparse (Diff-Quick stain). **B**, The cells are fragile, yielding smears with numerous naked nuclei, some of which are large and hyperchromatic; scattered large atypical nuclei are common in parathyroid adenomas (Diff-Quick). **C**, Papanicolaou-stained smear shows scattered compact clusters of small epithelial cells with distinct cell borders and a rim of clear cytoplasm; the nuclei are small and hyperchromatic.

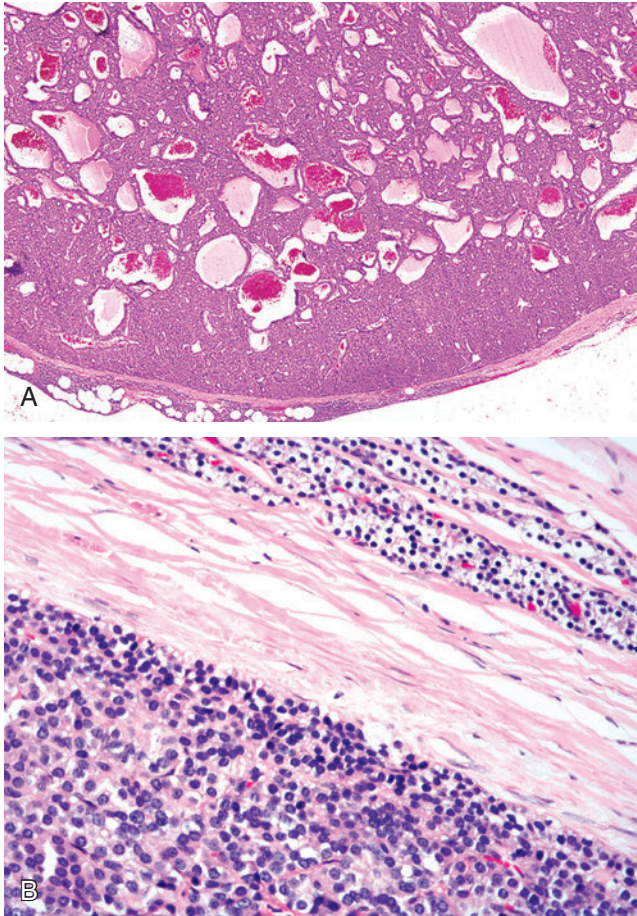


Fig. 33-8. Parathyroid adenoma.

A, Parathyroid adenoma characterized by hypercellular proliferation devoid of intraparenchymal fat, which in the lower portion of the illustration has a well-defined capsule separating the cellular proliferation from a thin rim of compressed normal parathyroid gland parenchyma. **B,** At higher magnification, the cells and nuclei of the adenoma (*bottom*) are larger than those of the residual non-neoplastic parathyroid gland parenchyma (*top*).

- Intraparenchymal fat cells absent but may focally be seen as single cells or groups in the peripheral aspect of the neoplasm:
 - Neoplastic cells usually have less intracellular fat than do the cells in the uninvolved (or suppressed) parathyroid tissue, either in other glands or in a rim of non-neoplastic parathyroid tissue in an adenomatous gland.
- Cells with markedly enlarged and hyperchromatic pleomorphic or bizarre-appearing nuclei may be present and when present:
 - Appear admixed with bland-appearing nuclei.
 - Tend to be focally and not diffusely identified.
 - Occur in the absence of increased mitotic activity and/or other features that may be associated with parathyroid carcinoma.

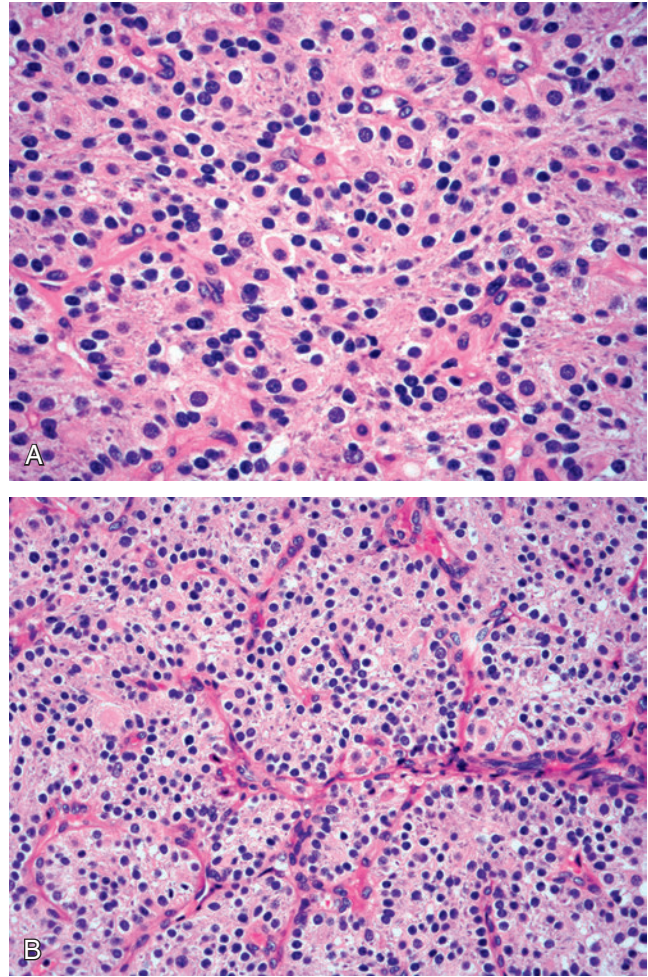


Fig. 33-9. Parathyroid adenoma.

A, Diffuse proliferation of chief cells with scattered admixed oncocytic cells. **B,** Tumor is traversed by delicate fibrovascular stroma.

- Reactive and degenerative changes may be present, including cyst formation, edema, fibrosis, hemorrhage (fresh or in the form of hemosiderin deposition), or infarction:
 - May occur spontaneously or may occur following a traumatic event such as prior surgery to the neck or fine-needle aspiration biopsy
 - Presence of reactive and degenerative changes, especially fibrosis, may cause adherence to adjacent structures, suggesting invasive growth and a possible diagnosis of parathyroid carcinoma.
 - Infarcted tumor may retain antigenicity for parathyroid hormone.
- Rarely, an associated mature lymphocytic cell infiltrate may be present.
- Uninvolved parathyroid parenchymal cells in patients with adenomas are typically smaller and often have more stromal fat cells than the glands in patients

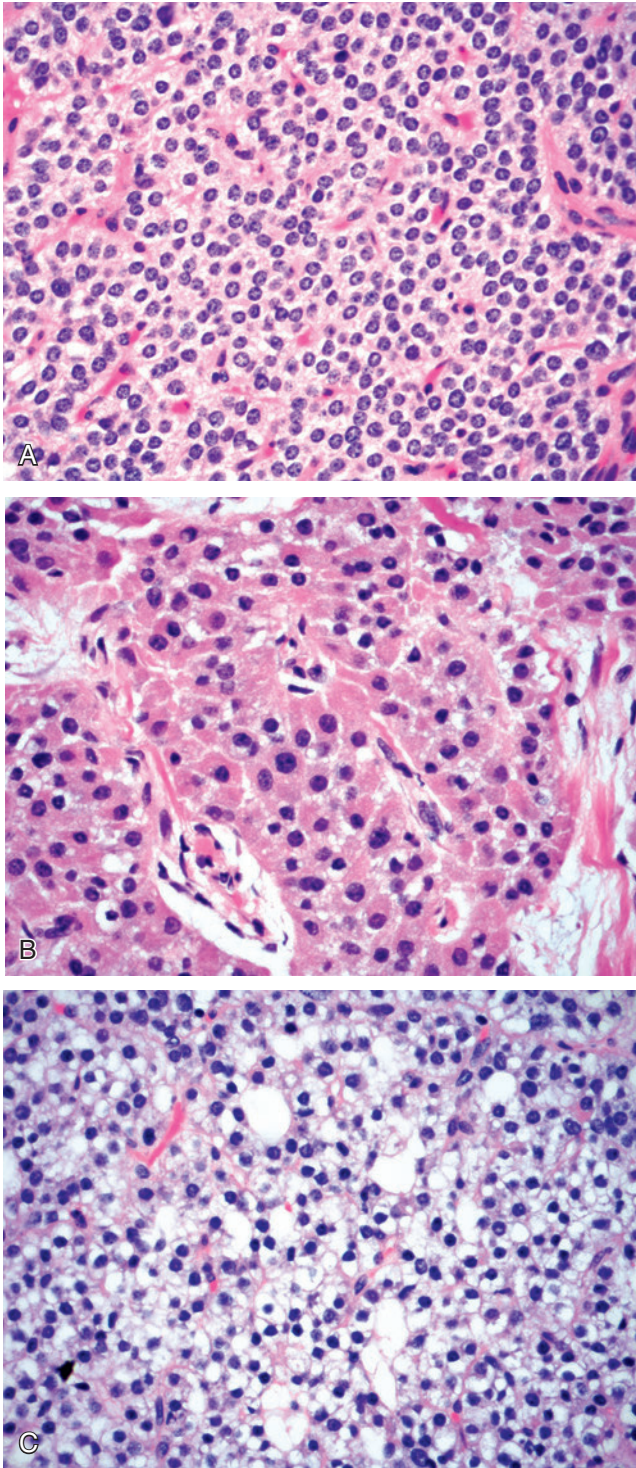


Fig. 33-10. Parathyroid adenoma.

Parathyroid adenomas may be composed of an admixture of (A) chief cells, (B) oncocytic cells, and/or (C) clear cells. In any given tumor two or all of the cell types may be present, creating a mosaic pattern.

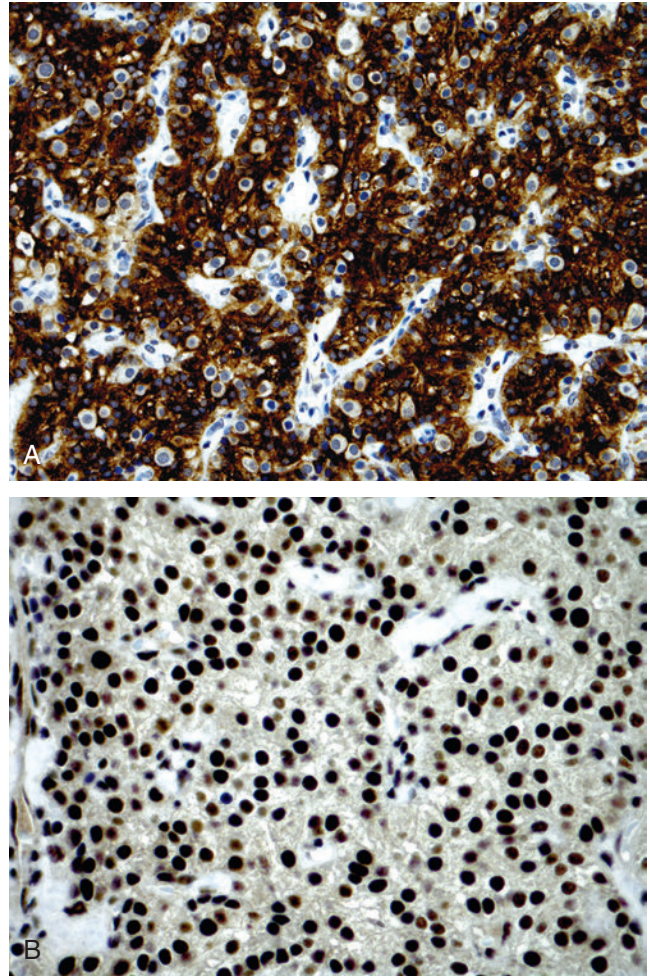


Fig. 33-11. IHC staining in parathyroid adenoma.

Lesional cells of parathyroid adenomas are immunoreactive for (A) parathyroid hormone and (B) parafibromin (diffuse nuclear staining).

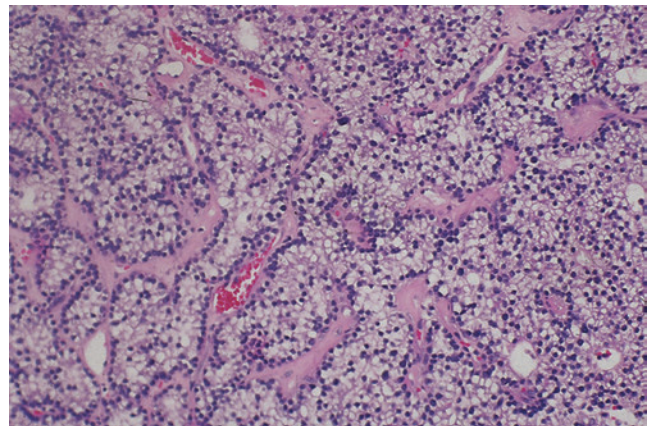


Fig. 33-12. Parathyroid adenoma.

Parathyroid adenoma showing cord-like or trabecular growth composed of cells with clear-appearing cytoplasm.

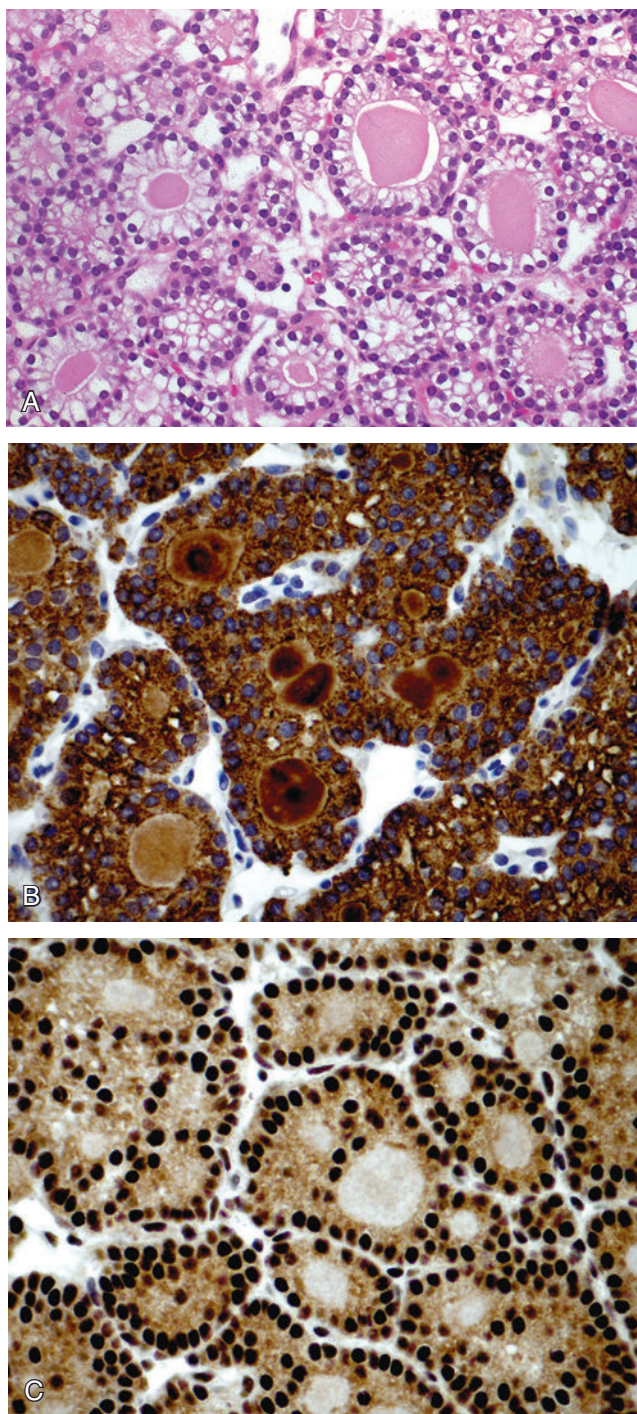


Fig. 33-13. Parathyroid adenoma.

A, Parathyroid adenoma showing a follicular pattern of growth (so-called follicular variant) that may cause confusion with thyroid follicular neoplasms; immunoreactivity for **(B)** parathyroid hormone and **(C)** parafibromin (nuclear), coupled to the absence of thyroglobulin and TTF1 (not shown) allow for differentiating parathyroid adenoma from a thyroid follicular lesion.

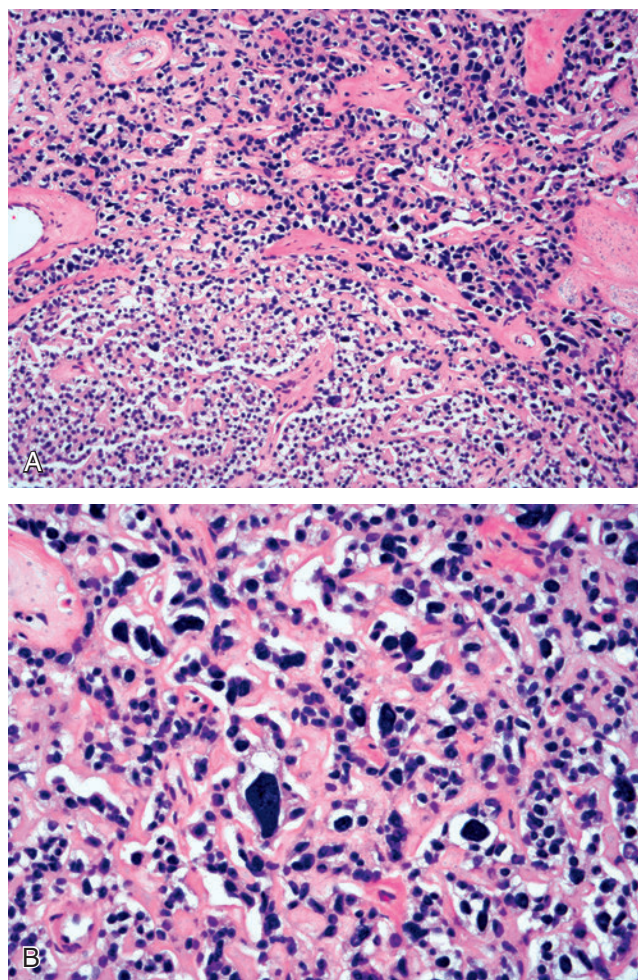


Fig. 33-14.

A, Parathyroid adenoma composed of uniform and bland-appearing nuclei in lower portion of image as well as numerous large cells with hyperchromatic nuclei; intralesional fibrosis is also present. **B**, Bizarre-appearing pleomorphic and hyperchromatic nuclei admixed with bland-appearing nuclei. Such findings in the absence of increased mitotic activity and/or other features associated with parathyroid carcinoma can be seen in parathyroid adenomas.

without hyperparathyroidism; they also have more cytoplasmic fat, often found as large droplets, than normally functioning parathyroid glands.

- Histochemical stains:
 - Colloid-like material in follicular structures are PAS positive.
 - Considerable variation in the literature regarding the utility of fat stains in the diagnosis of parathyroid proliferative diseases
 - Generally, hyperfunctioning cells have a significantly decreased amount of intracellular fat (using Sudan black or oil red O) compared with

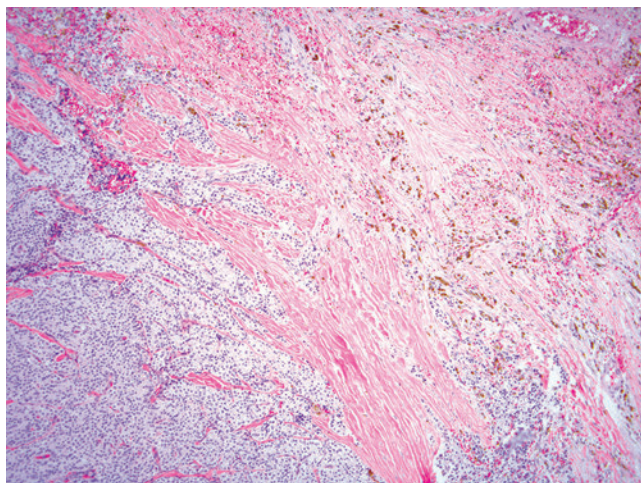


Fig. 33-15. Parathyroid adenoma.

Parathyroid adenoma with associated reactive and degenerative changes, including fibrosis and hemorrhage may result in adherence to surrounding structures, clinically suggesting a possible diagnosis of parathyroid carcinoma. Such changes may occur spontaneously or may occur following a traumatic event such as prior surgery to the neck or fine-needle aspiration biopsy.

normal or suppressed parenchymal cells; there is, however, variability in this finding.

- Fat stains, when used with adequate clinical information, intraoperative findings, and histologic examination, are useful if their limitations are kept in mind.
- Immunohistochemistry:
 - Positive for parathyroid hormone and parafibromin (nuclear staining):
 - Majority of parathyroid adenomas express parafibromin
 - Loss of parafibromin expression may be seen in patients with hyperparathyroidism-jaw tumor syndrome indicative of gene inactivation through mutation of the *HRPT-2* gene.
 - Cytokeratin, chromogranin A positive
 - Calcitonin and synaptophysin typically negative but in small percentage of cases may be focally positive
 - PAX8 (nuclear) reactivity present in approximately 40% of adenomas and hyperplasia
 - Galectin 3 rarely positive (< 5%).
 - Ki67 (MIB1) proliferative index is low:
 - An index greater than 5% should raise suspicion for carcinoma, but the diagnosis of carcinoma requires confirmatory diagnostic findings.
 - Proliferative indices in differentiating adenoma from carcinoma are of limited utility given overlapping findings in these lesions.

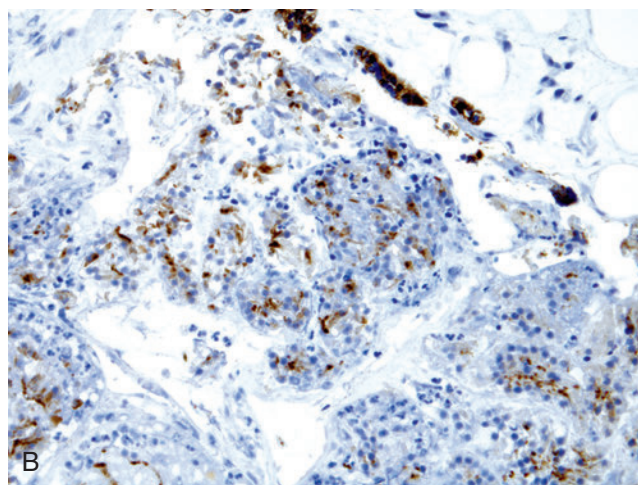
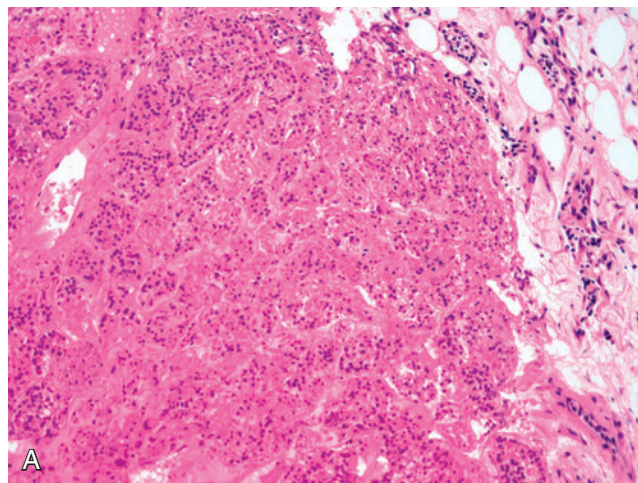


Fig. 33-16. Parathyroid adenoma.

A, Parathyroid adenoma with infarction but retention of ghost outlines of the neoplasm. Note the residual noninfarcted and non-neoplastic parathyroid parenchyma, including mature fat (*upper right*). **B**, Parathyroid hormone immunoreactivity is present in the infarcted tumor and in the residual non-neoplastic parathyroid parenchyma (*upper right*).

- Cyclin D1 staining in 39% of cases
- Negative for thyroglobulin and TTF-1
- Electron microscopy:
 - Adenomas associated with very high serum calcium levels may have a large number of microvilli, which are thought to reflect a higher level of endocrine activity
 - Adenomas often have more abundant rough endoplasmic reticulum and more prominent Golgi apparatus than non-neoplastic cells.
 - Annulate lamellae may be seen.
- Cytogenetic and molecular findings:
 - Approximately 5% show pericentric inversion of chromosome 11, causing translocation of cyclin

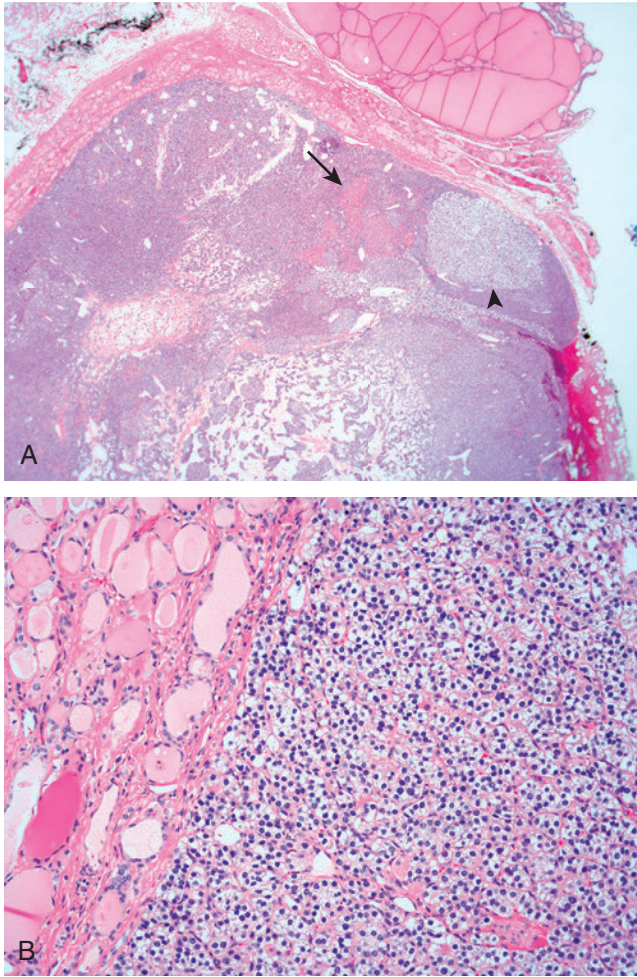


Fig. 33-17. Intrathyroidal parathyroid adenoma.

A, Intrathyroidal parathyroid adenoma (*lower*) predominantly composed of chief cells as well as oncocytic cells (*arrow*) and clear cells (*arrowhead*) surrounded by thyroid follicular epithelial cells and an adenomatoid nodule (*upper right*). **B**, Histologically, the intrathyroidal parathyroid adenoma shows typical morphologic findings predominantly composed of chief cells and sharply separated from the colloid-filled thyroid follicles (*left side*).

D1 (*CCND-1/PRAD-1*) gene with parathyroid hormone gene, resulting in overexpression of cyclin D1.

- Somatic mutation in *MEN-1* gene at 11q13 in 40% of cases
- Absence of *RET* mutation
- 5% have somatic mutation in *CDKN1B* gene (p27Kip1)

Double Parathyroid Adenomas

- Most “multiple adenomas” represent cases of asymmetric or nodular hyperplasia:

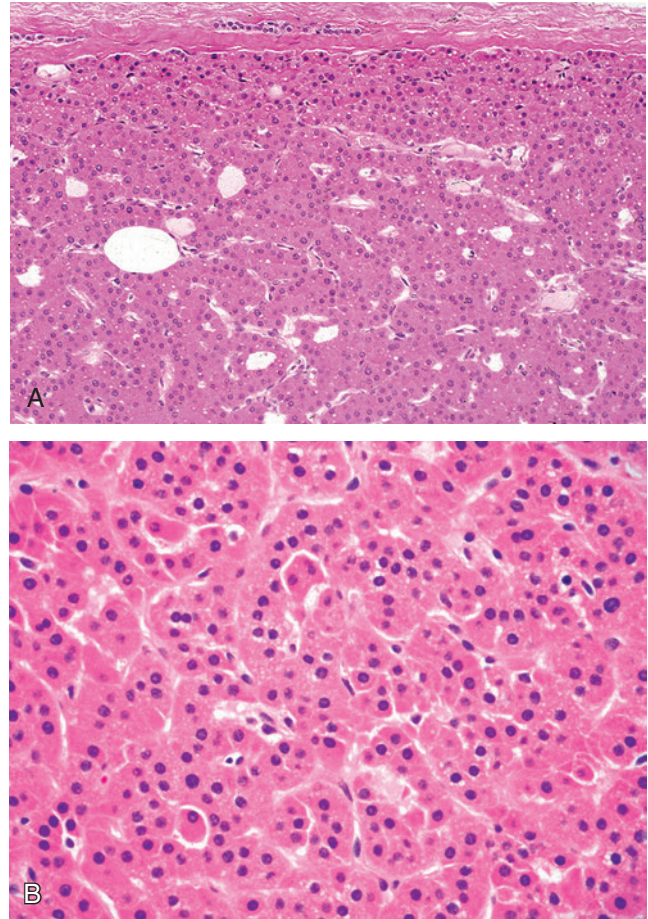


Fig. 33-18. Oncocytic parathyroid adenoma.

A, The tumor is encapsulated and (**B**) exclusively composed of cells with granular eosinophilic-appearing cytoplasm.

- Distinction between hyperplasia and adenoma may be extremely difficult and requires the pathologic examination of more than a single gland.
- Diagnostic criteria for double adenomas include:
 - 2 enlarged, hypercellular parathyroid glands
 - Intraoperative confirmation that remaining parathyroid glands are normal and/or biopsy proven histologically normal parathyroid glands
 - Absence of family history of MEN or familial hyperparathyroidism
 - Permanent cure of hypercalcemia following excision of enlarged glands:
 - Arguably the most definitive criterion
 - Requires years of follow-up to include monitoring of serum calcium and parathyroid hormone levels

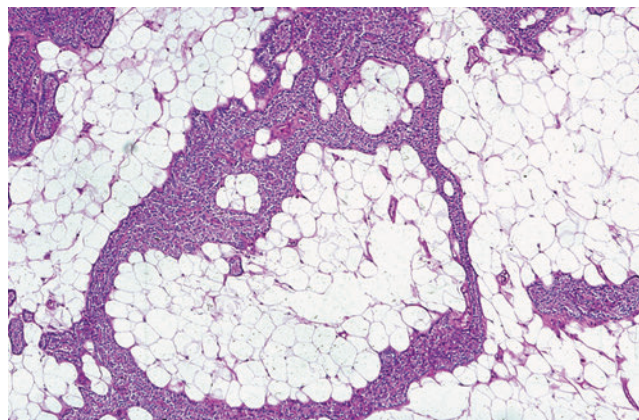


Fig. 33-19. Parathyroid lipoadenoma.

Lipoadenomas form cords, islands, and follicles admixed with stromal fat cells with mature adipocytes, the latter making up from 20% to 90% of the neoplasm. Lipoadenomas are encapsulated and may be associated with a rim of “normal” gland (not shown) and can be difficult to distinguish from normal parathyroid gland in small biopsies.

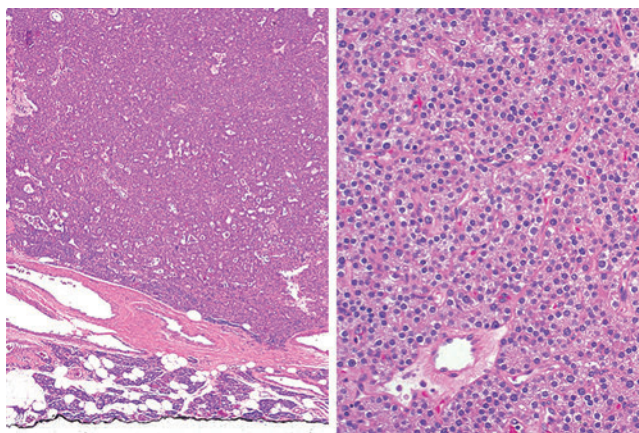


Fig. 33-20. Parathyroid adenoma associated with osteitis fibrosa cystica.

Left panel, The adenoma is typical with a distinct capsule and a rim of normal parathyroid parenchyma including mature fat (lower); *right panel*, the tumor is composed of chief cells. The patient had a pathologic fracture of the humerus as well as generalized osteopenia with multiple lytic skeletal lesions. At the time of presentation he had hypercalcemia. The initial clinical impression was metastatic carcinoma with secondary hypercalcemia.

- If the above criteria are fulfilled, then a diagnosis of double adenomas can be confirmed.
- True double parathyroid adenomas are rare:
 - Majority (greater than 70%) are bilateral
 - Predilects to superior glands

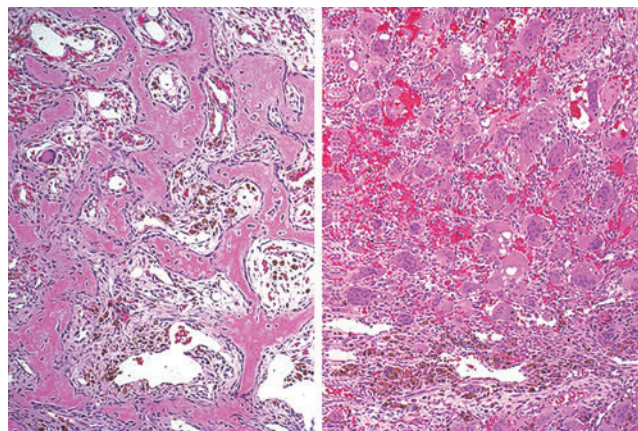


Fig. 33-21. Brown tumor of hyperparathyroidism.

The humeral lesion from the patient in Fig. 33-20. *Left panel*, Dissecting osteitis, with resorption of trabecular bone and replacement by fibrous tissue; the presence of hemosiderin indicates hemorrhage secondary to microfractures in the weakened bone. *Right panel*, Brown tumor of hyperparathyroidism develops after repeated cycles of bone resorption, microfractures, and hemorrhage, leading to large areas of cystic degeneration with aggregates of osteoclasts and foreign body giant cells in a fibroblastic stroma containing hemosiderin.

Histologic Variants of Parathyroid Adenoma

- Oncocytic (oxyphilic) adenoma (see Fig. 33-18):
 - Exclusively composed of oncocytic cells with prominent eosinophilic granular cytoplasm
 - Demographic features are similar to those of the more common adenomas composed of chief cells
 - Thought to be nonfunctional; usually associated with lesser degree of hypercalcemia; however, several reports document an association with primary hyperparathyroidism
 - Composed of large cells with abundant eosinophilic granular cytoplasm and hyperchromatic nuclei:
 - Scattered large atypical nuclei or multinucleated cells may be seen.
 - Cytoplasm is stuffed with mitochondria on electron microscopy.
 - An important differential consideration is the frequent presence of nodular oncocytic cell change seen in normal glands with increasing age.
 - Intrathyroidal localization may suggest a diagnosis of an oncocytic thyroid follicular (so-called Hürthle cell) neoplasm:
 - Parathyroid oncocytic adenomas have more distinct cell membranes.

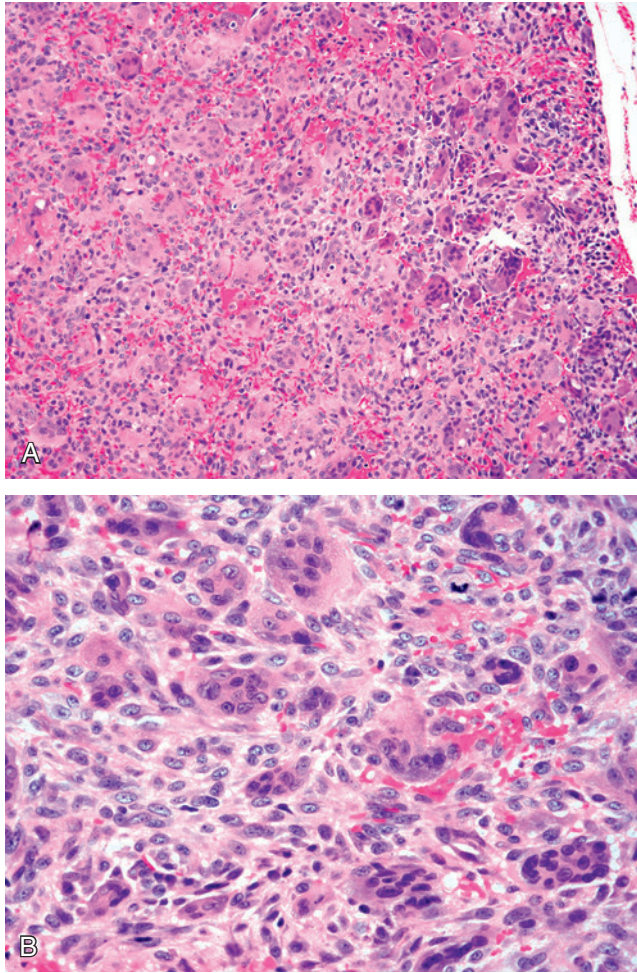


Fig. 33-22. Brown tumor of hyperparathyroidism.

Brown tumor of hyperparathyroidism characterized by (A) proliferation of numerous multinucleated giant cells and mononuclear cells, as well as foci of hemorrhage; the giant cells tend to be clustered rather than diffusely distributed. B, The nuclei of the multinucleated giant cells are rather bland and are similar to those of the surrounding mononuclear cells. A mitotic figure (arrow) is present. The brown tumor of hyperparathyroidism is histologically similar to giant cell (reparative) granuloma, thereby requiring clinical and laboratory correlation to differentiate these lesions.

- Presence of thyroglobulin and TTF1 support lesion of thyroid origin.
- Lipoadenoma (see Fig. 33-19)
 - Also referred to as parathyroid hamartoma
 - Rare benign neoplasm characterized by proliferation of chief and oxyphilic cells forming cords, islands, and follicles admixed with mature adipocytes:
 - Mature adipocytes make up from 20% to 90% of the neoplasm.
- Circumscription and/or encapsulation as well as large size (1 to 15 cm) support adenomatous nature:
 - May be associated with a compressed rim of “normal” gland
- May be difficult to recognize as “abnormal” parathyroid tissue in small biopsies, when they are easily mistaken for normal parathyroid tissue because of the abundance of stromal fat
- Stromal fat often contains areas of fibrosis or myxoid alteration.
- Most are associated with hyperparathyroidism.
- Other rare variants of parathyroid adenoma include:
 - Papillary variant characterized by prominent papillary architecture:
 - May not be a “true” variant but papillary architecture, especially in association with fibrosis and hemorrhage (recent and remote), likely is a reactive/degenerative phenomenon
 - Follicular variant characterized by prominent follicular (acinar) architecture
 - Water-clear variant characterized by presence of polygonal cells with clear cytoplasm and distinct cell membranes.
- Atypical parathyroid adenoma:
 - Definition: parathyroid tumor showing features worrisome for parathyroid carcinoma but lacking absolute diagnostic features for parathyroid carcinoma
 - Synonyms include atypical parathyroid neoplasm, parathyroid neoplasm of uncertain biologic significance, or parathyroid neoplasm inconclusive for malignancy
 - Atypical histologic features suggesting carcinoma but falling short for this diagnosis may include:
 - Capsular irregularities or invasion without infiltration into adjacent soft tissues
 - Increased mitotic activity (>5 per 10 high-power fields)
 - Intralesional fibrosis characterized by broad fibrous bands coursing through the lesion
 - Coagulative necrosis
 - Diffuse cellular atypia
 - Diffuse sheet-like growth of monotonous cells with increased nuclear-to-cytoplasmic ratio
 - Macronucleoli in many cells
 - Atypical parathyroid adenomas lack conclusive features diagnostic for carcinoma including:
 - Invasion of surrounding soft tissues
 - Invasion of surrounding structures including thyroid gland, larynx, trachea, pharynx, esophagus, carotid artery, recurrent laryngeal nerves
 - Angioinvasion
 - Perineural invasion
 - Metastasis

TABLE 33-1 Comparative Features of Parathyroid Proliferative Diseases

	Hyperplasia	Adenoma	Carcinoma
Gender; age	Slight female predilection; most common in 5th-6th decades	More common in women; most common in 4th decade	Equal gender predilection; wide age range
Clinical	Asymptomatic or complaints of lethargy, weakness, polyuria, polydipsia, arthralgia, constipation, and depression	Similar to hyperplasia	Similar to hyperparathyroidism of benign cause but more severe due to the higher serum calcium levels; higher proportion of renal disease (nephrolithiasis) and bone disease; peptic ulcer disease; palpable neck mass more common than in adenoma
Serum calcium	11.7 mg/dl (average)	12.5-13.5 mg/dl	Often >14 mg/dl
Intraoperative findings	2 or more glands enlarged, easily dissected; enlargement may be very asymmetric	1 gland enlarged; easily dissected; more frequent in lower glands or ectopic sites	1 gland enlarged; often adherent to surrounding tissues
Weight	Total gland weight usually <1 g, but may be up to 5 g	0.3-1.0 g commonly, but may weigh several grams in patients with bone disease	>1.5 g (often much larger)
Capsule	Circumscribed by capsule of parathyroid gland, may be incomplete. No compressed rim of atrophic or normal parathyroid tissue	Thin tumor capsule, often surrounded by rim of uninvolved parathyroid, which may appear atrophic	Thickened capsule; rim of normal parathyroid rarely seen
Gross appearance	Gray-brown, soft. Cut surface may be homogeneous or nodular. Lacks fibrous bands	Red-brown, firm. Usually homogeneous, lacks fibrous bands	Gray-white, firm, often lobulated or irregular. Fibrous bands often produce coarse nodularity
Histologic pattern	Diffuse or nodular, sometimes pseudofollicular or acinar	Diffuse or nodular, frequently pseudofollicular or acinar	Diffuse, nodular, pseudofollicular, or acinar; often trabecular pattern with distinctive nuclear palisading predominates
Cytologic features	Chief cells predominate; transitional and oncocytic cells often present	Chief cells predominate, but mixture of chief, transitional, and oncocytic cells may be seen; rarely, purely oncocytic	Cells usually resemble chief cells, but variable cytoplasmic oncocytic change may be seen; cell borders often indistinct
Intracytoplasmic lipid	Decreased	Decreased in tumor; abundant in atrophic rim of parathyroid	Usually absent
Stromal fat cells	Scanty to absent	Usually absent in tumor; present rim of atrophic parathyroid	Absent
Nuclear morphology	Normal to slightly increased N-to-C ratio; usually without nuclear pleomorphism	Nuclei enlarged, with variability in size; scattered groups of large pleomorphic, hyperchromatic nuclei, or multinucleated cells	Increased N-to-C ratio; enlarged atypical nuclei; often with monotonous (bland appearing) nuclei
Nucleoli	Inconspicuous to small	Inconspicuous to small	Frequently prominent and enlarged
Mitoses	Common (60% of cases; most with <1 mitotic figure/10 HPF)	Common (70% of cases; most with <1 mitotic figure/10 HPF)	Common (80% of cases), may include atypical mitoses; may be numerous

Continued

TABLE 33-1 Comparative Features of Parathyroid Proliferative Diseases—cont'd

	Hyperplasia	Adenoma	Carcinoma
Capsular and vascular invasion	Absent	Absent; entrapment of tumor cells may occur in capsule if degenerative changes present	Capsular invasion present in two thirds; may involve only capsule or extend into adjacent tissues Vascular invasion present in up to 15%; usually in capsular vessels
Remainder of gland	Entire gland is abnormal	Normal or atrophic	Normal
Degenerative changes	May be seen in very large glands Includes hemorrhage, areas of fibrosis, and cystic change	Common, especially in larger adenomas; includes hemorrhage, fibrosis, and cystic change, sometimes calcification	Tumor cell necrosis; calcification and cystic changes may be present
Treatment	Subtotal parathyroidectomy with surgical removal of three glands, leaving a remnant of the 4th or total parathyroidectomy* with autotransplantation of parathyroid tissue in forearm	Surgical removal of the enlarged gland	En bloc resection, including ipsilateral thyroid lobe and adjacent soft tissues
Prognosis	Excellent	Excellent	Up to 50% of patients are cured by en bloc resection; considered an indolent malignancy even in presence of recurrence or metastasis with long survival even after recognition of tumor recurrence; morbidity and mortality correlate to complications of severe hypercalcemia
Recurrence and metastasis	Recurrence in approximately 16% of cases due to inadequate neck exploration and may not be evident for years	Absent	Recurrence in two thirds of patients usually within 3 years of the first surgery; metastasis is 35%, is a late event usually preceded by local recurrence; most commonly to lung, cervical lymph nodes, and liver
Familial and/or MEN association	Yes, in approximately 20% of cases	Uncommon	Rare

g, Grams; HPF, high power fields; MEN, multiple endocrine neoplasia syndrome; N-to-C, nuclear-to-cytoplasmic.

*Particularly in cases of familial hyperparathyroidism.

- Most atypical parathyroid adenomas prove to be benign in long-term follow-up, but owing to the uncertainty in their malignant potential, they have been termed atypical.
- Treatment is similar to a typical parathyroid adenoma, but patients should be followed for potential recurrent hyperparathyroidism, local recurrence of tumor, and/or evidence of aggressive behavior (e.g., metastasis).

Differential Diagnosis

- Primary chief cell hyperplasia (see Table 33-1)
- Parathyroid carcinoma (see Table 33-1)
- Follicular neoplasm of thyroid gland

Treatment and Prognosis

- Most widely accepted therapy is excision of the adenomatous gland with biopsy of at least one additional gland that is “normal” in size

- Some favor a full bilateral neck exploration with subtotal parathyroidectomy and have reported a lower incidence of recurrent hypercalcemia that required reoperation:
 - There is an increased incidence of postoperative hypoparathyroidism with this procedure.
- Recurrence rates vary significantly and may reflect problems in classification, particularly in cases of hyperplasia with nodules, which may erroneously be designated as adenomas.
- Although generalized osteopenia is now more common, osteitis fibrosa cystica, also known as brown tumor of hyperparathyroidism is occasionally seen (see Figs. 33-20 to 33-22):
 - May occur in hyperparathyroidism of any cause but is related to degree and duration of serum calcium elevation
 - Lesions are characterized by resorption of bone, which is replaced by fibrous tissue, probably as a reparative response to microfractures
 - Hemorrhage within the fibrous tissue leads to the accumulation of hemosiderin and a proliferation of multinucleated giant cells in addition to the osteoclasts
 - With time degenerative changes lead to the formation of cystic spaces
 - Osteitis fibrosa cystica cannot be distinguished histologically from the giant cell (reparative) granuloma of the jaw; clinical information is essential.
- Recurrent hyperparathyroidism following surgery for an adenoma may also result from incomplete excision, rupture of the tumor capsule with spillage into the operative field, or from hyperfunction of autografted parathyroid tissue following subtotal parathyroidectomy.

PARATHYROID CARCINOMA

(Figs. 33-23 through 33-38,
see Table 33-1)

Definition: Malignant neoplasm of parathyroid parenchymal cells.

Clinical

- Rare neoplasm; responsible for approximately 2% of cases of hyperparathyroidism
- No gender predilection; most common in fifth and sixth decades:
 - Affect patients approximately a decade younger than those with adenomas
 - Rare cases reported in children
- Clinical findings associated with parathyroid carcinoma are listed in Box 33-2.

BOX 33-2 Clinical Features Associated with Malignancy in Parathyroid Neoplasms

- Serum calcium level >14 mg/dl
 - Serum parathormone levels 2 to 3 times normal
 - Severe metabolic manifestations: nephrolithiasis, bone disease, etc.
 - Palpable neck mass
 - Difficulty in surgical dissection owing to adherence to surrounding structures
- Most patients have severe hypercalcemia and hypophosphatemia:
 - Mean serum calcium 14.0 mg/dl, in contrast to mean serum calcium of 12.0 mg/dl in benign hyperparathyroidism
 - Occasional normocalcemic patients may occur.
 - Symptoms are due to excessive parathyroid hormone secretion and are similar to those in patients with hyperparathyroidism of benign cause but tend to be more severe due to the higher serum calcium levels:
 - Presenting symptoms include polyuria, polydipsia, fatigue and weakness, depression, bone pain and fracture (high incidence in earlier series), renal colic and nephrolithiasis (up to two thirds of patients in earlier studies, but probably decreasing with routine biochemical screening and earlier detection), peptic ulcer disease, and recurrent pancreatitis.
 - Palpable neck masses more common than in hyperplasia or adenoma.
 - Etiology is unknown:
 - Most cases are sporadic.
 - Loss of the retinoblastoma (Rb) tumor-suppressor gene may play an important role in the development of parathyroid carcinoma, and its absence may be helpful in distinguishing parathyroid adenoma from carcinoma.
 - Some cases occur in hyperparathyroidism-jaw tumor syndrome, MEN, or familial isolated hyperparathyroidism.
 - External beam irradiation to the neck may be a possible risk factor.
 - Rare cases occur in patients with secondary hyperparathyroidism, possibly linking the development of parathyroid carcinoma from parathyroid adenoma or hyperplasia.
 - May be associated with hyperparathyroidism-jaw tumor syndrome (HPT-JT):
 - Autosomal-dominant disorder with germline mutation in *HRPT-2* gene on chromosome 1q25-31
 - Characterized by:
 - Parathyroid adenoma or carcinoma
 - Fibro-osseous lesions of the jaw (e.g., ossifying fibroma of mandible or maxilla): 30% of cases

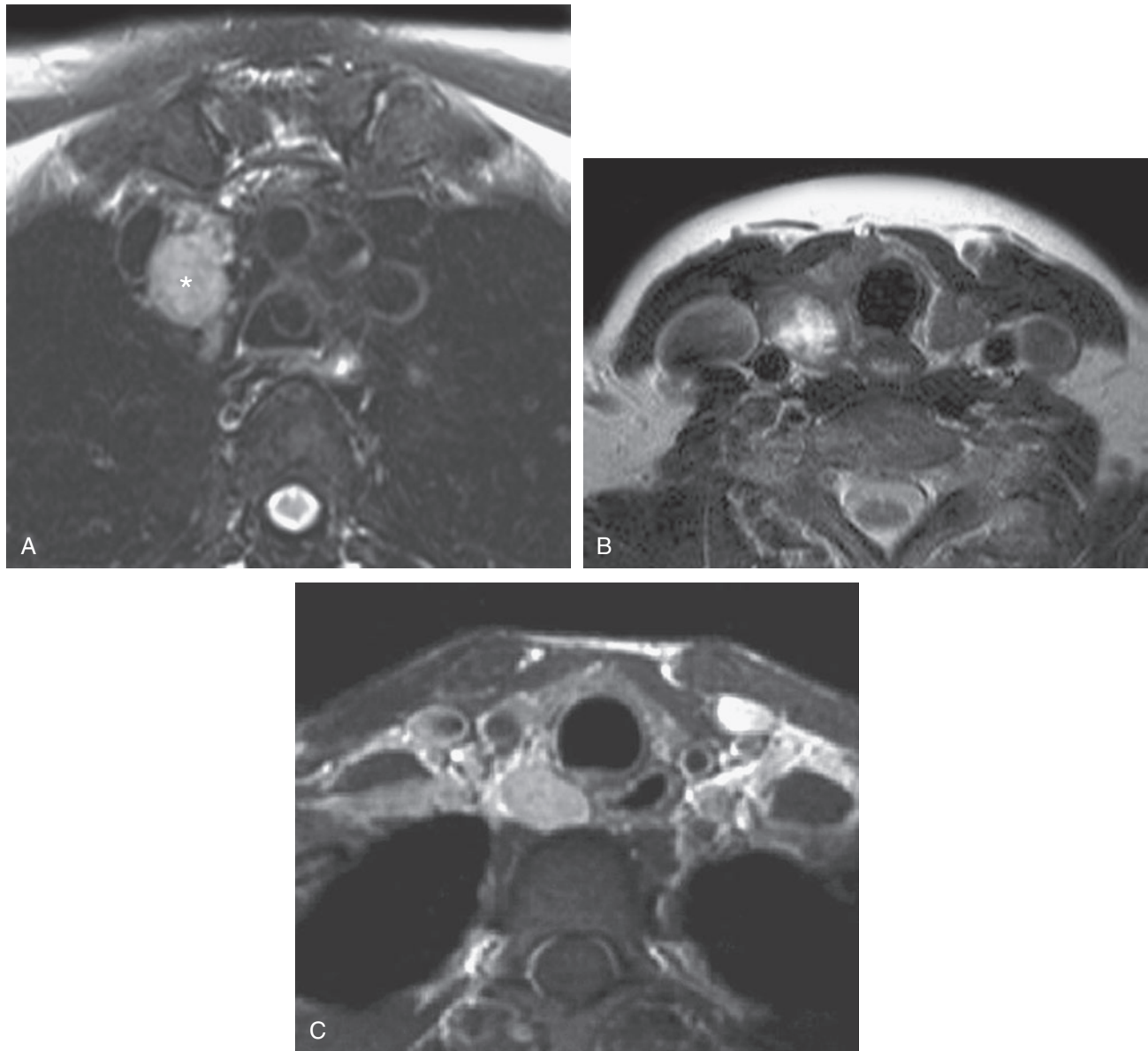


Fig. 33-23. Parathyroid carcinoma in a patient with severe hyperparathyroidism.

A, Axial T2-weighted MR image shows a demarcated 2.5-cm mediastinal mass (*) that represents a parathyroid carcinoma. **B**, Axial T2-weighted MR image of another patient with hypercalcemia shows a nonhomogeneous mass in the right tracheoesophageal groove. The margins are slightly unsharp. This is a parathyroid carcinoma. **C**, Axial T2-weighted MR image shows a large mass in the right tracheoesophageal groove in this patient with severe hypercalcemia. At surgery, this was a parathyroid carcinoma. (From Som PM, Curtin HD: *Head and neck imaging*, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-110, p 2674.)

- Renal cyst, hamartoma, carcinoma: 20% of cases
- Approximately 80% of patients develop hyperparathyroidism.
- Usually presents late in adolescence
- Hypercalcemia tends to be severe.
- Higher incidence of parathyroid carcinoma in comparison with patients with MEN-1 and MEN-2A
 - Renal lesions may include:
 - Renal cysts, polycystic renal disease, renal hamartoma
 - Papillary renal cell carcinoma, renal cortical adenomas, Wilms tumor

Radiology

- Imaging procedures are of similar utility as in parathyroid adenomas.



Fig. 33-24. Parathyroid carcinoma.

Parathyroid carcinoma appearing as a large tumor with areas of cystic degeneration associated with large nodules of viable tumor; the capsule is grossly thickened.

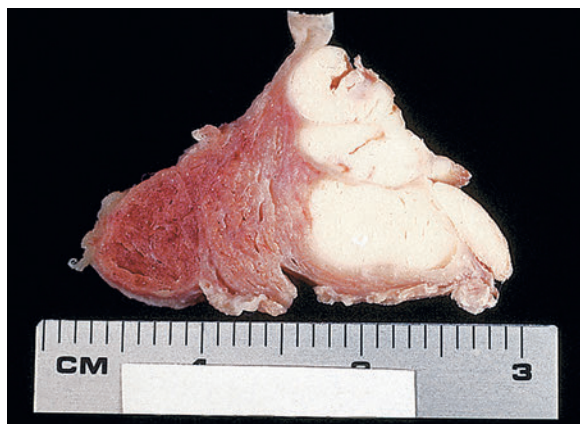


Fig. 33-25. Parathyroid carcinoma.

Parathyroid carcinoma appearing as an irregular, infiltrative, indurated, white neoplasm adherent to the adjacent thyroid lobe (*on the left*). Difficulties in dissection a parathyroid lesion from adjacent structures is suggestive, although not definitively diagnostic, for carcinoma. Histologic confirmation is always required for a diagnosis of parathyroid carcinoma.

Pathology

- Pathologic findings potentially associated with parathyroid carcinoma are listed in [Table 33-2](#).

Gross

- Average size is larger than parathyroid adenomas: mean weight 6.7 g (range 1.5 to 27 g), although smaller tumors are being identified more often in recent years.
- May be encapsulated or infiltrative



Fig. 33-26. Parathyroid carcinoma.

Some parathyroid carcinomas like this one are more advanced at presentation with extensive invasion of surrounding tissues. Cases such as this one are rare today as a result of routine biochemical screening of most populations in developed countries.

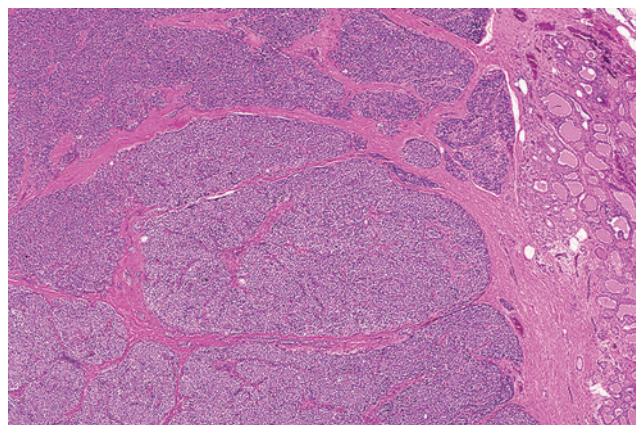


Fig. 33-27. Parathyroid carcinoma.

Parathyroid carcinoma characterized by a thickened capsule, and fibrous bands dissecting through the tumor dividing the tumor into separate nodules; the tumor was adherent to and invaded into the thyroid gland (*right*).

- Brown to gray-white, carcinomas may have a smooth, firm cut surface indistinguishable from an adenoma or may be distinctly indurated
- Difficulty in dissection of the tumor and adherence to the thyroid gland are common intraoperative observations.

Histology

- Histologic criteria in diagnosing parathyroid carcinoma are detailed in [Table 33-2](#).
- Many parathyroid carcinomas are encapsulated, and usually the capsule of a carcinoma is thicker than that seen in most adenomas:
 - Some adenomas with reactive and degenerative changes have thick and uneven capsules.

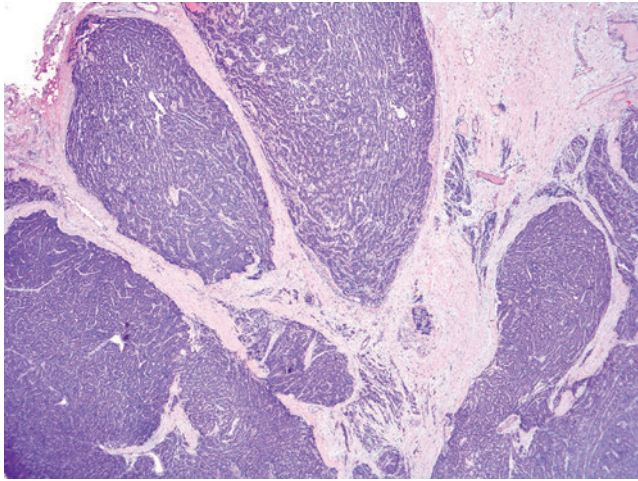


Fig. 33-28. Parathyroid carcinoma.

Parathyroid carcinoma with acellular fibrous bands coursing through the neoplasm dividing the tumor into multiple nodules.

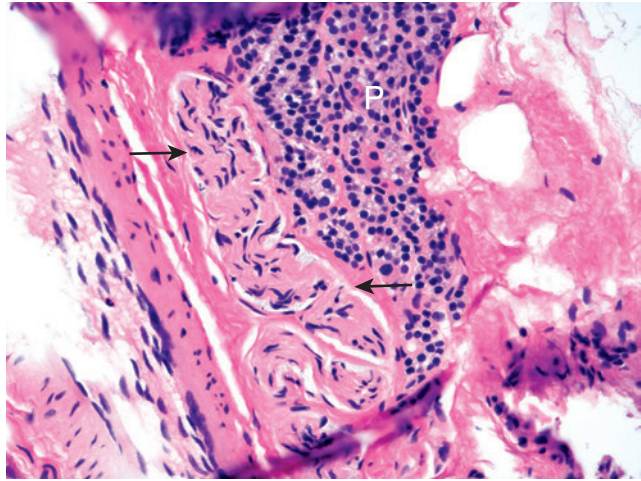


Fig. 33-30. Parathyroid carcinoma.

Parathyroid carcinoma (*P*) with perineural invasion (*arrows*). The neoplastic proliferation includes rather bland-appearing and uniform nuclei, but the presence of neurotropism represents invasive growth diagnostic for carcinoma.

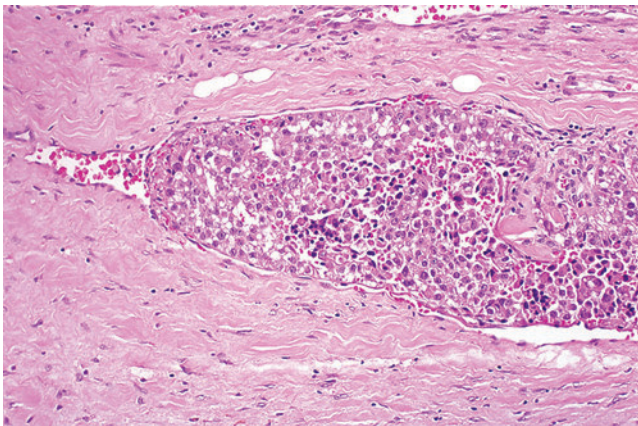


Fig. 33-29. Parathyroid carcinoma.

Parathyroid carcinoma showing vascular invasion within an endothelial-lined blood vessel.

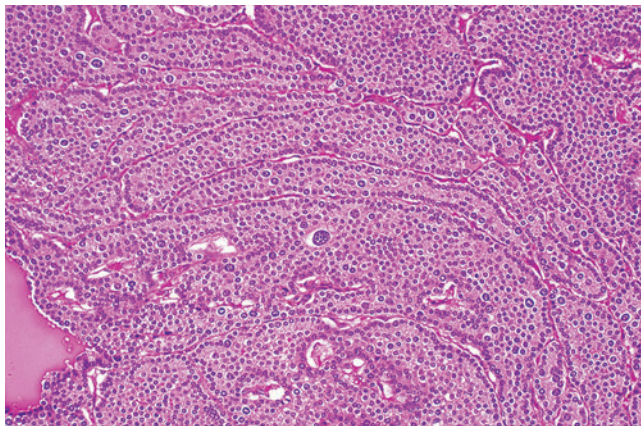


Fig. 33-31. Parathyroid carcinoma.

Parathyroid carcinoma characterized by hypercellularity and trabecular growth.

TABLE 33-2 Pathologic Features Associated with Malignancy in Parathyroid Neoplasms

Features Definitively Diagnostic for Malignancy	Features Worrisome for But Not Definitively Diagnostic for Malignancy
<ul style="list-style-type: none"> • Invasive growth including into: <ul style="list-style-type: none"> Surrounding soft tissues Surrounding viscera or vital structures (thyroid gland, larynx, trachea, esophagus, pharynx, carotid artery, recurrent laryngeal nerve) • Vascular invasion • Perineural invasion • Metastatic disease: <ul style="list-style-type: none"> Regional lymph nodes Distant sites 	<ul style="list-style-type: none"> • Large size (mean weight 6.7 g) • Adherence to surrounding structures (e.g., thyroid tissue, others) • Irregular contour; lack of distinct encapsulation • Thick capsule • Intralesional fibrous bands • Mitotic activity (especially >5 per 10 HPF) • Coagulative tumor necrosis • Diffuse cellular atypia • Diffuse sheet-like monotonous small cells with increased N:C • Macronucleoli in many tumor cells • Trabecular growth • Spindling of tumor cells

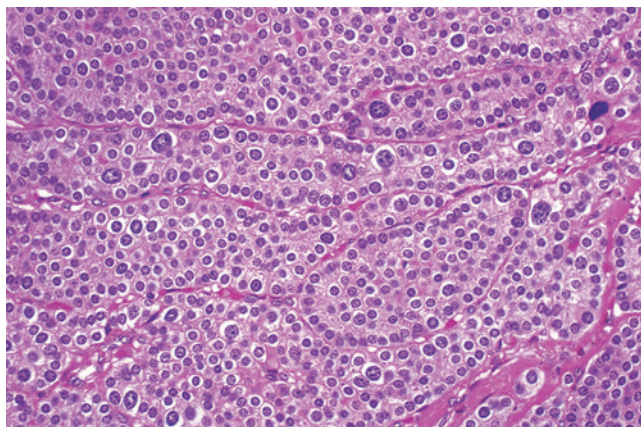


Fig. 33-32. Parathyroid carcinoma.

Higher magnification of the previous illustration shows the trabecular pattern of growth composed of fairly uniform, monotonous-appearing nuclei, although scattered enlarged (pleomorphic) nuclei are present. Such enlarged atypical nuclei can be seen in adenomas, and by itself is not a definitive diagnostic feature for carcinoma. Such enlarged atypical nuclei are considered to be an uncommon feature in parathyroid hyperplasia.

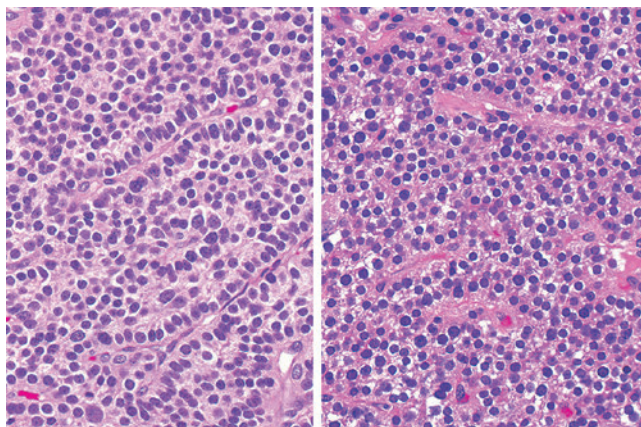


Fig. 33-33. Parathyroid carcinoma.

A comparison of the nuclei in parathyroid carcinoma (*left*) with parathyroid adenoma (*right*) shows the cells of the carcinoma to have a higher nuclear-to-cytoplasmic ratio than those of the adenoma. Such a feature is worrisome but in the absence of other findings is not diagnostic for carcinoma.

- Growth patterns also vary and include solid sheets, acinar formation, cords, rosettes, and, of particular differential diagnostic significance, trabecular pattern:
 - Trabecular pattern is a finding more often identified in association with parathyroid carcinoma than in adenoma or hyperplasia, and its presence,

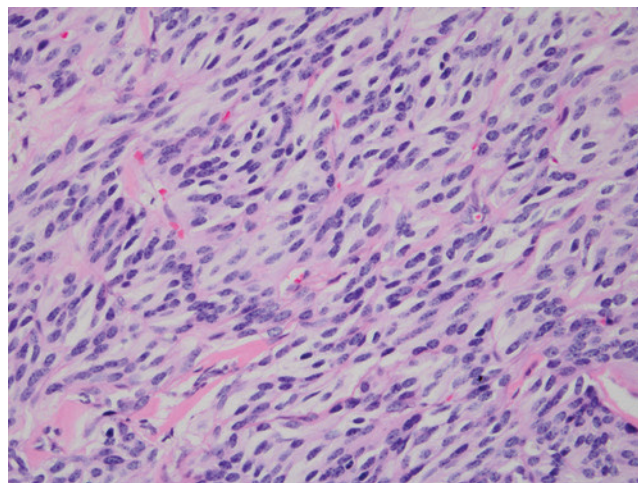


Fig. 33-34. Parathyroid carcinoma.

Parathyroid carcinoma with spindle-shaped tumor cells.

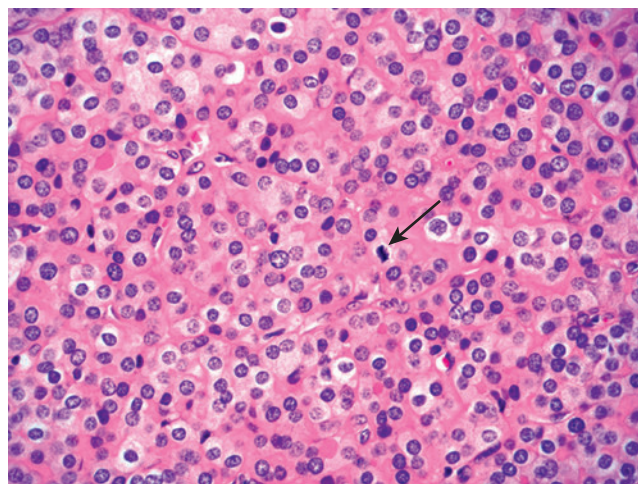


Fig. 33-35. Parathyroid carcinoma with mitotic figure (arrow).

Mitoses are not, by themselves, accurate predictors of malignancy, because they may be seen in parathyroid hyperplasia and adenomas.

even focally, should raise suspicion for the diagnosis of carcinoma.

- Nuclear palisading may be prominent in trabecular areas.
- Spindling of cells is also a feature more often seen in carcinomas than in benign proliferations.
- Trabecular pattern and spindle-shaped cells, although worrisome for a possible diagnosis of carcinoma, are not definitive diagnostic features for carcinoma.

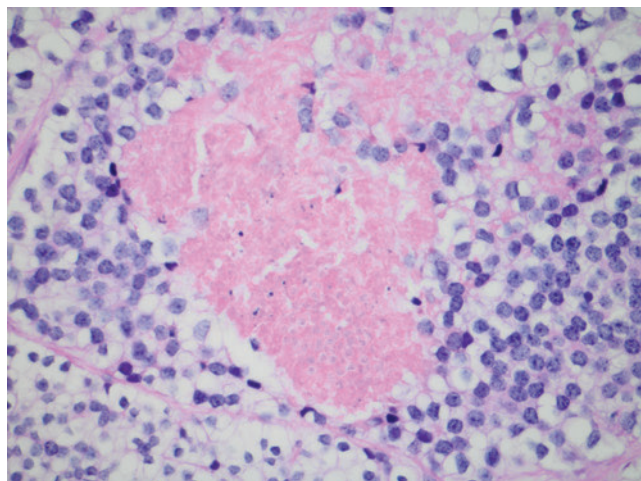


Fig. 33-36. Parathyroid carcinoma with necrosis.

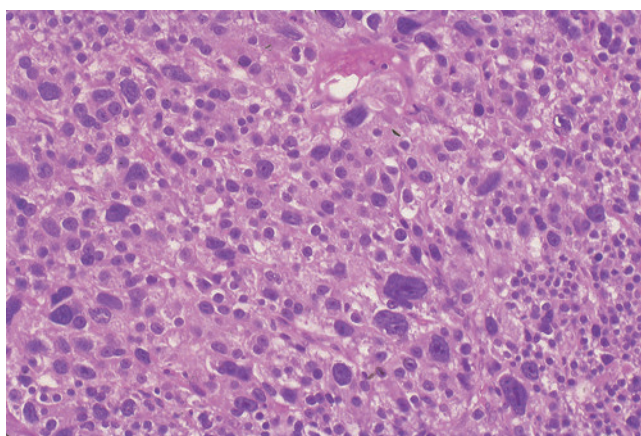


Fig. 33-37. Parathyroid carcinoma.

Parathyroid carcinoma showing markedly enlarged and hyperchromatic nuclei; although similar nuclear atypia can be seen in adenomas, the fact that these changes were diffusely present rather than focally present (as single atypical nuclei and/or in small clusters within the tumor) supports a diagnosis of parathyroid carcinoma and not parathyroid adenoma or hyperplasia. A monotonous nuclear pattern is, surprisingly, more often seen in carcinomas than in adenomas.

- Follicular pattern of growth not often if ever seen in parathyroid carcinomas
- Tumor cells may have variable morphology:
 - Some areas may show similar features as benign chief cells with slightly eosinophilic to clear cytoplasm.
 - Other areas may contain enlarged cells with more distinctly eosinophilic cytoplasm, large nuclei with prominent nucleoli.
 - Rare oncocytic cell variant identified.

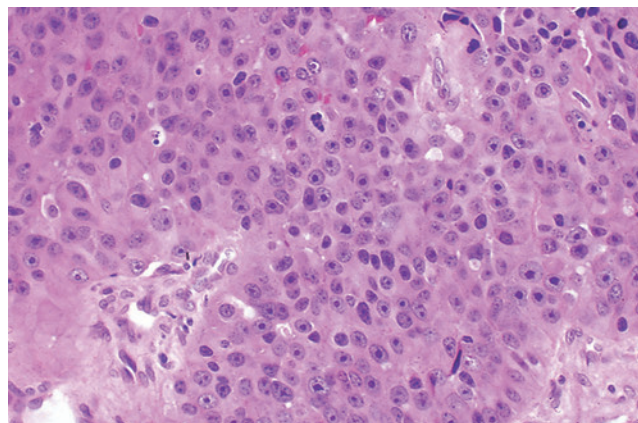


Fig. 33-38. Parathyroid carcinoma.

Parathyroid carcinoma characterized by a monotonous but crowded proliferation of cells with large nuclei and very large eosinophilic nucleoli (macronucleoli); these findings seen in some parathyroid carcinomas are not typically present in benign parathyroid lesions (i.e., adenoma, hyperplasia); mitotic figures can be seen (*middle upper, upper right*).

- Nuclear pleomorphism is less common than in adenomas, which often contain scattered foci with enlarged atypical nuclei:
 - Monotony of nuclear size and shape is frequently present in carcinomas.
 - Pleomorphism, when present, is usually more diffuse than in adenomas.
- Mitotic activity is identified in most, but not all, parathyroid carcinomas:
 - Presence of atypical mitoses is virtually diagnostic of malignancy
 - Although a high mitotic rate is a helpful feature, the presence of mitotic activity exceeding 1 per 10 high-power fields in a minority of parathyroid adenomas and in parathyroid hyperplasia may be seen.
 - Overlap in mitotic activity between all parathyroid proliferative diseases (i.e., adenoma, hyperplasia, and carcinoma) makes mitotic activity a useful finding only when coupled with other features of malignancy.
- Capsular invasion may be obvious in some cases, or may be represented only by irregular tongues or islands of parathyroid tissue protruding into the capsule; invasion beyond the capsule is indicative of malignancy:
 - Entrapped islands of parathyroid parenchymal cells in benign disease should be distinguished from these invasive foci by their rounded contours and lack of desmoplastic reaction.

- Fibrous bands extending from a thickened capsule frequently divide the tumor into irregular compartments and/or nodules.
- Angioinvasion is diagnostic of carcinoma but is present in a minority of cases:
 - Usually found within vessels in the thick tumor capsule
 - Artfactually displaced clumps of tumor cells in vascular spaces should be distinguished from true invasion by their frequently degenerated appearance and by their lack of attachment to the vessel wall.
- Perineural invasion, although rarely seen, is also virtually diagnostic of malignancy.
- Immunohistochemistry:
 - Positive for cytokeratins, chromogranin as well as for parathyroid hormone
 - Loss of (nuclear) parafibromin staining is common but not invariably identified:
 - Only about 50% of carcinomas lack parafibromin staining
 - Some carcinomas may show positive parafibromin staining
 - Loss of parafibromin reported in sporadic adenomas (unassociated with hyperparathyroidism-jaw tumor syndrome)
 - High frequency of cyclin D1 expression (reported in more than 90% of cases):
 - May result from loss of parafibromin expression
 - May reflect increased cellular proliferation
 - High levels of expression also present in hyperplasia (approximately 61%) and adenomas (approximately 39%) so not uniquely seen in carcinoma.
 - Galectin-3 reactivity frequently seen:
 - More than 90% of cases reported positive
 - Seen in less than 5% of parathyroid adenomas
 - Diffuse strong staining for protein gene product 9.5 (PGP9.5) frequently found
 - Ki67 (MIB1) proliferative index may be increased:
 - An index greater than 5% should raise suspicion for carcinoma but the diagnosis of carcinoma requires confirmatory diagnostic findings.
 - Proliferative indices in differentiating adenoma from carcinoma are of limited utility given overlapping findings in these lesions.
 - Loss of immunoreactivity for retinoblastoma (Rb) protein
 - Negative for thyroglobulin and TTF-1
- Cytogenetic and molecular biology:
 - Mutations of tumor suppressor gene *HRPT-2* may be important in the pathogenesis of parathyroid carcinoma:
 - Inactivation of germ line mutations in *HRPT-2* believed to play a significant role in the development of parathyroid carcinoma
 - Located on 1q25
 - Encodes parafibromin known to function in the suppression of cyclin D1
 - Implicated in the hyperparathyroidism-jaw tumor syndrome
 - Identified in two thirds of cases of sporadic occurring parathyroid carcinoma
 - Practically never found in parathyroid adenomas
 - Allelic loss of the retinoblastoma (Rb) tumor-suppressor gene is common:
 - May play an important role in the development of parathyroid carcinoma
 - Loss of immunoreactivity for Rb protein reported in 20% to 100% of parathyroid carcinomas
 - Absence may be helpful in distinguishing parathyroid adenomas from carcinomas but not considered sufficiently reliable in differentiating adenoma from carcinoma
 - Somatic mutation in *MEN-1* gene:
 - Found in 13% of carcinomas
 - Suggests a role in the development of carcinoma
 - Allelic loss of the p53
 - Reduced expression of cyclin-dependent kinase inhibitor protein p27 commonly identified:
 - In contrast, adenomas show higher labeling index.

Differential Diagnosis

- Parathyroid adenoma (see [Table 33-1](#))
- Parathyroid hyperplasia (see [Table 33-1](#))
- Parathyromatosis:
 - Represents microscopic foci of hyperplastic parathyroid tissue in the soft tissues of the neck in association with primary chief cell hyperplasia
 - May be the cause of recurrent disease after an apparently complete resection of the grossly evident hyperplastic glands
 - Should not be mistaken for invasion as seen in parathyroid carcinoma; differentiating features may include:
 - Absence of associated fibroblastic reaction or infiltrative contour
 - Absence of an intravascular location of these nests
 - Absence of other histologic features of carcinoma should help exclude malignancy.
- Metastatic carcinoma from another site

Treatment and Prognosis

- Surgery is the primary treatment modality with recommended treatment including en bloc resection, to include the ipsilateral thyroid lobe, strap muscles, recurrent laryngeal nerve, trachea, or esophagus if involved:
 - Offers the best chance for cure
 - Up to 50% of patients are cured by en bloc resection.
- Prophylactic lymphadenectomy not recommended due to the low rate of nodal disease (reported to be 6%):
 - Neck dissection warranted if there is clinical evidence of neck (nodal) disease
- Adjuvant radiotherapy may improve local control and limit the occurrence of local relapse, especially when the carcinoma is incompletely excised with involvement of resection margins.
- Efficacy of chemotherapy not proven
- In general, parathyroid carcinomas are generally indolent behaving:
 - 5-year survival from 60% to 85%
 - 10-year survival from 40% to 79%
- Recurrences generally manifest within 3 years of the first surgery with locally recurrent disease:
 - Recurrence rates range from approximately 33% to 50%
 - Lower rates of recurrence reported (8%) with en bloc resection
 - Higher recurrence rates reported (51%) when treated by parathyroid gland excision
- Metastatic disease occurs rather late in the course of disease:
 - Found in approximately one third of patients
 - Usually occurs several years after primary diagnosis
 - Sites of metastases include regional lymph nodes, mediastinum, lungs, liver, and bones.
- Surgical resection of metastatic or locally recurrent disease is frequently helpful due to the rather indolent nature of parathyroid carcinoma:
 - Patients usually survive for several years after recognition of tumor recurrence.
- Recurrence and/or metastatic disease often manifest with recurrent hypercalcemia:
 - Lifelong monitoring for recurrent and/or metastatic disease most effectively accomplished with serum calcium levels.
- Major difficulty in management of recurrent disease is severe hypercalcemia and its complications.
- Death is related to excessive hormonal production with subsequent hypercalcemia rather than directly to tumor burden.
- Prognosis has been shown to be related to tumor stage:

- Stage I: invasion of surrounding soft tissues; 90% disease-free survival
- Stage II: vascular invasion; 46% disease-free survival
- Stage III: invasion of vital organs or regional lymph node metastasis; 50% disease-free survival
- Stage IV: distant metastases; no disease-free survival

SECONDARY NEOPLASMS

(Fig. 33-39)

Definition: Contiguous involvement from tumors in adjacent structures or metastatic neoplasms from distant sites involving the parathyroid gland.

Clinical

- Usually asymptomatic; may present with a neck mass; other symptoms may include hoarseness, dysphagia, and neck pain; rare cases have been associated with clinical hypoparathyroidism due to massive replacement of multiple glands
- May result from direct extension, especially from thyroid or laryngeal tumors, or from metastatic spread
- Metastasis to parathyroid glands is rare; among the more common primary malignancies that may metastasize to the parathyroid glands include:
 - Breast carcinoma (most common)
 - Hematologic malignancies

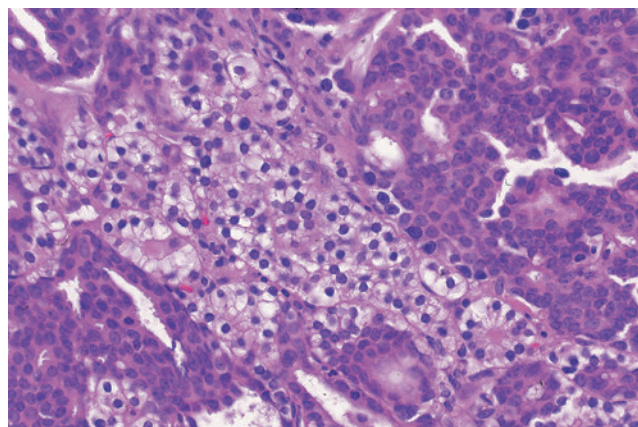


Fig. 33-39. Metastatic breast carcinoma.

Metastatic breast carcinoma to the parathyroid gland. Residual parathyroid parenchyma is present in the center of the image surrounded by a malignant glandular lesion. The patient had a known history of breast carcinoma that was widely metastatic, including the parathyroid gland. Immunohistochemical staining (not shown) included reactivity for mammaglobin, BRST-2, and GATA-3.

- Malignant melanoma
- Lung carcinoma
- Renal cell carcinoma
- Sarcomas

Pathology

- Found in 11.9% of cancer patients in autopsy studies
- May involve one or multiple glands
- Immunohistochemistry:
 - A variety of organ-specific markers may be helpful in the diagnosis of a metastatic tumor to the parathyroid gland
 - Presence of specific immunomarkers helpful in distinguishing between primary and secondary neoplasms:
 - Breast carcinoma: mammaglobin, BRST2, GATA-3
 - Hematologic malignancies: CD45 (leukocyte common antigen), B-cell (CD20, others), T-cell (CD3, others)
 - Malignant melanoma: S100 protein, HMB45, melan A, tyrosinase, MITF1, Sox10, vimentin

- Lung carcinoma: Napsin A, TTF1
- Renal cell carcinoma: RCC antibody, CD10, PAX2, PAX8, CAIX
- Prostate carcinoma: PSA, PAP, prostatein

Differential Diagnosis

- Parathyroid carcinoma:
 - Reactivity for parathyroid hormone, chromogranin

Treatment and Prognosis

- Treatment based on primary site of origin
- Prognosis poor, related to dissemination of primary disease

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Intraoperative Consultation (Frozen Section) in Parathyroid Gland and Parathyroid Proliferative Disease (PPD)/Hyperparathyroidism

CONSIDERATIONS

- Optimal management of primary hyperparathyroidism is achieved by selective removal of parathyroid glands guided by the histologic findings in each gland.
- Surgical management of a patient with primary hyperparathyroidism is to remove one or more enlarged parathyroid glands.
- Pathologists play a primary role in the clinical care of the patient.
- At the time of parathyroid exploration the initial assessment of the excised tissue is the intraoperative histopathologic determination of whether the excised tissue is parathyroid tissue and, if so, whether it is or is not abnormal:
 - In the majority of cases the identification of parathyroid tissue is rather simple, but at times this determination may prove difficult.
 - It is well established that the differentiation of an adenoma from hyperplasia in a single enlarged gland cannot be made by histopathologic evaluation and that detailed clinical information (pre- and postoperative) is required to arrive at the diagnosis.
- The most common developmental anomaly of the parathyroid glands is ectopia, which usually represents a variation in embryologic migratory pattern.
- Parathyroid agenesis is very rare:
 - DiGeorge syndrome includes complete or partial absence of the third and fourth pharyngeal pouches and their derivatives, including the thymus, the parathyroid glands, and thyroid C-cells.
 - Manifests as multiple facial malformations, hypoplasia of the thyroid, hypoparathyroidism, and cardiac abnormalities

NORMAL SIZE AND WEIGHT (Table 34-1)

- The parathyroid glands are soft yellow-brown to dark-brown, circumscribed, ovoid structures; some parathyroid glands are bilobed or flattened.

TABLE 34-1 Comparison of Normal Parathyroid Tissue to Abnormal Parathyroid Tissue

Parameter	Normal Range	Abnormal Changes
Number	Usually 4, sometimes 5	Ectopia
Size	Length 3-6 mm Width 2-4 mm Thickness 0.5-2.0 mm	Enlarged gland greater than 6 mm
Weight	Approximately 0 ± 3.5 mg women; 142 ± 5.2 mg men Approximately 30 mg each: men: 120 ± 5.2 mg women 142 ± 5.2 mg (lower glands usually heavier than upper glands)	Any gland weighing greater than 60 mg
Percentage fat	Approximately 17%, rarely more than 50%; more in women than in men	Complete absence or very few intraparenchymal fat cells
Intracytoplasmic lipid	Abundant	Absent or scanty

Modified from Chan JKC: The parathyroid gland. In Fletcher CDM: Diagnostic histopathology of tumors, ed 4, Philadelphia, 2013, Elsevier Saunders, p 1274.

- Each gland measures approximately 3 to 6 mm in length.
- The combined weight increases from early infancy (mean, 5 to 9 mg) to the third or fourth decade (mean for males, 120 mg; for females, 142 mg).
- The actual parenchymal cell mass represents about 74% of the weight of adult parathyroid glands.
- Second rule, which is mutually inclusive of the first rule, is to recognize the resected tissue as parathyroid parenchyma:
 - Once recognized as parathyroid tissue, the determination of whether the resected tissue is normal, abnormal, or indeterminate can be undertaken (see [Table 34-1](#)).

INDICATIONS FOR INTRAOPERATIVE CONSULTATION FOR HYPERPARATHYROIDISM

- The purpose of intraoperative consultation of patients with hyperparathyroidism is to determine the underlying pathologic process, which directly affects treatment.
- A diagnosis of parathyroid adenoma results in excision of the involved gland alone, and this treatment is curative.
- A diagnosis of parathyroid hyperplasia results in subtotal parathyroidectomy (three and a half glands), leaving behind a small amount of parathyroid tissue (approximately 50 g).
- A diagnosis of parathyroid carcinoma usually necessitates en bloc resection to include the involved gland and adjacent thyroid lobe with or without selective neck dissection; this approach offers the best opportunity for a cure.

SURGEONS' EXPECTATIONS OF THE INTRAOPERATIVE ASSESSMENT OF PARATHYROID EXPLORATION

- Surgeons' expectations include:
 - Identify the tissue as being of parathyroid gland origin.
 - Attempt to differentiate a parathyroid adenoma from hyperplasia.
 - Identify carcinoma.
 - Do this all in a short time period.

PRACTICAL REALITY OF THE INTRAOPERATIVE ASSESSMENT OF PARATHYROID EXPLORATION

- First rule in the intraoperative consultation of parathyroid diseases is “do not believe the surgeon that the resected tissue is of parathyroid gland origin.”

HANDLING OF RESECTED PARATHYROID GLANDS

- Record location of excised tissue.
- Record the size and weight of the excised glands after removing the surrounding fat (inform surgeon of these findings):
 - Glands weighing greater than 60 mg are considered pathologic, whereas a normal gland typically weighs 35 mg.
 - Do not remove fat that is closely apposed to any nodules because this tissue may be representative of a cap of normal parathyroid tissue, a potential key histologic feature in the diagnosis of parathyroid adenoma.
- Gross examination with attention to the external appearance, color, and consistency of the excised gland
- Perform frozen section.

INKING OF PARATHYROID GLANDS

- Is the inking of parathyroid glands necessary?
 - Typically excised parathyroid glands do not require surgical ink, but if the excised gland is adherent to surrounding structures, suggesting the possible diagnosis of carcinoma, then evaluation of surgical margins becomes important and requires the inking of the tissue.

MICROSCOPIC FINDINGS AT FROZEN SECTION

([Figs. 34-1 through 34-8](#))

- In the presence of an enlarged (size and weight) parathyroid gland, the histologic findings are almost invariably abnormal.
- These changes may include increased cellularity and decreased stromal fat.
- A capsule may or may not be present, and a rim of residual normal or atrophic parathyroid tissue may or may not be present:
 - In this setting if the surgeon indicates that the remaining parathyroid glands are normal and/or

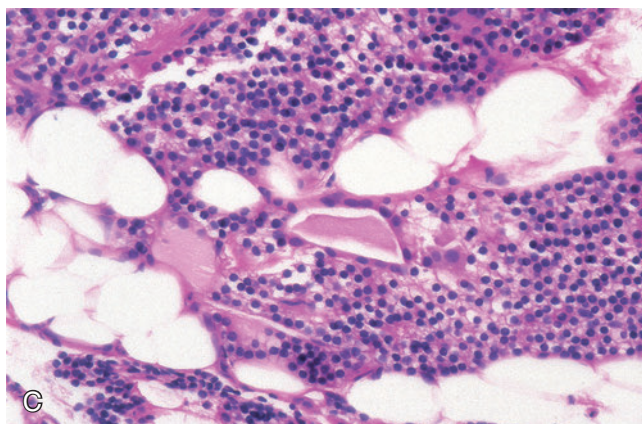
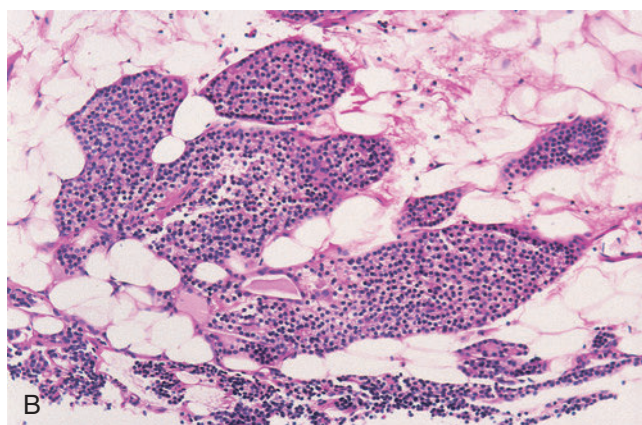
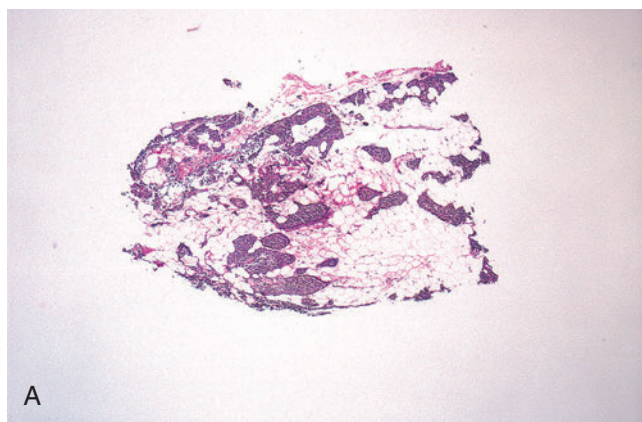


Fig. 34-1. Frozen section of normal adult parathyroid gland.

A, Low magnification shows an admixture of parenchymal (chief) cells and fat. **B**, The parenchymal (chief) cells are arranged in solid groups, cords, and nests with a single follicle-like structure containing eosinophilic material resembling colloid. **C**, Higher magnification shows a predominance of chief cells with round, hyperchromatic nuclei and amphophilic or slightly eosinophilic to somewhat clear cytoplasm, interspersed, scattered oxyphilic cells characterized by an eosinophilic granular cytoplasm, a follicle-like structure containing eosinophilic material resembling colloid, and associated fat cells (adipocytes).

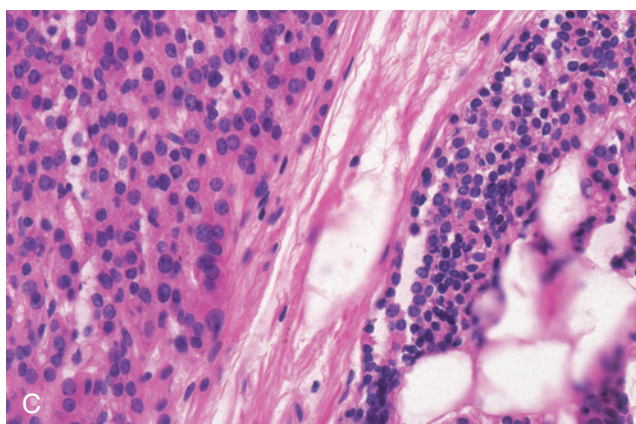
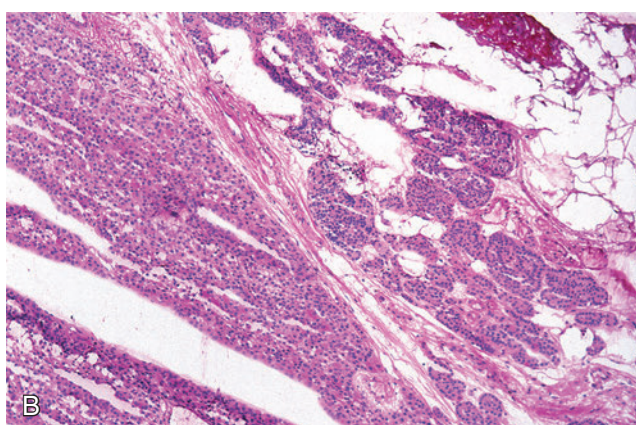
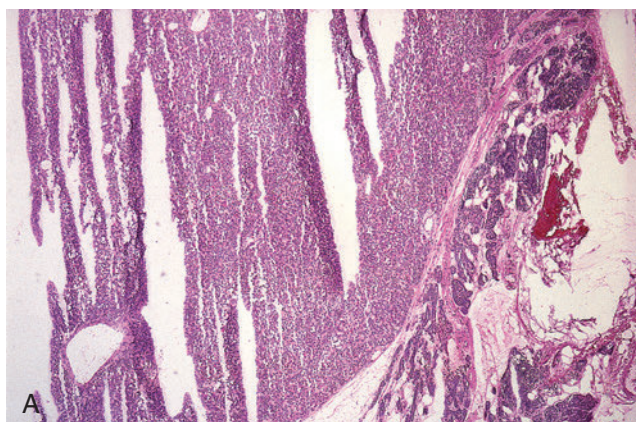


Fig. 34-2. Intraoperative findings, parathyroid adenoma.

A, The parathyroid proliferative disease cellular proliferation (*middle and left*) is devoid of stromal fat, is encapsulated (*right of center*) separated from a "rim" of residual normal (non-proliferative) parathyroid gland with parenchymal fat (*lower right*). **B**, At slightly higher magnification, a thin fibrous capsule (*center*) separates the cellular proliferation (*left*) and residual normal parathyroid gland including adipocytes (*right*). **C**, At higher magnification, the fibrous capsule separates the adenoma (*left*) lacking intraparenchymal fat from the residual parathyroid parenchyma (*right*) with associated adipose cells. Note the nuclei of the adenoma are larger with a higher nuclear-to-cytoplasmic ratio as compared to the smaller nuclei with lower nuclear-to-cytoplasmic ratio of normal (residual) parathyroid gland.

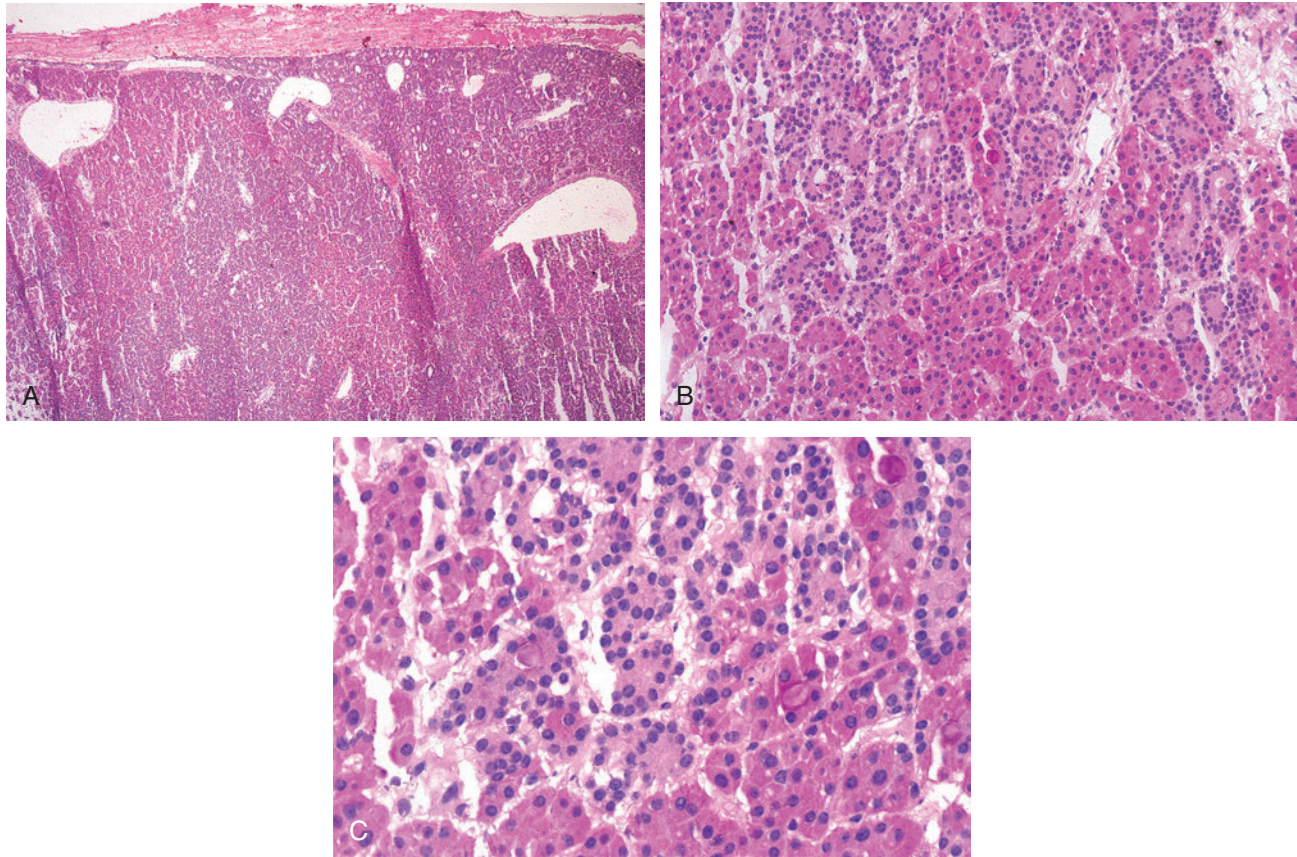


Fig. 34-3. Intraoperative findings, parathyroid adenoma.

A, In this example, the cellular proliferative parathyroid lesion lacking associated intraparenchymal fat is surrounded by a fibrous capsule (*top*) but residual (normal or atrophic) parathyroid gland parenchyma was not identified. **B**, The parathyroid proliferative process shows a microfollicular pattern composed of chief cells and oncocytic cells; some of the microfollicular structures contain colloid-like material; stromal fat is absent. **C**, Higher magnification shows the relatively uniform nuclei of and admixture of chief cells and oncocytic cells. Clinically, this was the only enlarged gland, biopsy and frozen section of another gland was normal, and the rapid intraoperative parathyroid hormone level decreased to normal following removal of the enlarged gland. All of these features assisted in confirming the histologic consideration of a parathyroid adenoma.

samples of additional parathyroid glands show no abnormalities, then a diagnosis of “enlarged parathyroid gland consistent with adenoma” can be made.

- If more than one parathyroid gland is enlarged, including microscopic evidence of increased cellularity with decreased fat, the patient may have parathyroid hyperplasia:
 - Clinical information of whether the patient has a primary diagnosis of PPD, secondary hyperparathyroidism, or familial disease is helpful in the diagnosis.
 - Such examples can be signed out as “cellular parathyroid tissue” or “parathyroid proliferative disease,” with the definitive diagnosis pending permanent sections with appropriate clinical correlation.

MICROHYPERPLASIA

- In grossly normal (size and weight) glands classified into two groups:
 - Class II: hypercellularity only, not thought to produce hypercalcemia
 - Class III: nodular hyperplasia, abnormal cytology, or oxyphilic nodules are considered clinically significant
- The differentiation of an adenoma from hyperplasia in a single enlarged gland cannot always be determined by histopathologic evaluation:
 - Detailed clinical information (pre- and postoperative) is required to render this diagnosis.
 - In the face of abnormal parathyroid tissue in a single gland reported as “abnormal parathyroid gland [parathyroid proliferative disease]

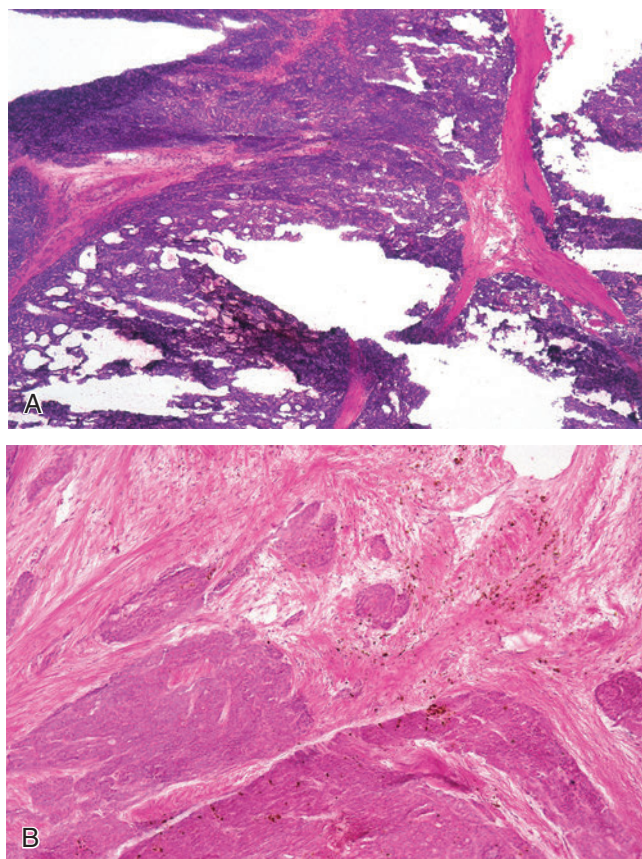


Fig. 34-4. Intraoperative findings, parathyroid adenoma.

A, In this parathyroid proliferative disease process, acellular hyalinized fibrous bands course through the lesion, separating the proliferation into separate nodules. This feature is one often present in association with parathyroid carcinoma but may be seen in parathyroid adenomas too. **B**, Another example of a parathyroid adenoma with associated fibrosis and the appearance along the periphery of the lesion suggests the possible presence of infiltrative growth; in the middle to upper right of the image there is associated hemosiderin deposition. These are reactive and degenerative changes that resulted from a prior surgical procedure in the neck. These changes caused adherence to surrounding tissues, making the gland difficult to surgically excise, raising clinical concerns for a diagnosis of parathyroid carcinoma. However, the overall clinical and pathologic findings were those of a benign process, and long-term follow-up of the patient confirmed the diagnosis of a parathyroid adenoma.

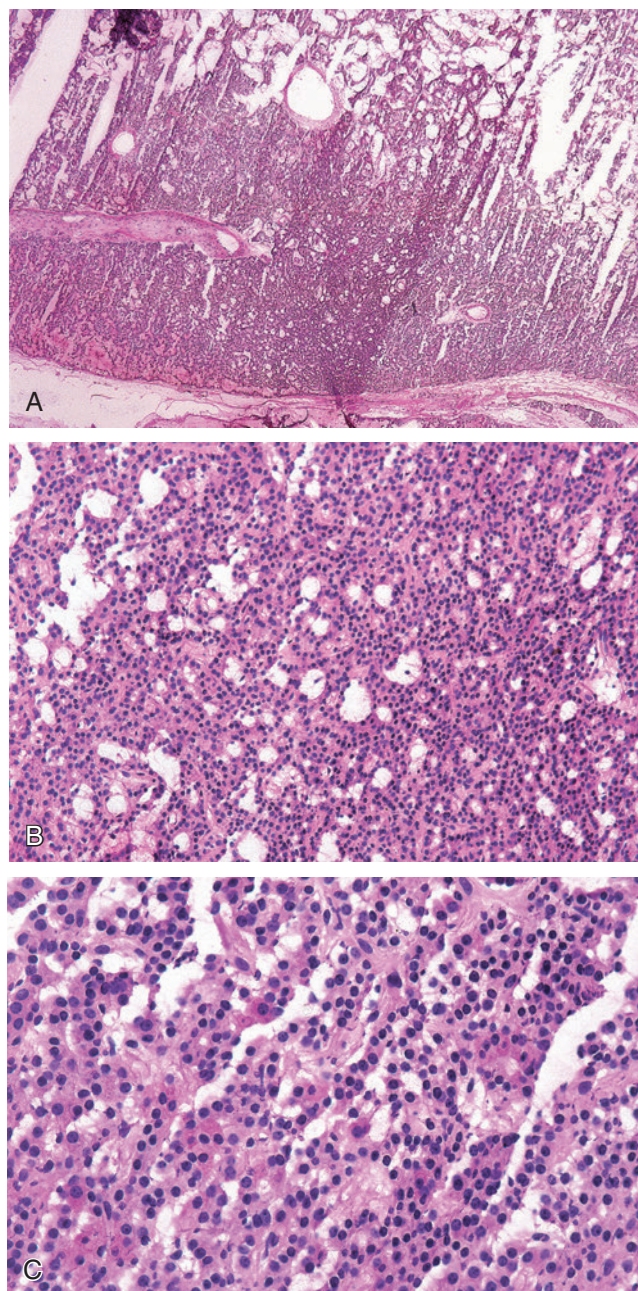


Fig. 34-5. Intraoperative findings, parathyroid hyperplasia.

A, This enlarged parathyroid gland shows a diffuse cellular proliferation with absent intraparenchymal fat and no identifiable residual normal/atrophic parathyroid gland. **B**, The cellular proliferation is arranged in solid sheets, microfollicles, and gland-like structures. **C**, At higher magnification an admixture of chief cells and oncocyctic cells can be seen.

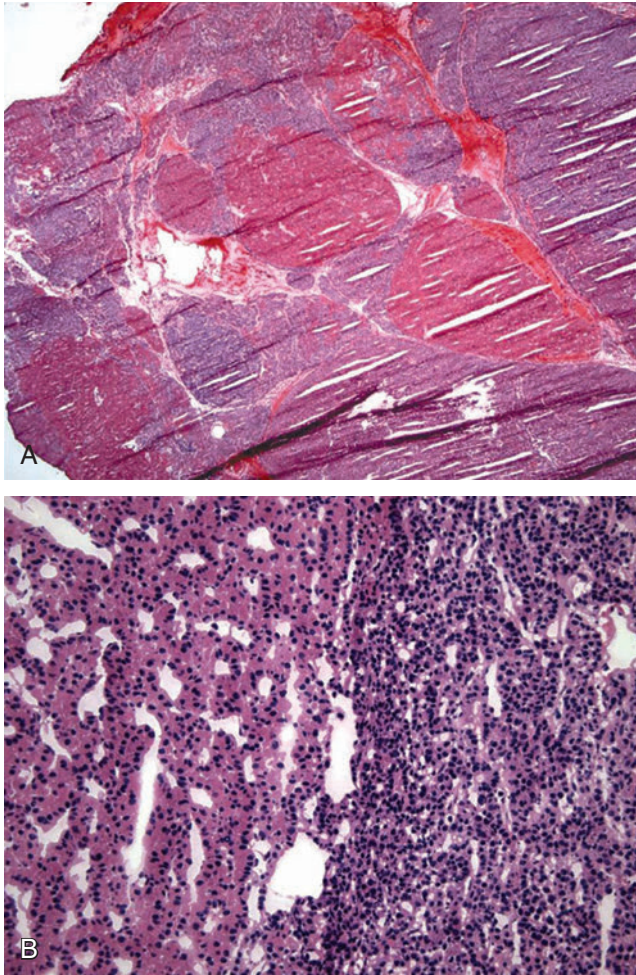


Fig. 34-6. Intraoperative findings, parathyroid hyperplasia.

A, This enlarged parathyroid gland shows nodular hyperplasia, absence of intraparenchymal fat, and no identifiable residual normal/atrophic parathyroid gland.

B, At higher magnification the nodules are composed entirely of chief cells or oncocytic cells.

consistent with adenoma or hyperplasia,” the pathologist should ask the surgeon about the status of the other parathyroid glands and should also request a biopsy (i.e., incisional biopsy) from one or more of the other parathyroid glands.

- In the presence of a borderline enlarged parathyroid gland with the other glands reported as normal, the considerations include:
 - An adenoma is present that has not been identified and continued surgical exploration is indicated.
 - The borderline enlarged gland is responsible for the hyperparathyroidism but this requires clinical correlation.
 - The elevated biochemical findings may be due to nonparathyroid hypercalcemic diseases.

FLOW CHART FOR INTRAOPERATIVE ASSESSMENT FOR HYPERPARATHYROIDISM

- Parathyroid confirmed → determine hypercellularity → enlarged, hypercellular gland confirmed → report as parathyroid proliferative disease c/w adenoma or hyperplasia → examine at least one additional parathyroid gland:
 - If other gland is normal or atrophic → c/w parathyroid adenoma
 - If other gland is abnormal (hypercellular) → c/w hyperplasia
- Parathyroid not confirmed → repeat biopsy

PITFALLS AND/OR ISSUES IN THE INTRAOPERATIVE EVALUATION OF PARATHYROID GLANDS

- Parathyroid tissue may be difficult to distinguish grossly from other tissues in the neck, including thyroid, lymph nodes, fat, and ectopic thymus; frozen section may be requested on these tissues:
 - The differentiation of parathyroid tissue from thyroid tissue may be problematic and is the most common reason for a deferred or incorrect frozen section diagnosis.
 - Histologic patterns that may result in misinterpretation include:
 - Follicle formation: in the presence of a micro-follicular pattern, features that may point to parathyroid gland rather than thyroid tissue include:
 - The presence of solid, sheet-like growth in the nodule
 - Variety of cell types (e.g., chief cells, clear cells, oncocytic cells)
 - The absence of a lymphocytic cell infiltrate
 - Fat cells within the nodule
 - A cap of normal, fat-containing parathyroid tissue adjacent to the nodule
- Lymph nodes can be mistaken for parathyroid tissue as a result of freezing artifact with the presence of tissue clefts and formation of ice crystals, giving the impression of stromal fat.
- Presence of a rim of adjacent parathyroid tissue is helpful in the diagnosis of parathyroid adenoma; however, this finding is not unequivocally diagnostic of a parathyroid adenoma:
 - A rim of adjacent parathyroid tissue is seen in 30% to 50% of cases at the time of frozen section,

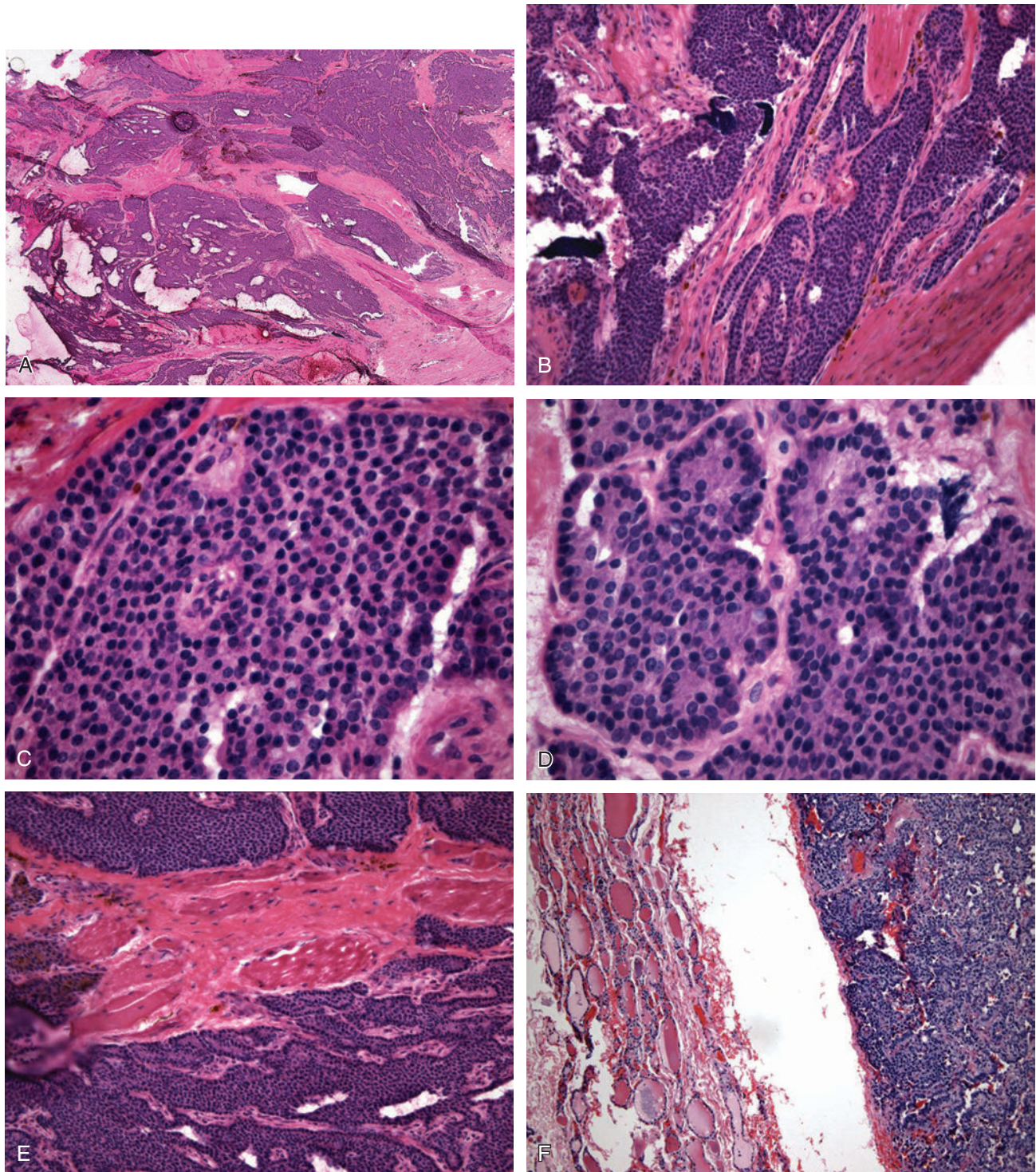


Fig. 34-7. Intraoperative findings, parathyroid carcinoma.

A, Cellular parathyroid proliferative disease process showing acellular fibrous bands coursing through the proliferation and dividing it into multiple nodules. **B**, Trabecular growth. **C**, Solid growth and **(D)** acinar-type growth. **C** and **D**, The cells are rather monotonous appearing with limited nuclear pleomorphism and no increase in nuclear-to-cytoplasmic ratio, no macronucleoli and no increase in mitotic activity. Infiltrative growth including **(E)** into skeletal muscle and **(F)** adherence to and invasion of (not shown in this image) the thyroid gland (left) allow for intraoperative diagnosis of parathyroid carcinoma. Clinically, this patient had very high serum calcium and parathyroid hormone levels, and due to invasion the surgeon had difficulty resecting the gland.

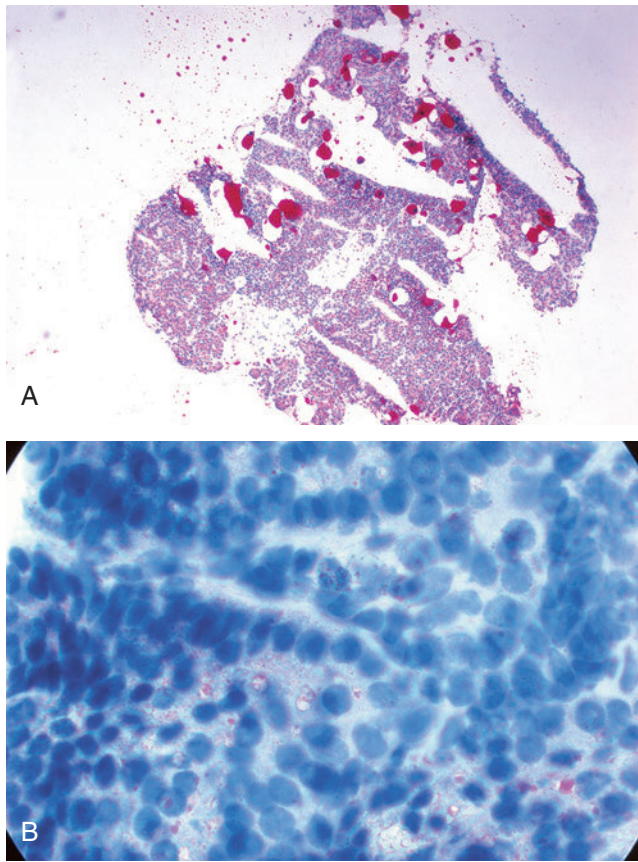


Fig. 34-8. Intraoperative fat stain (Sudan IV).

A, Parenchymal cells in normal glands contain abundant cytoplasmic lipid droplets. **B**, Decrease intracellular/parenchymal lipid content in this hyperfunctioning chief cell proliferation.

and the pathologist cannot rely on this criterion alone to diagnose parathyroid adenoma.

- Further, a rim of normal parathyroid tissue may be seen in association with parathyroid hyperplasia.
- The most reliable distinction between parathyroid adenoma and parathyroid hyperplasia is made by thorough histologic evaluation of one or more additional parathyroid glands.
- Parathyroid hyperplasia may be dyssynchronous, so a hyperplastic gland may be only minimally enlarged.
- The greatest source of error in the intraoperative diagnosis of PPD is the overdiagnosis of parathyroid hyperplasia; however, this issue is currently less likely to be problematic because pathologists have become more aware of this diagnostic pitfall and there is a tendency for surgeons to favor resection of only grossly enlarged glands:

- As such, the false-positive diagnosis of hyperplasia is close to zero.
- Pathologists can minimize the overall error rate by being aware of the diagnostic pitfalls surrounding the intraoperative evaluation of parathyroid glands and by working in close communication with surgical colleagues.
- Presence of stromal fat cannot be used to exclude the diagnosis of adenoma as adenomas may contain variable amounts (some to abundant) of stromal fat.
- Issue of double (multiple) parathyroid adenomas is controversial:
 - Multiple adenomas have been reported with as high an incidence as 9.4%.
 - 9.4% reported incidence is challenged by reports in which multiple adenomas were not present in a large cohort of cases of consecutive explorations for primary hyperparathyroidism.
 - Surgeons who accept the existence of double adenomas advocate for routine bilateral neck exploration as the enlarged glands are approximately equally distributed on both sides of the neck.
- False-positive and false-negative diagnoses can occur in the interpretation of parathyroid carcinoma.

REEXPLORATION FOR PERSISTENT OR RECURRENT HYPERPARATHYROIDISM

- Persistent disease is defined as hyperparathyroidism that occurs within 6 months of prior surgery.
- Recurrent disease is defined as hyperparathyroidism that occurs more than 6 months after prior surgery.
- Due to alterations of the surgical anatomy, the identification of parathyroid glands during reexploration may prove difficult and the abnormal gland may be ectopically situated:
 - Scarring in the area may result in adhesions, creating surgical difficulty in removal of the parathyroid glands.
 - This clinical information may suggest a parathyroid carcinoma (see next section).

PARATHYROID CARCINOMA

- Parathyroid carcinoma typically presents as a mass that is adherent to adjacent structures; the latter would be indicative of invasion and invasion would be diagnostic for carcinoma.
- In cases of suspected parathyroid carcinoma, sampling the peripheral aspects of the lesion may provide the greatest yield in identifying invasion.

- In the face of a parathyroid carcinoma, the mass is excised en bloc and the evaluation of surgical margins is critical to determining that the tumor has been completely excised; however, in the absence of invasion, the light microscopic features may be suggestive of parathyroid carcinoma, but the frozen section diagnosis of parathyroid carcinoma can be extremely challenging.
- Pitfalls in the diagnosis of parathyroid carcinoma may include:
 - Prior violation of the neck by previous surgery or fine-needle aspiration biopsy or spontaneous infarction may result in adherence of the gland to adjacent structures, fibrous bands coursing within the gland, and/or necrosis.
 - In contrast to carcinoma, the adhesions in benign disease are usually easily dissected, there is evidence of hemorrhage (and other degenerative changes) within the fibrous bands, and the necrosis due to trauma or spontaneous infarction is usually large and confluent.
 - Mitotic figures can be seen in benign parathyroid lesions; the presence of mitoses is not in and of itself indicative of carcinoma.

PARATHYROID PROLIFERATIVE DISEASE (PPD) IN "ECTOPIC" SITES

- PPD may occur within the thyroid gland or thymus.
- These lesions are uncommon and typically benign (i.e., adenoma).
- Differentiating parathyroid from thyroid may be problematic (see above) and may require immunohistochemical stains (e.g., chromogranin, PTH, parafibromin, thyroglobulin and TTF1).
- Rare examples of intrathyroid parathyroid carcinoma have been reported.

ADJUNCT METHODS IN THE INTRAOPERATIVE EVALUATION OF PARATHYROID PROLIFERATIVE DISEASE

Fat Stains

- The use of intraoperative fat stains for the evaluation of parathyroid tissue is based on the fact that parenchymal cells in normal glands contain abundant cytoplasmic lipid droplets, whereas the intracellular or parenchymal lipid content is decreased or absent in hyperfunctioning chief cells.

- Fat stains may include Sudan IV, oil red O, and osmium carmine.
- Intraoperative fat stains are technically difficult and therefore not widely used.
- Cytoplasmic lipid droplets can be evaluated in air-dried cytologic preparations with Wright-Giemsa stain; in this setting lipid droplets are visible as clear vacuoles.

Density Gradients

- Mannitol density test or measurement provides an objective evaluation of the ratio of parenchymal-to-fat cells and is based on the differences in density between parenchymal cells and stromal fat cells.
- The density of the parathyroid is an indirect estimate of the lipid content of the parenchymal cell content.
- With knowledge of the glandular weight and estimate of parenchymal content, it is possible to calculate the parenchymal weight.
- This test is not widely used.

INTRAOPERATIVE MONITORING OF PARATHYROID HORMONE LEVELS

- Rapid intraoperative parathormone (IOPTH) evaluation levels by highly sensitive immunoradiometric assay (IRMA) are used for immediate biochemical confirmation of the result of parathyroid surgery.
- The parathyroid lesion is localized preoperatively and removed through a small incision.
- Because of the short half-life of PTH, a serum PTH level can be drawn 15 minutes after excision of the presumed diseased gland.
- Absence of a second or multiple lesions is confirmed by immediately checking blood parathyroid hormone level via the analyzer rather than by the standard method of exploration and biopsy of all the remaining parathyroid glands:
 - Adjunctive IOPTH monitoring facilitates a high cure rate for initial surgery of sporadic primary hyperparathyroidism.
 - Final IOPTH level that within the normal range dropping by more than 50% from baseline is a strong predictor of operative success.
 - Patients with a final IOPTH level between 41 and 65 pg/ml should be followed beyond 6 months for long-term recurrence.
- Rapid intraoperative parathormone evaluation allows for less invasive surgery and decreased operating time.

ACCURACY OF INTRAOPERATIVE CONFIRMATION OF PARATHYROID TISSUE AND INTRAOPERATIVE DIAGNOSIS

- Frozen section is a highly reliable means of identifying tissue type during parathyroid exploration.
- The frozen section accuracy rate of distinguishing parathyroid tissue from nonparathyroid tissue is reported to be 99.2%.

- A deferral rate of 0.4% due to difficulties in distinguishing between parathyroid gland and thyroid gland or lymph node
- Factors that may contribute to confounding the frozen section diagnosis include (separately or in combination): frozen section artifact, sampling error, and judgmental errors.

FURTHER READING

References may be accessed online at [ExpertConsult.com](#).

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Multiple Endocrine Neoplasia (MEN) Syndromes

INTRODUCTION

See Chapter 28 under Medullary Thyroid Carcinoma for additional discussion.

- Multiple endocrine neoplastic (MEN) syndromes represent primarily autosomal dominant inherited disorders characterized by hyperplastic or neoplastic proliferations of more than one endocrine gland and include:
 - MEN type 1
 - MEN type 2 further divided into:
 - MEN-2A
 - MEN-2B
 - Familial medullary carcinoma (FMTc)

MEN TYPE 1

Synonym: Wermer syndrome

- Autosomal dominant disease:
 - May occur sporadically:
 - De novo mutations appear in 10% of all patients with MEN-1.
- Characterized by combined occurrence of two or more tumors involving:
 - Parathyroid glands
 - Pancreas
 - Anterior pituitary gland
- MEN-1 gene (MEN-1) is located on chromosome 11q13:
 - Composed of 10 exons that encode a 610 amino acid protein called menin
 - Menin interacts with several different proteins and plays an important role in regulation of cell growth, cell cycle, genome stability, and synapse plasticity.
- Tumors caused by a heterozygous germline-inactivating mutation in the MEN-1 gene (first hit) followed by somatic inactivating mutation or loss of the normal copy of the gene (second hit) leading to complete loss of function of encoded protein menin
- Familial MEN-1 has high degree of penetrance with clinical or biochemical manifestations of disease in 80% and 98%, respectively, by the fifth decade.
- Clinical manifestations related to tumor localizations and their secretory products:
 - Parathyroid glands:
 - Most common, occurring in 95% of MEN-1 patients
 - Chief cell hyperplasia
 - Clinically results in primary hyperparathyroidism
 - Pancreatic tumors
 - Occur in 40% to 70% of MEN-1 patients:
 - Tumors include:
 - Gastrinoma (G-cell tumors)
 - Most common pancreaticoduodenal tumor in MEN-1 (50%): approximately 20% of gastrinomas occur in MEN-1 patients; 20% to 60% of MEN-1 patients develop gastrinomas
 - Not always located in pancreas: significant proportion primarily arise in duodenum; other primary sites may include stomach, jejunum, bile ducts
 - Results in Zollinger-Ellison syndrome: clinical signs and symptoms related to gastric acid hypersecretion including: peptic ulcer disease; diarrhea; esophageal reflux disease
 - Insulinoma (beta cell tumors):
 - Occur in approximately 30% of MEN-1 patients
 - Clinical signs and symptoms related to insulin hypersecretion include hypoglycemic symptoms (hyperinsulinemic hypoglycemia); visual disturbances (blurred vision, diplopia); mental status changes including confusion, amnesia, behavioral changes.
 - Secondary effects of catecholamine release include hunger, weakness, nausea, palpitations, anxiety, perspiration.
 - Symptoms of Whipple triad include: hypoglycemia, low blood glucose levels, symptomatic relief with glucose administration.
 - Vasoactive intestinal peptide (VIP) cell tumors (VIPoma):
 - Occur in approximately 12% of MEN-1 patients

- Clinical signs and symptoms related to VIP hypersecretion include watery diarrhea associated with hypokalemia and achlorhydria (Verner-Morrison syndrome; pancreatic cholera; WDHA).
- Glucagonoma (alpha cell tumors):
 - Occur in less than 5% of MEN-1 patients
 - Clinical signs and symptoms related to glucagon hypersecretion include dermatitis (necrolytic migratory erythema), which is most common and usually found intertriginous and periorificial, especially groin and buttocks; diabetes mellitus and glucose intolerance; weight loss; anemia; hypohaminoacidemia.
- Pituitary tumors
 - Occur in 30% to 40% of MEN-1 patients
 - Anterior pituitary adenoma
 - Clinically results in acromegaly or hypopituitarism
- Other tumors described, including:
 - Adrenal cortical tumors
 - Carcinoid tumors (foregut, primarily thymus, and lung)
 - Nonendocrine tumors, including:
 - Lipomas, angiofibromas, collagenomas, and meningiomas
- Correlation between genotype and phenotype not found:
 - Combinations of tumors may be different in members of same family.
- Treatment for each type of endocrine tumor:
 - Generally similar as in non-MEN-1-associated tumors
 - Results are less successful owing to:
 - Multiplicity of tumors
 - Higher metastatic disease
 - Larger and more aggressive tumors
 - More resistant to treatment
- Untreated patients:
 - Have decreased life expectancy with 50% probability of death by the age of 50 years
 - Cause of death mostly directly related to MEN-1 is malignant pancreatic neuroendocrine tumors (NET) and thymic carcinoids
- Prognosis might improve by preclinical tumor diagnosis and appropriate treatment.

MEN TYPE 2

- Autosomal dominant disease caused by germline mutation of *RET* (REarranged during Transfection) gene
- Characterized by various endocrine tumors of:
 - Thyroid gland
 - Adrenal gland

- Parathyroid glands
- As well as abnormalities of nonendocrine organs
- Three clinical subtypes:
 - MEN-2A
 - MEN-2B
 - Familial medullary thyroid carcinoma (FMTC)
- Hallmark of MEN-2 is very high lifetime risk of developing medullary thyroid carcinoma (MTC):
 - >95% in untreated patients
 - Collectively associated with a 70% to 100% risk of MTC by age 70 years
- Recent report that germline mutations in *CDKN1B* can predispose to development of multiple endocrine tumors in rats and humans:
 - New MEN syndrome named MEN-X and MEN-4, respectively

MEN-2A

Synonym: Sipple syndrome

- Most common of three subtypes, accounting for 75% to 90% of familial cases
- Germline point mutation of *RET* protooncogene
 - Usually involve exon 10 and 11
 - Most common genetic abnormality found in 95% of families with MEN-2A
- Characterized by presence of:
 - Thyroid lesions/tumors often multiple and bilateral, including:
 - Medullary thyroid carcinoma (MTC)
 - Usual first manifestation of syndrome
 - C-cell hyperplasia:
 - May precede clinically obvious MTC
 - Pheochromocytoma (approximately 50%):
 - Often bilateral
 - Accompanied by adrenal medullary hyperplasia
 - Primary parathyroid (chief cell) hyperplasia (20% to 30%)
 - Rare cases associated with Hirschsprung disease and cutaneous lichen amyloidosis
- Genetic testing for *RET* protooncogene has largely replaced serum calcitonin measurement (following gastrin administration) for diagnosis.

MEN-2B

Synonyms: Gorlin syndrome; Wagenmann-Froboese syndrome

- Least common of 3 subtypes, accounting for approximately 5% of familial cases
- Germline mutation of *RET* protooncogene:
 - Point mutation at exon 16:
 - Replacement of methionine by threonine at codon 918
 - Identified in 95% of cases with MEN-2B

- Characterized by presence of:
 - Medullary thyroid carcinoma
 - Pheochromocytoma (approximately 50%)
 - Mucosal neuroma (oral mucosa, lips, tongue, eyelids):
 - Most constant feature
 - Gastrointestinal ganglioneuromatosis (100%)
 - May represent initial manifestation of disease
 - May present with clinical picture identical to Hirschsprung disease
 - Rectal biopsy reveals proliferation rather than absence of ganglia
 - Marfanoid appearance (100%)
 - Rarely associated with parathyroid hyperplasia
 - Genetic testing for RET protooncogene has largely replaced serum calcitonin measurement for diagnosis of hereditary MTC.

Familial MTC (FMTC)

Synonym: MTC alone

- Second most common of three subtypes, accounting for approximately 15% of familial cases
- Not associated with lesions of other organs (hence designation as MTC alone)
- Germline mutation of RET protooncogene
 - 85% of families will show mutations in codons of exons 10 and 11
 - Mutations in codons 768, 790, 791, 804, 848, 883, 891, 904
- Genetic testing for RET protooncogene has largely replaced serum calcitonin measurement for diagnosis of hereditary MTC.

Treatment and Prognosis

- Early detection and curative surgery can result in cure in virtually all children after appropriate genetic testing at a young age.
 - Genetic testing should be performed before surgical intervention in all patients diagnosed with MTC.
- In MTCs seen clinically because genetic testing was not performed or because patient represents index case in a family, prognosis mirrors that of sporadic tumors (see Chapter 28) except for high frequency of multiple primary tumors.
- Effective management of patients with MEN-2A, MEN-2B, and FMTC depends on understanding of variable behavior of disease expression in patients with a specific RET mutation.
- Strong genotype-phenotype correlations exist with respect to clinical subtype, age at onset, and aggressiveness of MTC.
 - Used to determine age at which prophylactic thyroidectomy should occur and whether screening

for pheochromocytoma or hyperparathyroidism is necessary

- Specific RET mutations can impact management in patients presenting with apparently sporadic MTC.
- Relative aggressiveness of MTC associated with specific RET mutations, including:
 - Presence of codon 918 mutation:
 - Indicative of aggressive disease phenotype whether mutation is hereditary (MEN-2B) or acquired as somatic mutation
 - Surgery performed in first month of life or as soon as phenotype identified
 - Presence of codon 634 RET mutation:
 - Aggressive phenotype accounting for approximately 80% of hereditary MTC
 - Surgery performed <5 years of age
 - Presence of mutations of codons 768, 790, 791, and 804:
 - In certain kindreds these mutations associated with metastasis and death
 - In other kindreds these mutations never associated with death
 - Consideration for surgery <5 years of age or delay in following criteria met:
 - Less aggressive family history
 - Normal serum calcitonin
 - Normal neck ultrasound
- RET analysis in MEN has revolutionized management of MEN-2 and allowed surgical prediction and prophylaxis to take place.
- Prognosis related to pheochromocytoma and parathyroid tumors similar to that of sporadic counterparts

INHERITED SYNDROMES WITH DIFFERENT ENDOCRINE NEOPLASMS

- Heterogeneous group of cancer susceptibility syndromes that affect one or more of endocrine glands or neuroendocrine tissues that include:
 - Hyperparathyroid-jaw tumor syndrome: (see Sections 2 and 9)
 - Endocrine tumor:
 - Parathyroid adenoma or carcinoma
 - Fibroosseous lesions of mandible or maxilla
 - Renal cysts and tumors
 - von Hippel-Lindau disease (see Section 7)
 - Endocrine tumors:
 - Pheochromocytoma, pancreatic endocrine tumors
 - Hemangioblastoma
 - Renal cell carcinoma

- Endolymphatic sac papillary tumor
- Others
- Carney complex (see Section 7)
 - Endocrine tumor:
 - Pituitary adenoma
 - Primary pigmented nodular adrenocortical disease
 - Cardiac myxoma
 - Psammomatous melanotic schwannoma
- Neurofibromatosis type 1 (see Section 4)
 - Endocrine tumor:
 - Pheochromocytoma
 - Paraganglioma (rare)
 - Neurofibromas
 - Café-au-lait skin pigmentation
 - Axillary freckling or freckling in inguinal region
 - Iris hamartomas (Lisch nodules)
 - Central nervous system gliomas
- Cowden syndrome (see Section 8)
 - Endocrine tumor/lesion:
 - Follicular neoplasms (adenoma and carcinoma)
 - Adenomatoid nodules (goiter)
 - Macrocephaly
 - Intestinal hamartomatous polyps
 - Benign skin tumors (trichilemmoma, papillomatous papules, acral keratoses)
- Familial paraganglioma-pheochromocytoma syndromes (see Section 4)
- McCune-Albright syndrome (see Section 2)
 - Endocrine lesions:
 - Autonomous endocrine hyperfunction (e.g., gonadotropin-independent precocious puberty)
 - Other endocrine syndromes may include hyperthyroidism, acromegaly, and Cushing syndrome.
 - Polyostotic fibrous dysplasia
 - Café-au-lait skin pigmentation

FURTHER READING

References may be accessed online at ExpertConsult.com.

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